AWARD NUMBER: W81XWH-15-1-0605

TITLE: Prevention of Posttraumatic Contractures with Ketotifen (PERK)

PRINCIPAL INVESTIGATOR: Kevin A. Hildebrand

CONTRACTING ORGANIZATION: University of Calgary, Calgary T2N1N4

REPORT DATE: September 2018

TYPE OF REPORT: **Fi**nal

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2018	Final	30Sep2015 - 29Jun2018

4. TITLE AND SUBTITLE

Prevention of Posttraumatic Contractures with Ketotifen (PERK)

5a. CONTRACT NUMBER
W81XWH-15-1-0605

5b. GRANT NUMBER
OR140142

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Kevin 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 Materiel 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

All goals have been achieved in this Clinical Trial Development Award to develop the infrastructure to complete a multicenter randomized clinical trial. We have secured funding for a trial from the Department of Defense (Contract No. W81XWH-17-1-0665). We have received approval from the Food and Drug Administration, Human Research Protections Office, and Health Canada to conduct the study. Seventeen centers across Canada and the United States will recruit for the trial. Training sessions for these centers were completed and startup funds to finalize institutional review board applications have been awarded. Contracts have been signed with organizations to support central core functions including procurement, packaging, and distribution of study medication and placebo across North America; database and study management for randomization and coordination of medication distribution; image archiving; outcome measurement tool validation; study monitoring and safety committees; and centralized trial support for contracts/regulatory, budget, and recruitment/follow up/data entry. Knowledge translation has included reports of this work in University and Health Services media and through the annual program report by the Peer Reviewed Orthopaedic Research Program.

15. SUBJECT TERMS

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	352	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

This Clinical Trial Development Award (CTDA) pertains to the FY14 Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Development Award (CTDA) announcement to identify and reduce secondary health effects (e.g., joint contracture) that follow reduced mobility from traumatic neuromusculoskeletal injury. This CTDA facilitates an opportunity to design a Phase III RCT on the use of ketotifen in post-traumatic joint contractures. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. This will facilitate applications for operational funds to complete the Phase III RCT. The identified funding mechanisms are PRORP or Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award (CTA) competitions and the Canadian Institutes of Health Research (CIHR) for the Phase III RCT.

2. KEYWORDS:

Post-traumatic contractures, elbow fractures, randomized clinical trial, multicenter, ketotifen, placebo, FDA, HRPO, database, training, contracts, institutional review board, Health Canada.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Goal 1: Recruit Sites
Major Goal 2: Regulatory Applications
Major Goal 3: Medication Packaging and Distribution
Major Goal 4: Data Management and Safety
Major Goal 5: Phase III Randomized Clinical Trial (RCT) Design
Major Goal 6: Transition Plan

What was accomplished under these goals?

Major Goal 1: Recruit Sites

1) Major Activities:
    a. Identify sites
    b. Train sites
    c. Institutional Review Board (IRB) and Contract completion
2) Specific Objectives:
    a. Develop a cadre of sites to complete a multinational, multicentre trial
    b. Assist and develop relationships with these sites
3) Results:
    a. Seventeen sites (14 Canada, 3 United States) were identified through the American Society for Surgery of the Hand, the Canadian Orthopaedic Trauma Society, and the Major Extremity Trauma Research Consortium
    b. Training meetings were held in Calgary November 3-4, 2017 and Toronto December 1-2, 2017 (appendices pages 13–92)

Major Goal 1: Recruit Sites (Continued)

c. Contracts completed for startup awards, translation of consents into French or Spanish where required, IRB applications, Local Pharmacy setup, and negotiation of contracts for the Department of Defense operational award for the Phase III (Contract No. W81XWH-17-1-0665) – appendices pages 93-165
d. Human Research Protections Office Approval received August 30, 2018 for the trial- appendices pages 166-168

Major Goal 2: Regulatory Applications

1) Major Activities:
    a. Complete an IND application to the Food and Drug Administration (FDA)
    b. Complete a Clinical Trial Application to Health Canada
2) Specific Objectives:
    a. To obtain approval of the use of Ketotifen fumarate for the prevention of Post-traumatic Joint Contractures
3) Results:
    a. FDA asked for an analysis of the medication, which was completed with EXOVA
    b. FDA received the application August 1, 2017 and indicated August 30, 2017 that a full clinical hold was in place
    c. FDA removed the full clinical hold November 13, 2017 allowing the trial to go ahead – appendices pages 169-171
    d. Health Canada received the Clinical Trial application July 12, 2018 and asked July 30, 2018 for revisions by August 1, 2018
    e. Health Canada granted a No Objection Letter August 9, 2018 allowing the trial to go ahead – appendices page 172

Major Goal 3: Medication Packaging and Distribution

1) Major Activities:
    a. Identify a Manufacturer of Ketotifen fumarate and a placebo
    b. Identify an Organization to Acquire active medication and placebo and package
    c. Develop a distribution method based on need at each site
    d. Coordinate ordering from manufacturer, packaging, distribution to pharmacy at sites, and dispensing appropriate treatment based on allocation
2) Specific Objectives:
    a. Secure a source of active medication and placebo
    b. Package in a way to keep participants and study personnel blinded to treatment
    c. Ensure participants receive correct allocated treatment
3) Results: - appendices pages 173-204
    a. TEVA has supply of Ketotifen fumarate (Zaditen®) for 3 years and will charge – unsuccessful application for investigator sponsored study
    b. Bay Area Research Logistics (BARL), Hamilton Ontario CANADA will obtain lactose placebo and methyl cellulose filler from Medisca
    c. BARL will manufacture blinded trial medication by overencapsulation of the Ketotifen, lactose, and methyl cellulose in a Capsugel® pill
    d. BARL will distribute batches of medications intermittently directly to site

Major Goal 3: Medication Packaging and Distribution (Continued)

e. StudyManager from the Clinical Research Unit (CRU) at the University of Calgary will coordinate the site needs with BARL to ensure adequate supplies with intermittent (re)orders based on site recruitment rates

Major Goal 4: Data Management and Safety

1) Major Activities:
    a. Develop a database for the case report forms
    b. Secure an image archiving system
    c. Licenses for Patient report Outcomes
    d. Data monitoring and Quality Assurance Plan
2) Specific Objectives:
    a. Consistent central data capturing across multiple sites
    b. Validated Patient Reported Outcome Measures
    c. Ensure data quality and participant safety
3) Results:
    a. CRU at the University of Calgary has developed a centralized electronic data capturing system using the FDA approved DataFax. DataFax interacts with StudyManager for recruitment and allocation – appendices page 205-266
    b. Calgary Image Processing and Analysis Centre will store and archive Xrays – appendices pages 267-268
    c. Patient reported outcomes licenses – appendices pages 269-293
        i. Disability Arm Shoulder Hand is free and no licenses required
        ii. Licenses for the Oxford Elbow Score and Pain Catastrophizing Scale obtained
        iii. Contract with Oxford University Innovation limited to develop validated United States English and Spanish, and Canadian English and French, versions of the Oxford Elbow Score
    d. Data Monitoring and Quality assurance
        i. Adverse event committee chaired by Dr. Carmen Brauer, medical monitor
        ii. Trial Steering Committee chaired by Dr. Kevin Hildebrand
        iii. Data Safety and Monitoring Board Committee – 3-member committee composition to be finalized
        iv. Study monitor provided by the CRU for site visits at start up, mid study and study completion to verify data with source documents and study conduct practices
        v. Logic inherent in the database, and 10% sampling of data centrally to validate data

Major Goal 5: Phase III RCT Design

1) Major Activities:
    a. Use Pilot RCT to inform
    b. Incorporate emerging preclinical data
    c. Solicit input from site investigators
2) Specific Aims:
    a. To develop grant applications

Major Goal 5: Phase III RCT Design (Continued)

b. To inform development of key core support functions

3) Results:

a. Pilot RCT (ClinicalTrials.gov Identifier NCT01902017) interpreted to narrow study population to more severe injuries – defined as elbow fractures requiring an operation

b. Preclinical studies show a dose response – a second dose of ketotifen added

c. Pilot RCT (ClinicalTrials.gov Identifier NCT01902017) provided data on primary outcome measure for sample size calculation – 702 participants required necessitating a multicentre trial

d. Patient reported outcomes modified in Phase III to include Oxford Elbow score, and based on feedback at the site training meetings, to add Pain Catastrophizing Scale

e. Inclusion criteria expanded to include participants with multiple injuries as long as they can complete physiotherapy of elbow – based on feedback at site training meetings

f. Study design was used for Department of Defense grant applications

g. Case report forms used to develop database in DataFax with CRU

h. BARL engaged for medication acquisition, packaging and distribution

Major Goal 6: Transition Plan

1) Major Activities:
   a. Submit grant applications to national funding agencies in Canada and United States
   b. Share research activities with research community and public
2) Specific Aims:
   a. To secure operation funds to conduct the RCT designed in Major Goal 5
   b. To disseminate research activities / findings
3) Results:
   a. Department of Defense application OR160026 was successful and culminated in contract number W81XWH-17-0665 as the source of operating funds – see appendices pages 294-311
   b. Feature in the University of Calgary UToday October 26, 2017 – see appendices pages 312-314
   c. Inclusion in the next annual program report by the Peer Reviewed Orthopaedic Research Program – see appendices pages 315-319

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

Training Activities: Site PI and Research Coordinator training sessions were conducted by Dr. Kevin Hildebrand and Alex Garven on November 3-4, 2017 and December 1-2, 2017 – see appendices pages 13-92

Professional Development: - see appendices pages 320-321

Alex Garven - SOCRA conference May 2018 – FDA Clinical Trials Requirements Regulations Compliance and GCP
- Regulatory 2018 - Good Documentation and Practices-Records Module June 2018

How were the results disseminated to communities of interest?

An article in the UToday, an electronic daily report by the University of Calgary for the general public featured the research on joint contractures and the upcoming Phase III RCT on October 26, 2017

The Peer Reviewed Orthopaedic Research Program (PRORP) will include a feature in the soon to be released annual report on the research program on Joint Contracture prevention focusing both on the Clinical Trial Development Award (CTDA, OR140142) and the Clinical Trial Award (CTA, OR160026)

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

Nothing to Report

4. IMPACT:

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

The Orthopaedic Community is aware of the pilot trial (ClinicalTrials.gov Identifier NCT01902017) and now the upcoming Phase III trial (ClinicalTrials.gov Identifier NCT30582176). This work has been shared with the American Society for Surgery of the Hand, the Canadian Orthopaedic Trauma Society and the Canadian Orthopaedic Association. Through these organizations, seventeen sites have agreed to be recruiting sites for the Phase III RCT.

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:

A budget extension of 3 months and redistribution of budget was submitted March 19, 2018. The purpose was to extend the time to get start-up funds, to the sites. In addition, the amount of start-up funds was increased to accommodate the increased work for sites with the pharmacy component of the trial, and to pay for translations of forms into French and Spanish at certain sites. Another major initiative was the formation and validation of the Oxford Elbow Score in Canadian and US English, Canadian French and American Spanish. – see appendices pages 322-352

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

Nothing to report

Changes that had a significant impact on expenditures

The budget extension and redistribution mentioned previously was accomplished within the approved budget. There were no additional funds.

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

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.

Nothing to report

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

An article in the UToday, an electronic daily report by the University of Calgary for the general public featured the research on joint contractures and the upcoming Phase III RCT on October 26, 2017
http://www.ucalgary.ca/utoday/issue/2017-10-26/asthma-medication-…20may%20prevent%20loss%20of%20joint%20motion%20following%20injury

The Peer Reviewed Orthopaedic Research Program (PRORP) will include a feature in the soon to be released annual report on the research program on Joint Contracture prevention focusing both on the Clinical Trial Development Award (CTDA, OR140142) and the Clinical Trial Award (CTA, OR160026) – report expected Later fall 2018

- **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:	5
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:	8
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.

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?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report

QUAD CHARTS: See appendices – page 12

9. APPENDICES:

Prevention of Posttraumatic Contractures with Ketotifen (PERK)

OR140142
W81XWH-15-1-0605

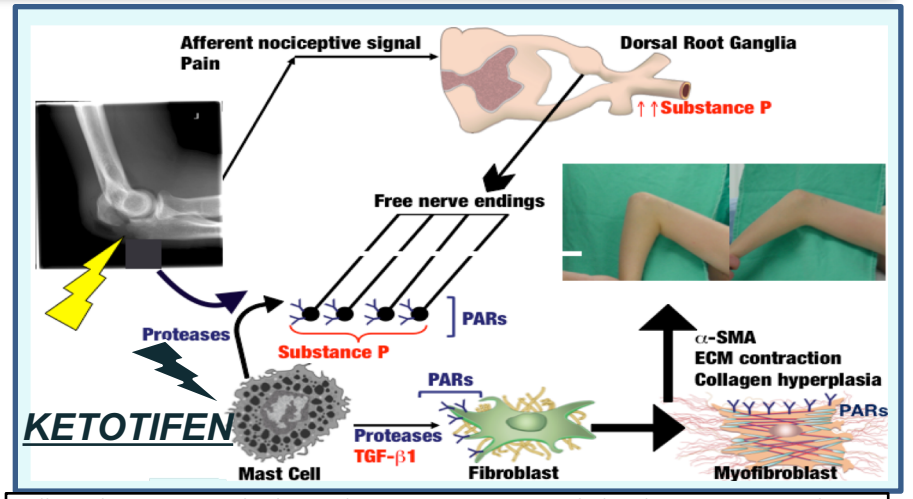
PI: Kevin A. Hildebrand **Org:** University of Calgary **Award Amount:** $238,420

Study/Product Aim(s)

- Major Task 1 – Recruit sites
- Major Task 2 – Regulatory applications
- Major Task 3 – Medication Packaging & Distribution
- Major Task 4 – Data Management and Safety
- Major Task 5 – Phase III RCT design
- Major Task 6 – Transition Plan

Approach

This is a clinical trial development award. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. Regulatory; Ethics; data base and study management; medication acquisition, double blind production, and distribution; identification and training of sites personnel; and applications to PRORP or PRMRP Clinical Trial Award competitions and to the Canadian Institutes of Health Research (CIHR) for operational funds will occur.



All regulatory approvals obtained. Operating grant awarded and contract initiated. Centralized medication manufacture and distribution coordinated with Study Manager and Database. 17 sites have received start up funds. Validated OES.

Timeline and Cost

Activities CY	15	16	17	18
PRORP-CTA Contract		■	■	
Regulatory applications			■	■
Site recruitment		■	■	■
Core Support facilities			■	■
Estimated Budget ($K)	**$0**	**$28**	**$34**	**$143**

Updated: (September 28, 2018)

Goals/Milestones

CY16/17 Goal – PRORP-CTA
☑ Contract W81XWH-17-01-0665 was awarded for funding September 30, 2017

CY18 Goals – HRPO application
☑ Approved August 30, 2018

CY16/17 Goal – IND/Health Canada
☑Clinical Hold removed November 13, 2017
☑ No objection letter from Health Canada August 9, 2017

CY17 IRB application– Site Recruitment
☑ Calgary – Peter Lougheed Centre approved 11 Sep 2017
☐ Other 16 sites

CY18 Core Support
☑ Central database and randomization
☑ Medication acquisition, manufacture and distribution
☑ Central Xray image processing and archiving

Budget Expenditure to Date
Projected Expenditure:$238,420 Actual Expenditure: $205,685

PERK II Investigator's Meeting

PrEvention of posttraumatic joint contRactures with Ketotifen II

December 1-2, 2017

Toronto

McCAIG INSTITUTE FOR BONE AND JOINT HEALTH

UNIVERSITY OF CALGARY CUMMING SCHOOL OF MEDICINE

Alberta Health Services

Investigator's Meeting Outline

1. Introduction
2. Background
3. PERK II
4. Study Preparation
5. Breakout Sessions

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PrEvention of post-traumatic contractuRes with Ketotifen II (PERK II): Background

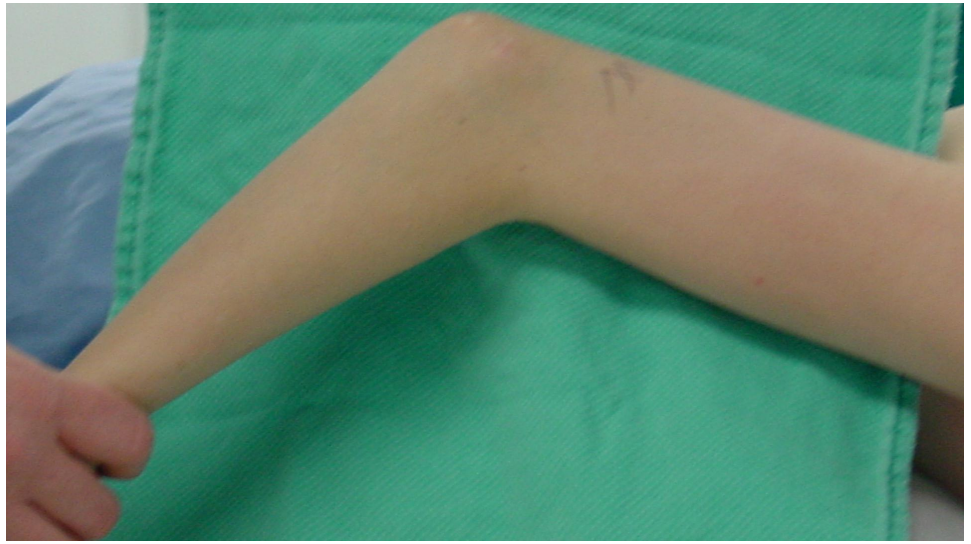
Kevin A. Hildebrand, MD, FRCSC
Chief, Orthopaedic Surgery
Professor, Department of Surgery
Deputy Director, McCaig Institute for Bone and Joint Health
Cumming School of Medicine
University of Calgary

Mobility for Life.

Alberta Health Services

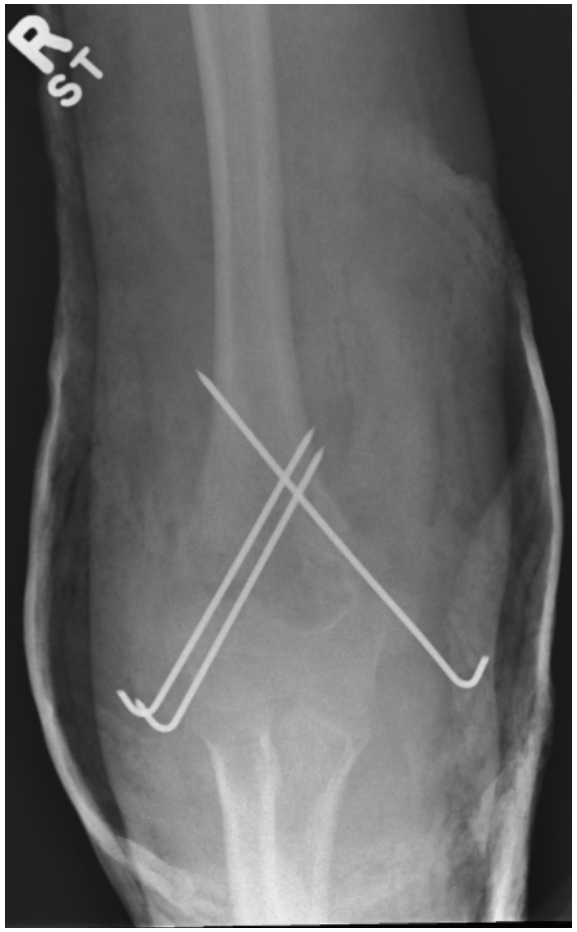
UNIVERSITY OF CALGARY

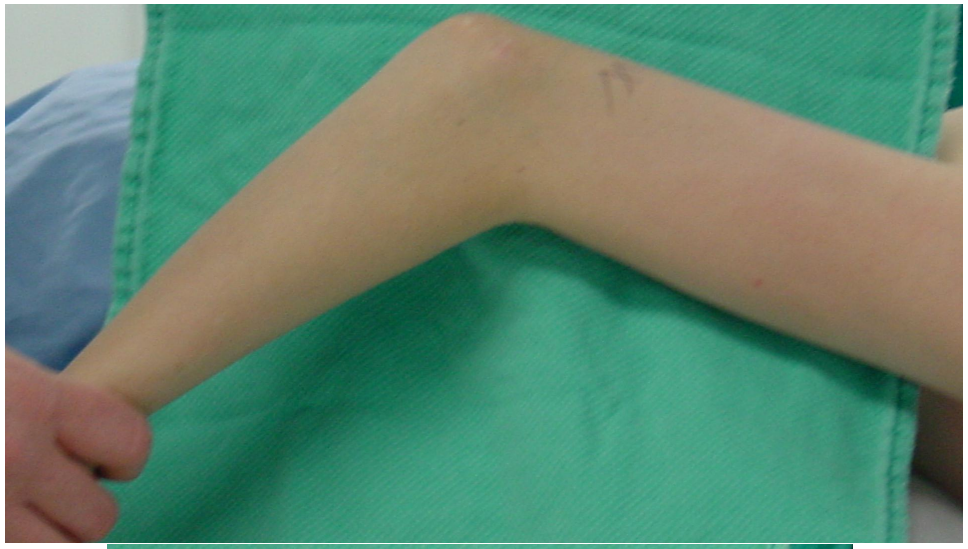
Outline

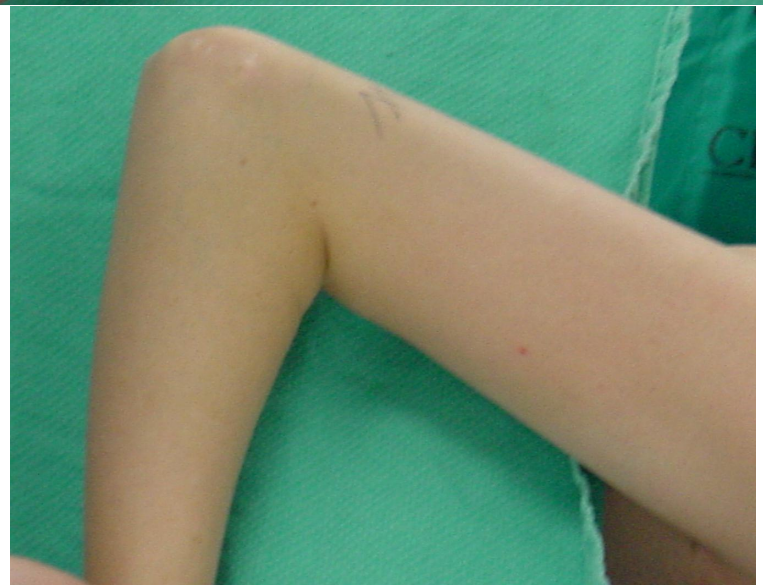


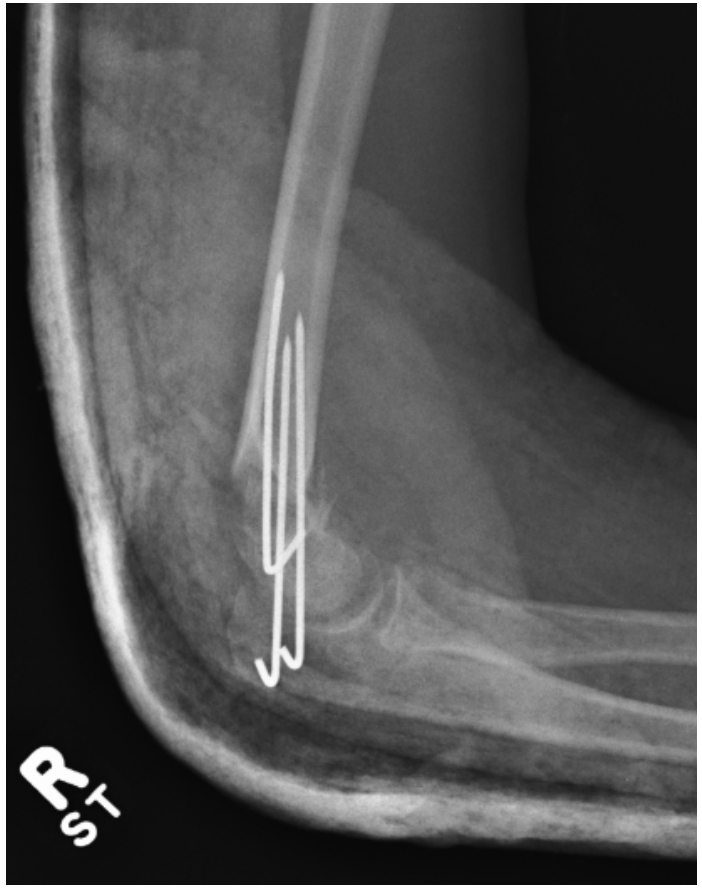
- Post-traumatic Elbow Contracture
- PERK II Trial
- Why Ketotifen? Dosing, timing
- Why ROM? Why 12 weeks?
- What are the Confounding Variables?

Post-traumatic Elbow Contracture









Photos: Kevin Hildebrand, MD

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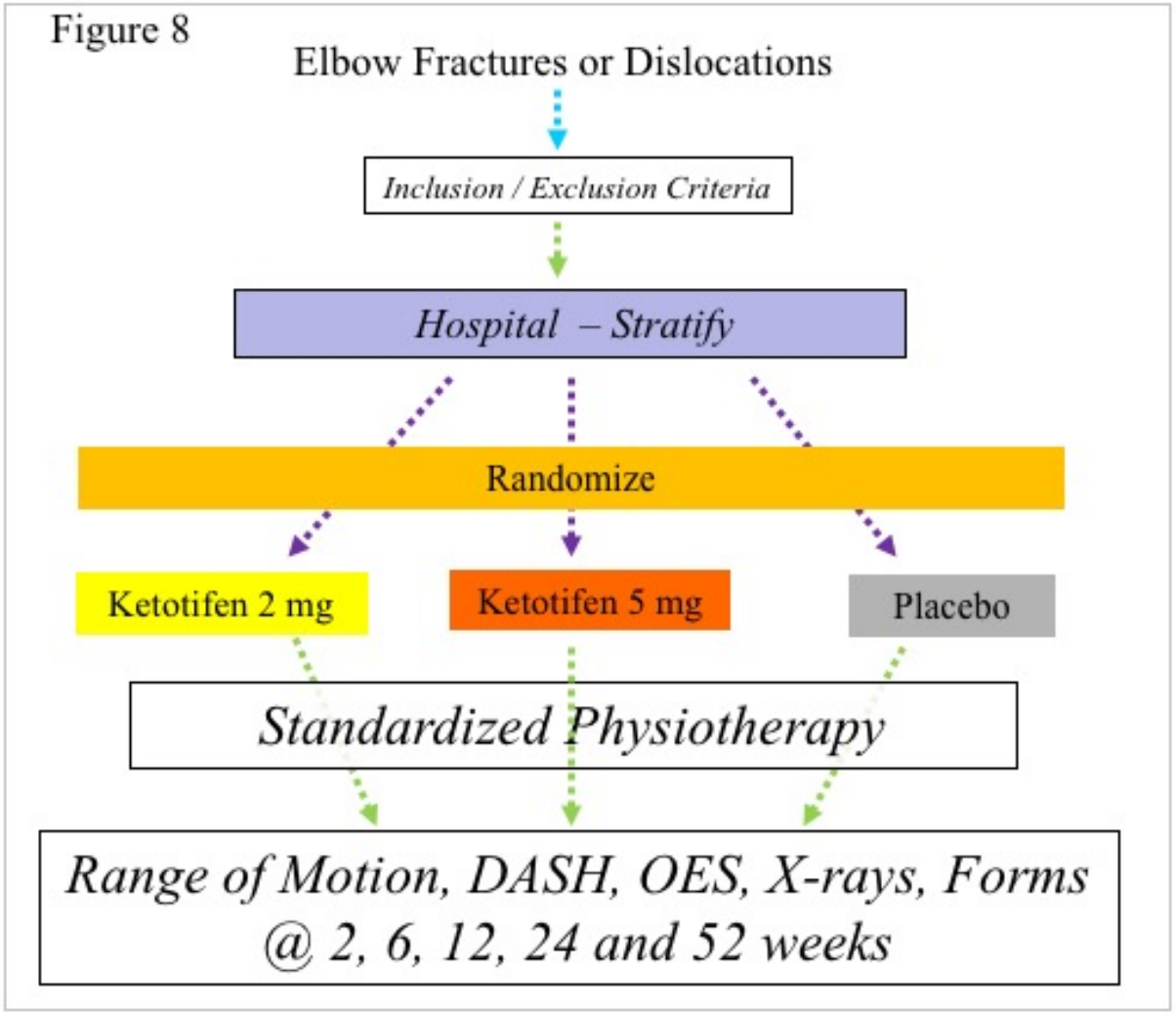
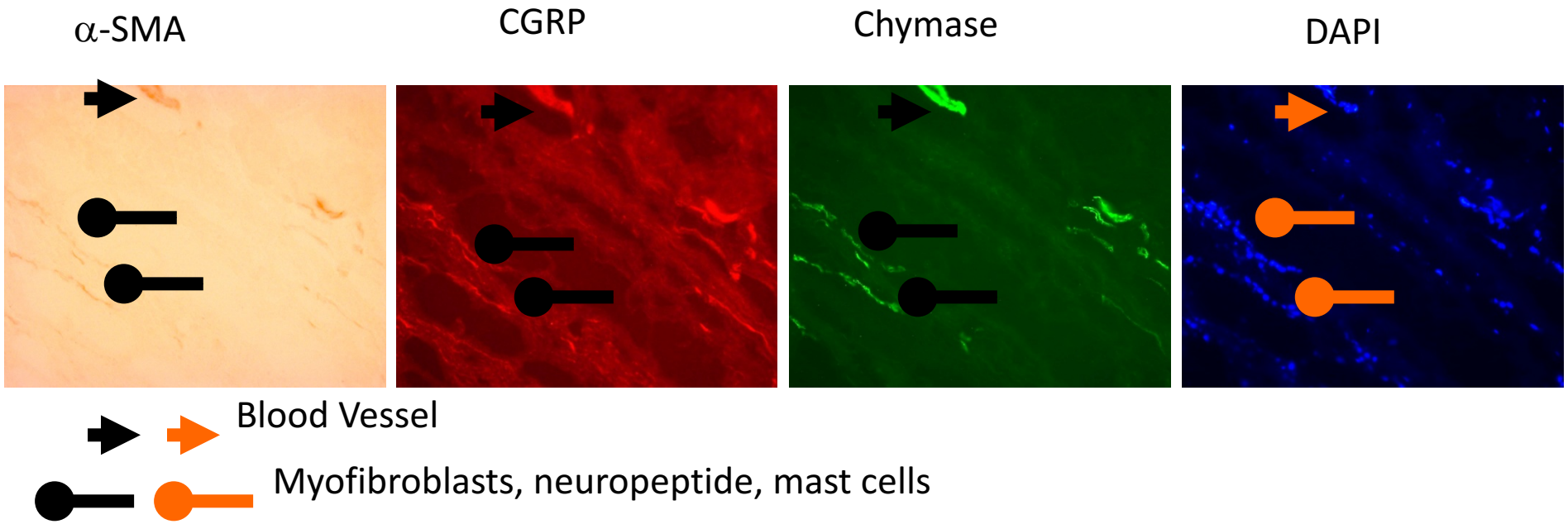
Alberta Health Services

PERK II Design

RESEARCH HYPOTHESIS:
Ketotifen is superior to a lactose placebo in reducing joint contracture severity in adult participants with isolated elbow fractures or dislocations.

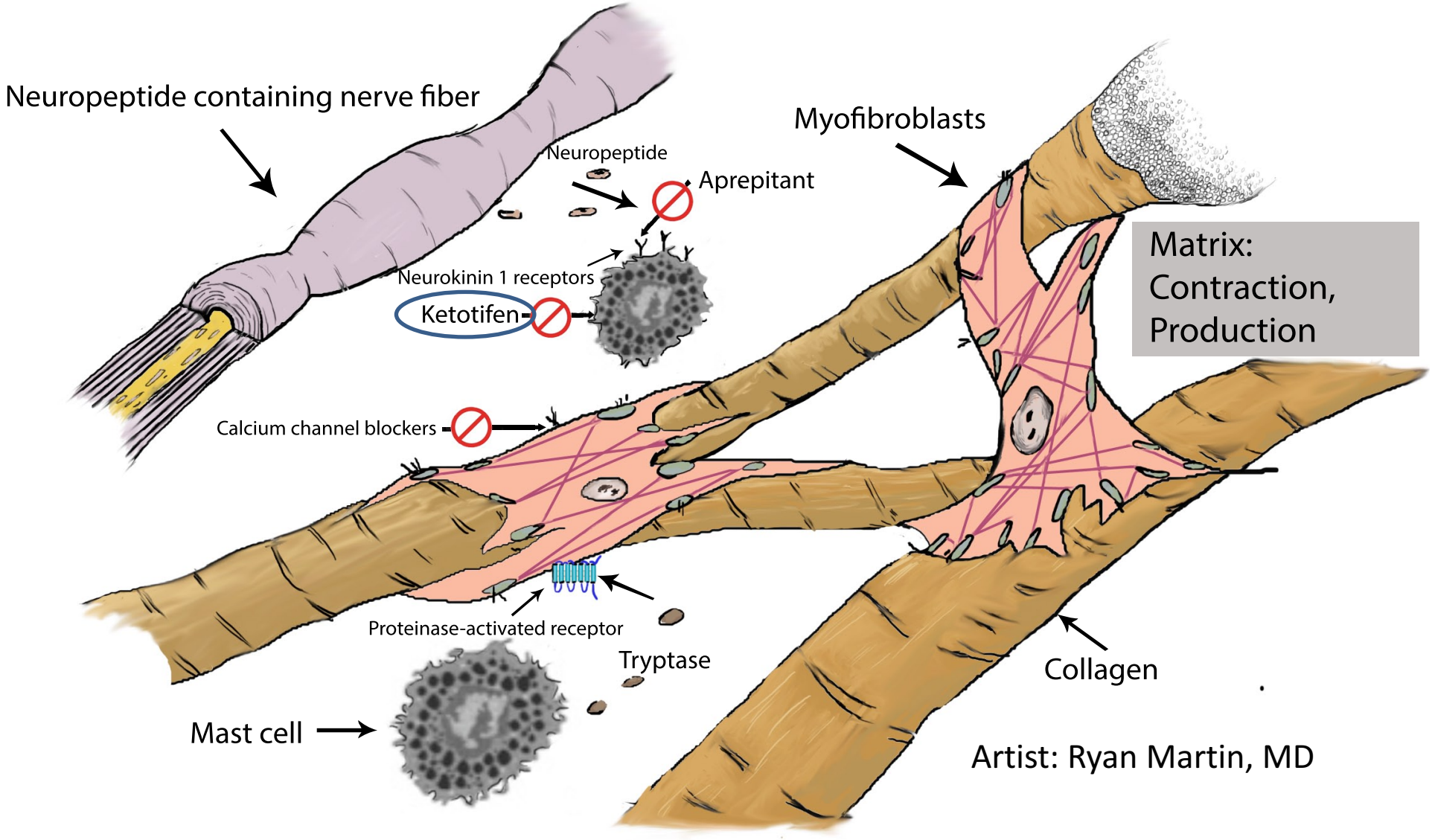


Myofibroblasts Mast Cells Neuropeptides

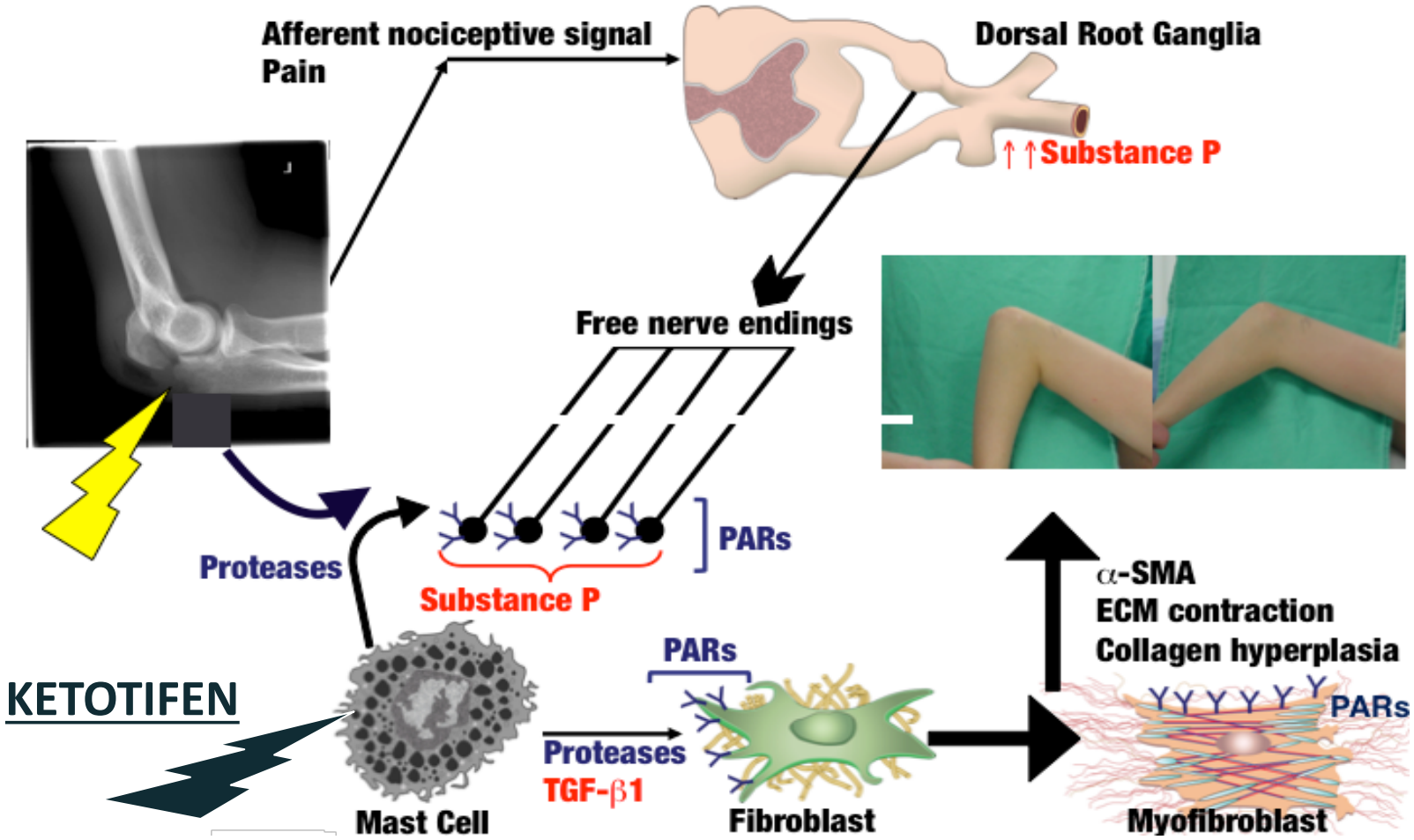


- Myofibroblasts, Mast Cells and neuropeptides elevated human, rabbit
  - Hildebrand CORR 2004, JOR 2004, JOR 2008

Myofibroblast-Mast Cell-Neuropeptide Network



Myofibroblast-Mast Cell-Neuropeptide Network



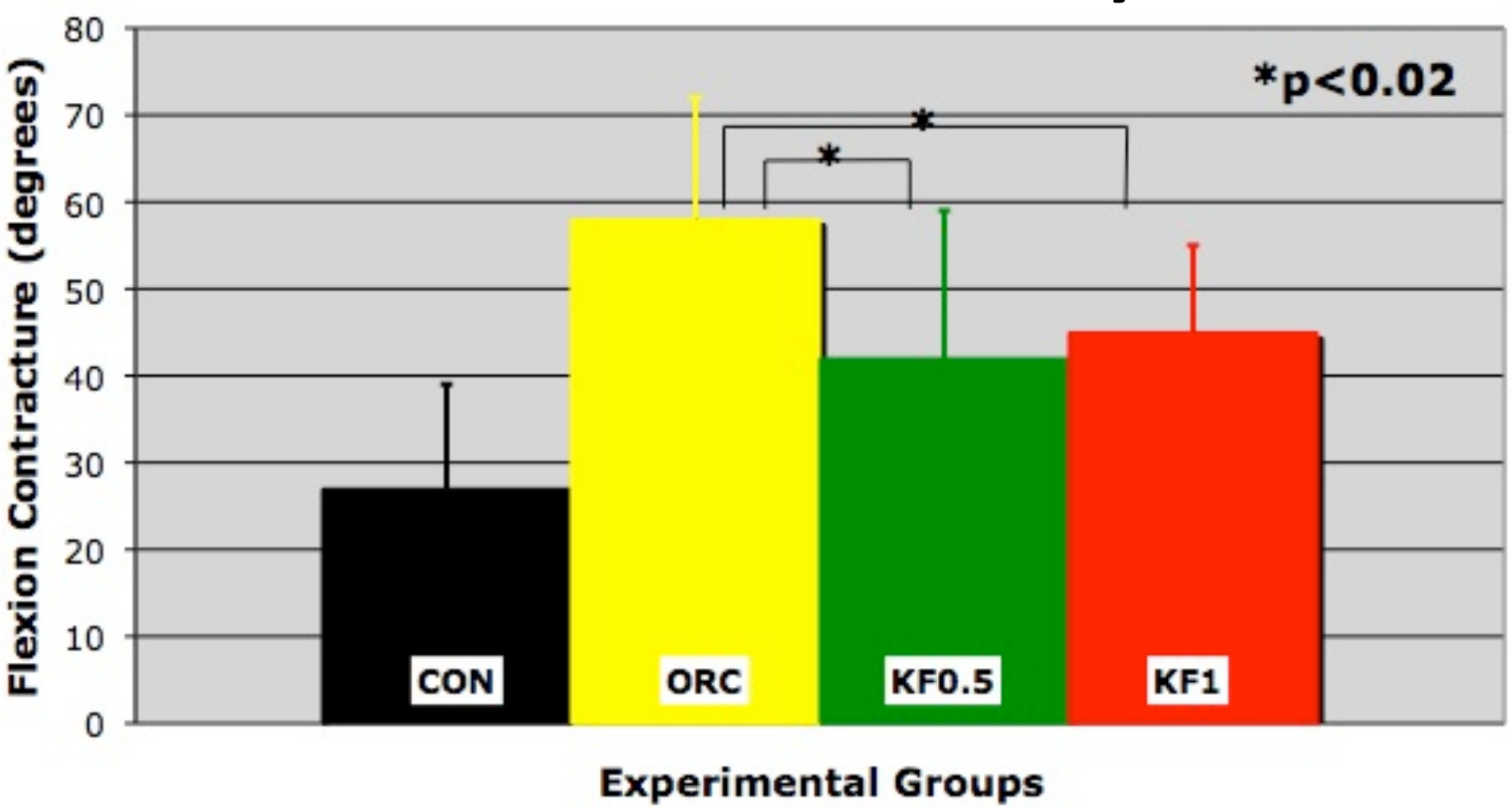
KETOTIFEN

- 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

KETOTIFEN – PRECLINICAL STUDIES

- Rabbit Knee
- 0.5 or 1 mg/kg
- Immediate after injury
- 8 weeks
- ROM – standardized torque

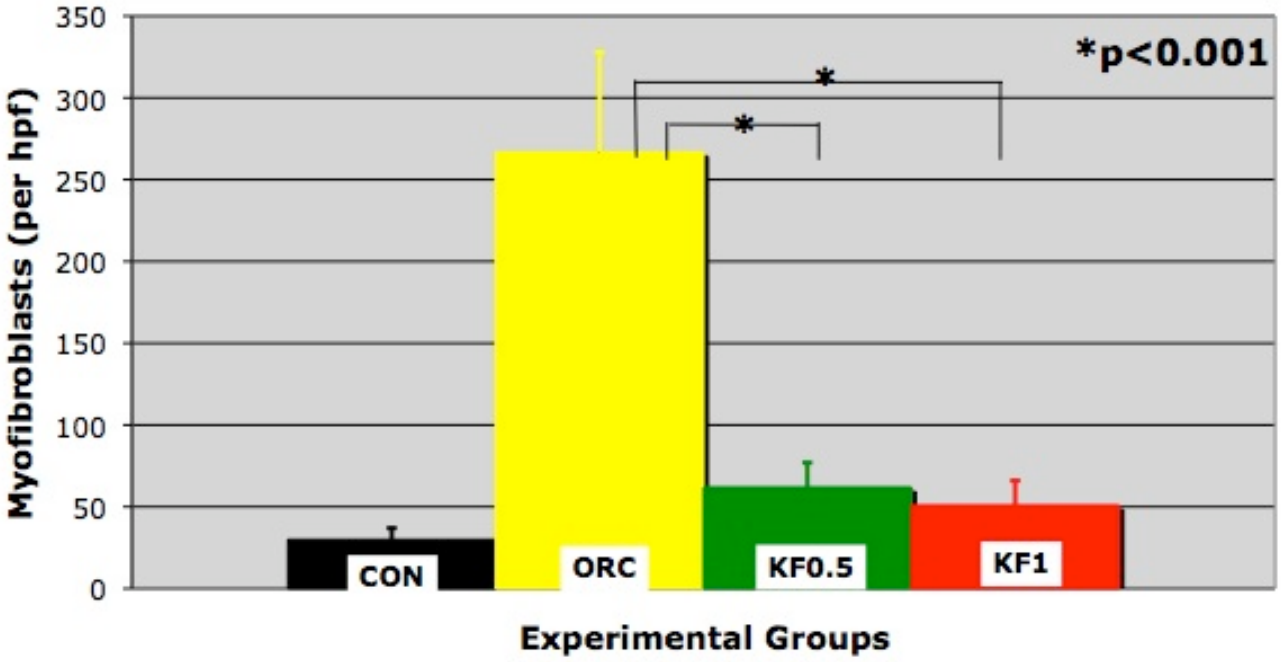
- **↓ Contracture Severity 50%**

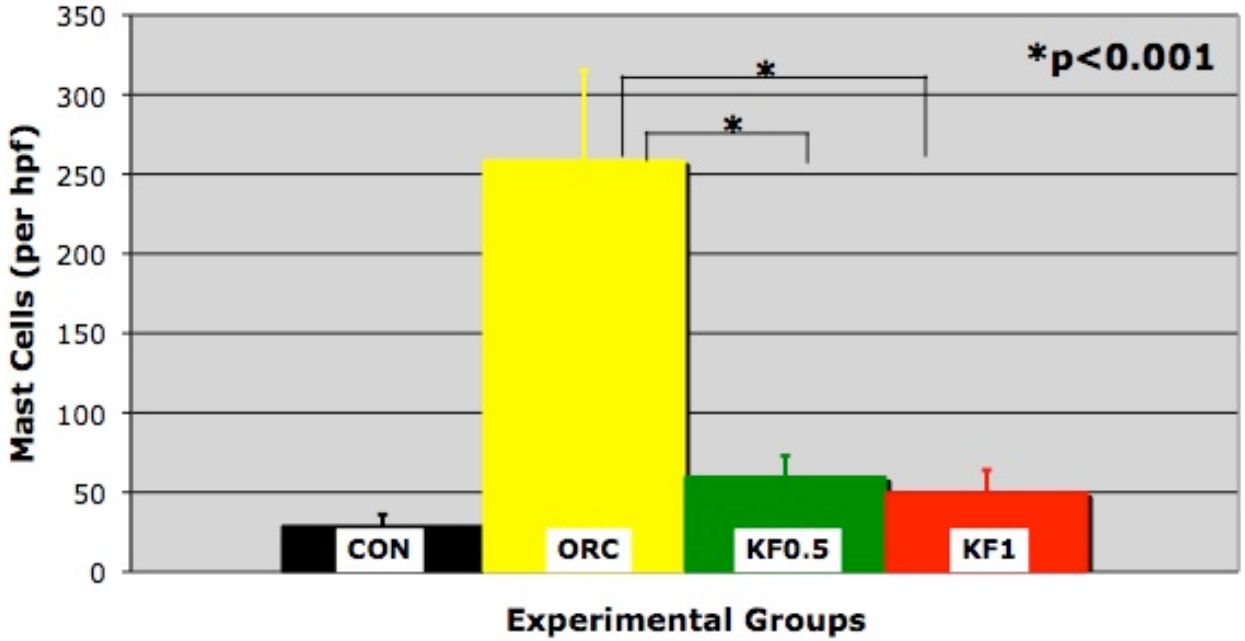


Monument et al, JBJS-Am 2010 92:1468

KETOTIFEN – PRECLINICAL STUDIES

- ↓ Myofibroblasts 50%
- ↓ Mast Cells 50%



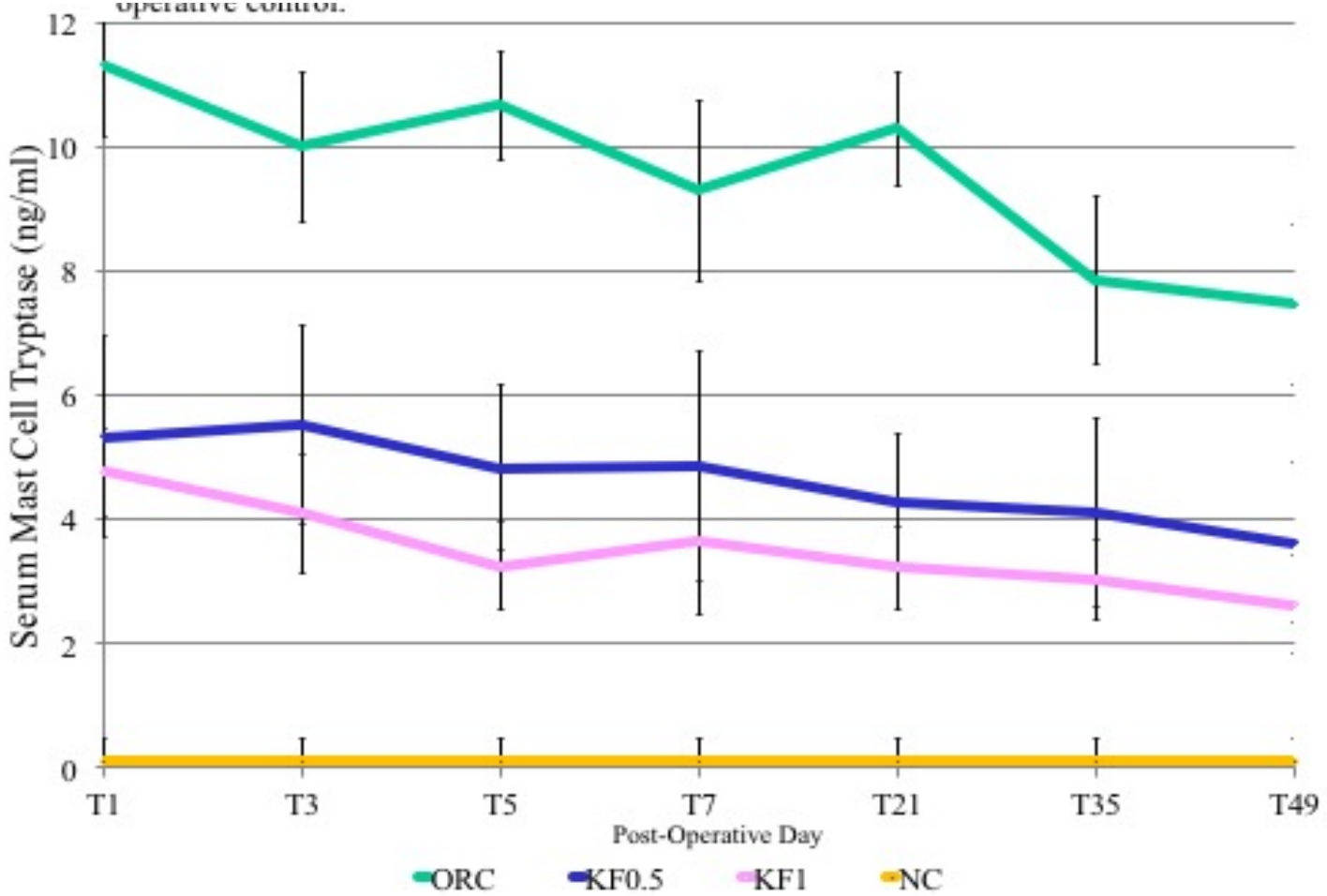


Monument et al, JBJS-Am 2010 92:1468

KETOTIFEN – PRECLINICAL STUDIES

- Rabbit Knee
- 0.5 or 1 mg/kg
- Immediate after injury
- Serum samples 1 – 49 days
- Serum Mast Cell Tryptase (SMCT)

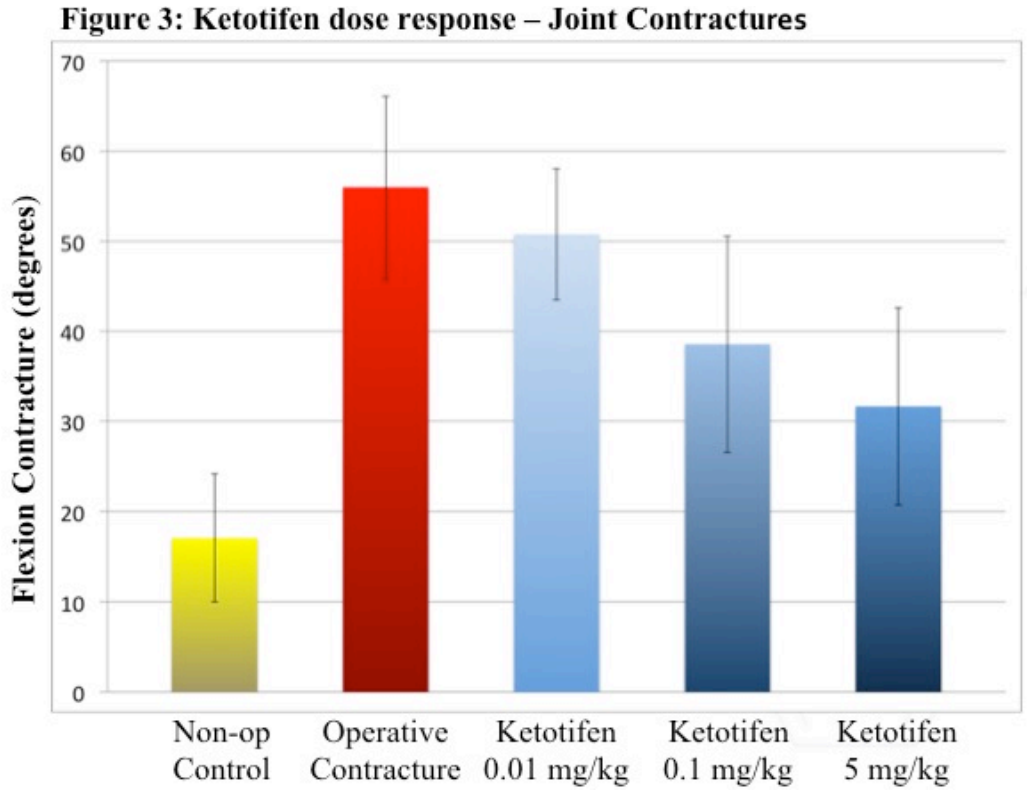
- **↓ SMCT 50%**

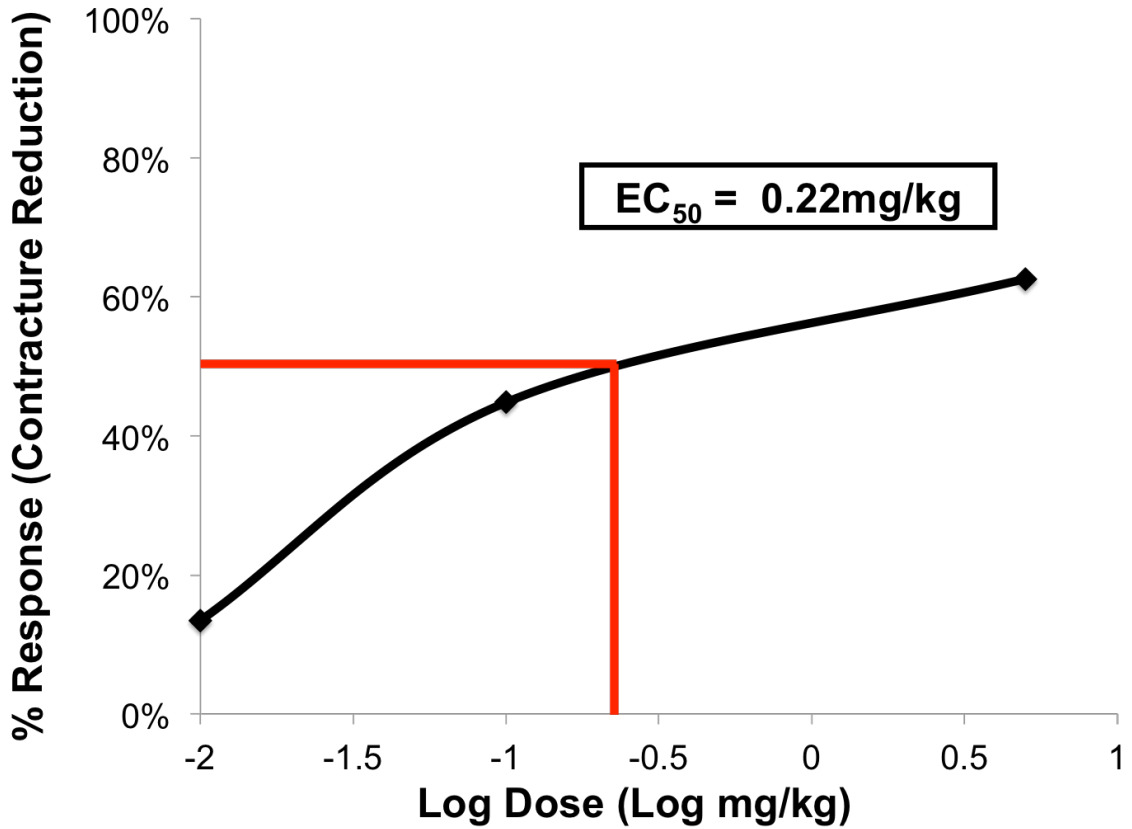


Kopka et al, JOT 2017 31:e86

KETOTIFEN – PRECLINICAL STUDIES

- Rabbit Knee
- DOSE Effect
- 2nd time





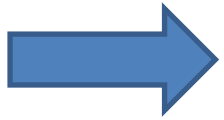
Schneider et al, Trans ORS 2016 41:221

KETOTIFEN DOSING

- ***Asthma***: 1 – 2 mg or 0.01 – 0.03 mg/kg twice daily
- ***Animal models***: Rabbit knee contractures 0.1 – 5 mg/kg, Pig wound healing 0.01 – 0.03 mg/kg
- ***Human clinical research***: 4 – 6 mg bid scleroderma, irritable bowel disease, 2 mg qid for idiopathic anaphylaxis
- ***Overdoses***: range 10 mg (paeds), 20 mg adult – 120 mg
- ***Packaging***: Supplied as 1 mg tablets, 5 mg can fit in this capsule
- ***High dose***: 5 mg below overdose, similar to other studies
- ***Low dose***: 2 mg is upper dose for asthma

KETOTIFEN TIMING

- Compromise – more eligible with longer time vs literature saying ASAP best
- Recommendations for HO prophylaxis within 3 days
  - Hughes et al JSES 2010 19:e1
- Rabbit knee model shows changes present by 2 weeks
  - Hildebrand et al Acta Orthop 2008 79:116
- Pig wound healing effect of ketotifen lost by 5 weeks
  - Gallant-Behm et al Wound Rep Regen 2008 16:226



Start within 7 days of injury

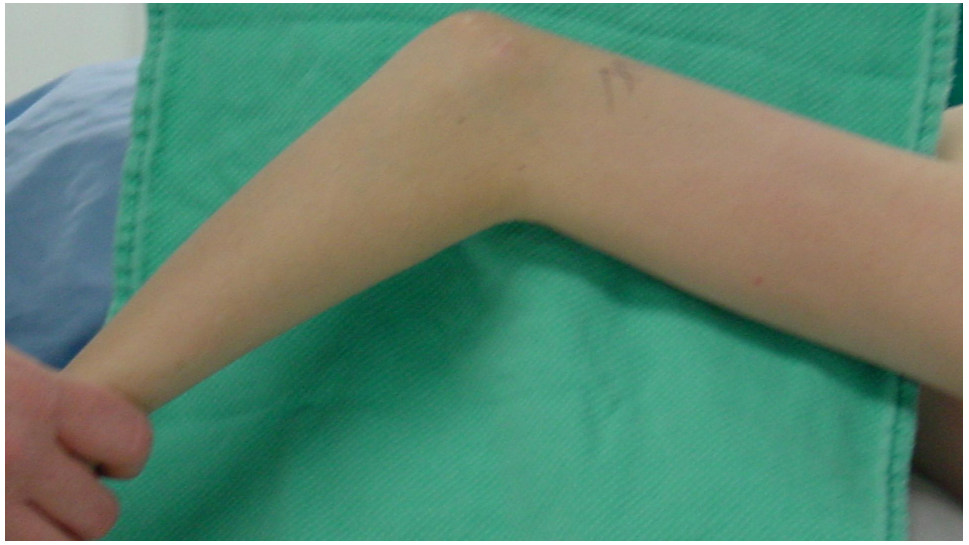
KETOTIFEN DURATION

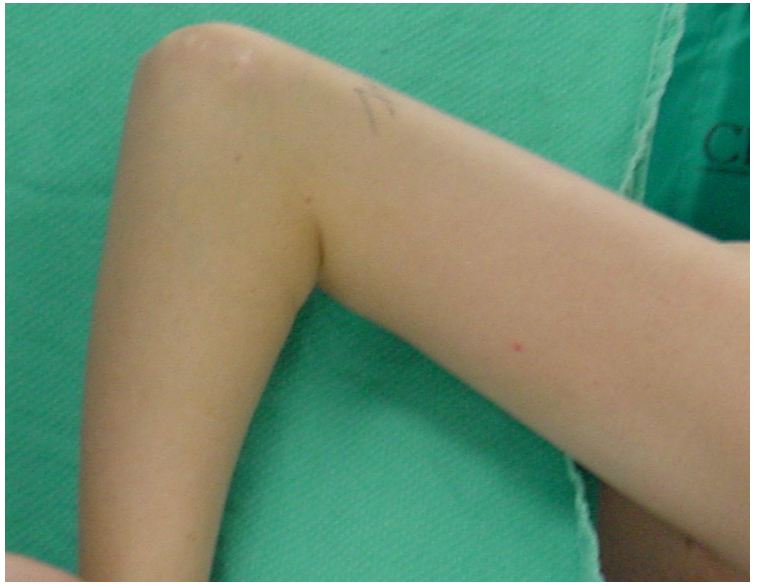
- Compromise – Shorter duration increases compliance, longer duration seems necessary to ensure effect
- Recommendations for HO prophylaxis is 3 – 6 weeks
  - Hughes et al JSES 2010 19:1
- Rabbit knee model & Pig wound healing 8 - 10 weeks
  - Hildebrand et al Acta Orthop 2008 79:116, Gallant-Behm et al Wound Rep Regen 2008 16:226
- Typical clinical follow up includes 6 weeks

→ ***Duration is 6 weeks***

OUTCOME MEASURES

- ROM – Range of Motion extension/flexion

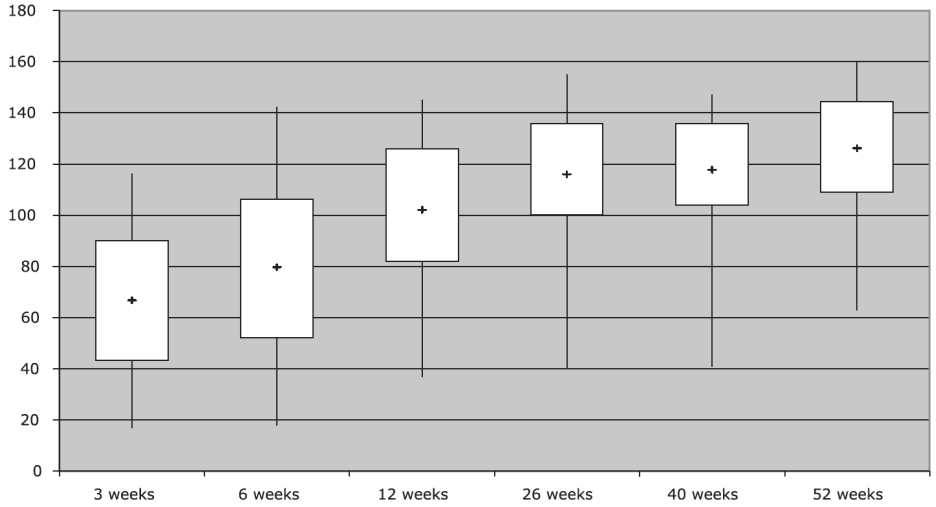




- PROM's – Patient Reported Outcome measures
  - Oxford Elbow Score (OES) – MCID, Responsive to postop, trauma
  - Disability Arm, Shoulder, Hand (DASH) – MCID, trauma, not as responsive elbow

PRIMARY OUTCOME – 12 WEEKS

- ROM improves over 1 year



From Myden et al JSES 2011 20:39

- Earliest time impending contractures 12 weeks
- Confounding variables more impact after 12 weeks – before all could use, after 12 weeks likely only those with contractures
- 12 weeks more likely to reach 1° outcome compared to later times

CONFOUNDING VARIABLES - ROM

- 1) Physiotherapy
  - "Standardize" first 12 weeks - Handout
  - Use in first 12 weeks more of a function of injury than trial intervention
  - Discussion on breakout sessions what is available / strategy
- 2) Stretching Braces
  - Limit use until after 12 weeks
  - Not ethical to limit use entirely
    - Cochrane review – No benefit Harvey et al Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD007455.
    - Case series reports suggest benefit
- 3) NSAID
  - HO prevention, RCT ongoing in London for elbow contractures
  - Possible role nonunion
  - Analgesic, available OTC, alternative to opioids
  - Will document use in CRF

PERK I

- TAKE IT TO THE CLINIC!

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PrEvention of post-traumatic contractuRes with Ketotifen II (PERK II): PERK I Lessons

Kevin A. Hildebrand, MD, FRCSC
Chief, Orthopaedic Surgery
Professor, Department of Surgery
Deputy Director, McCaig Institute for Bone and Joint Health
Cumming School of Medicine
University of Calgary

Mobility for Life.

Alberta Health Services

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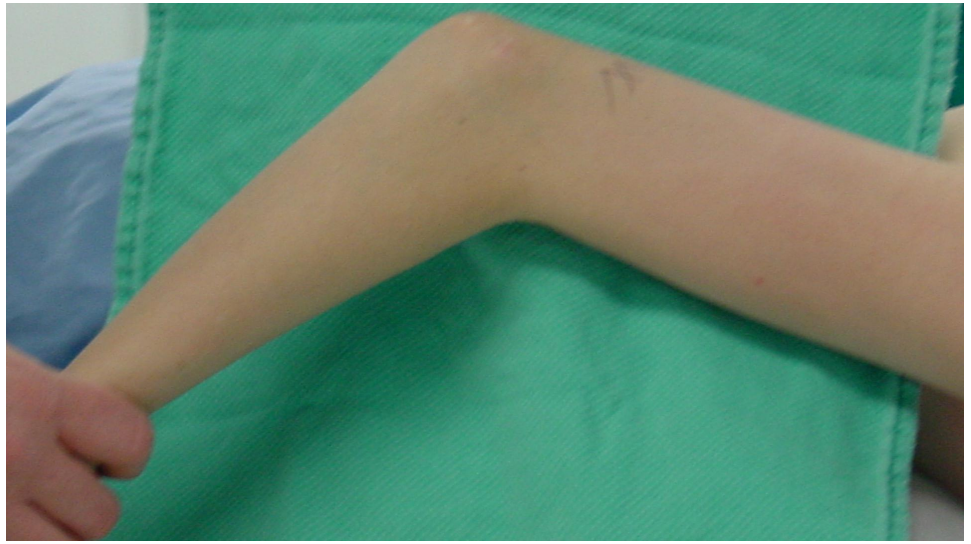
Outline

- PERK I Trial
- Study Flow
- Results
- Safety
- Why limit to Operative cases?
- Why Multicentre?
- Why Multidose?



PERK I

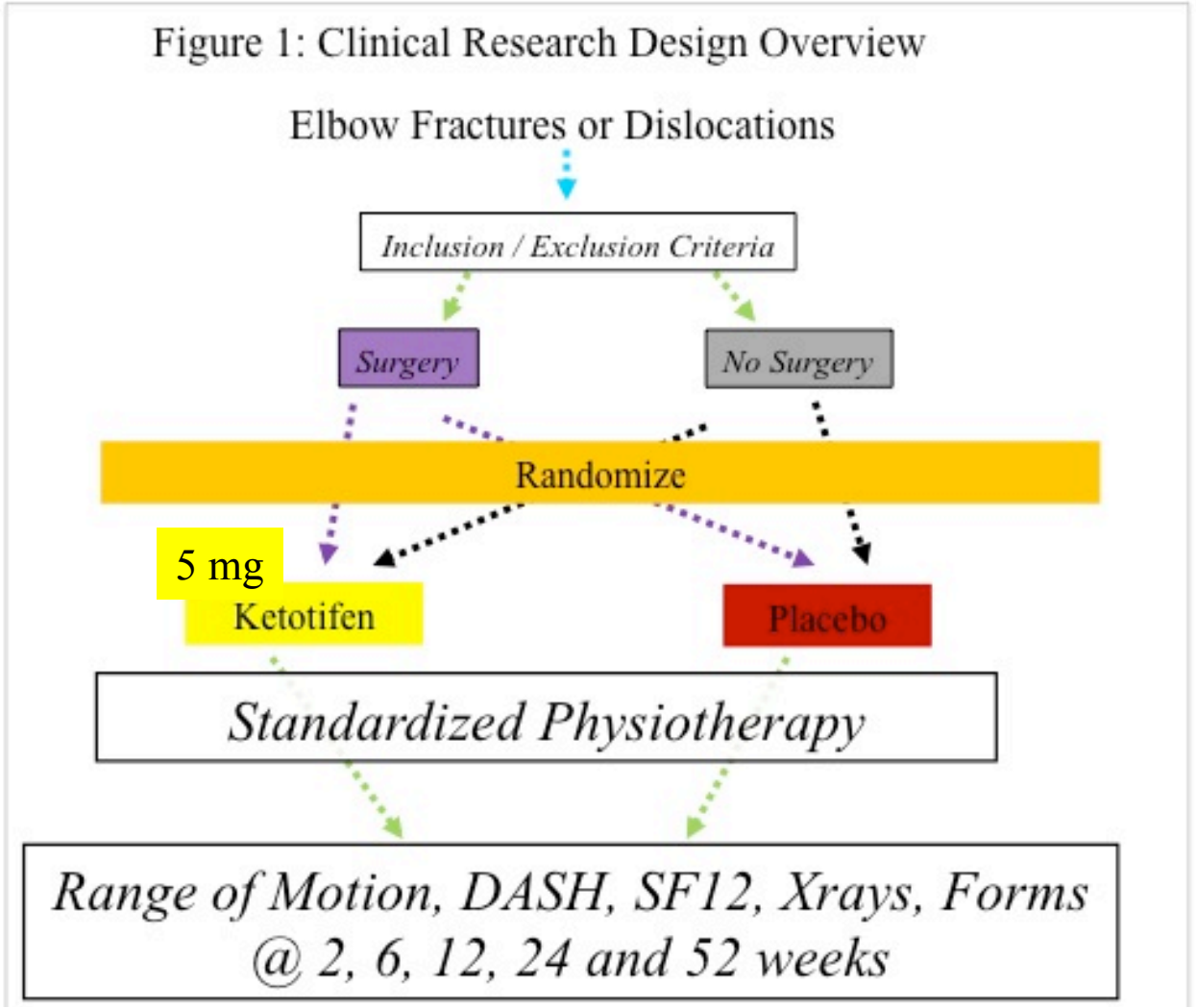
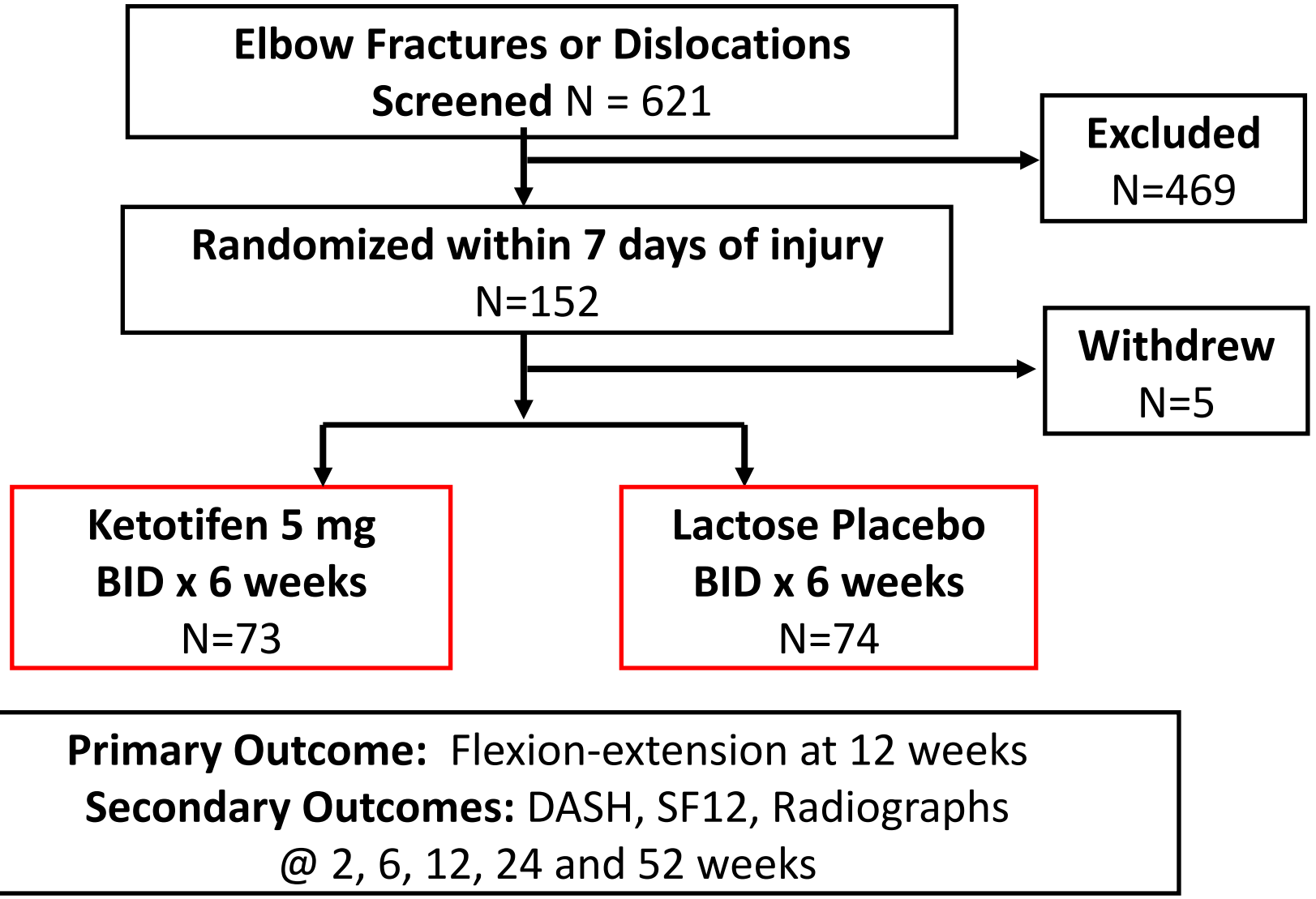


Figure 1: Clinical Research Design Overview
Elbow Fractures or Dislocations
Inclusion / Exclusion Criteria
Surgery
No Surgery
Randomize
5 mg
Ketotifen
Placebo
Standardized Physiotherapy
Range of Motion, DASH, SF12, Xrays, Forms
@ 2, 6, 12, 24 and 52 weeks

STUDY FLOW

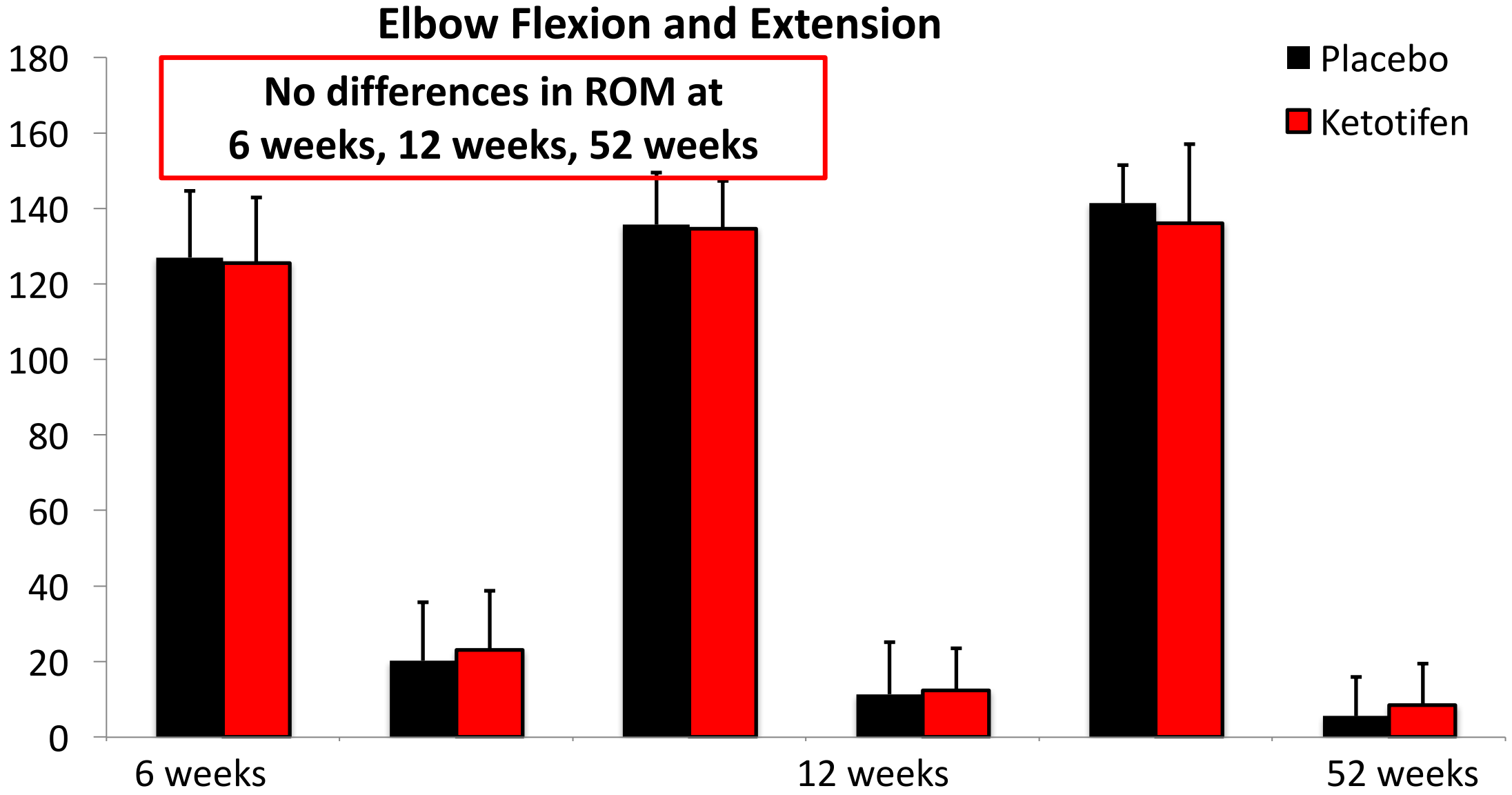


Primary Outcome: Flexion-extension at 12 weeks
Secondary Outcomes: DASH, SF12, Radiographs
@ 2, 6, 12, 24 and 52 weeks

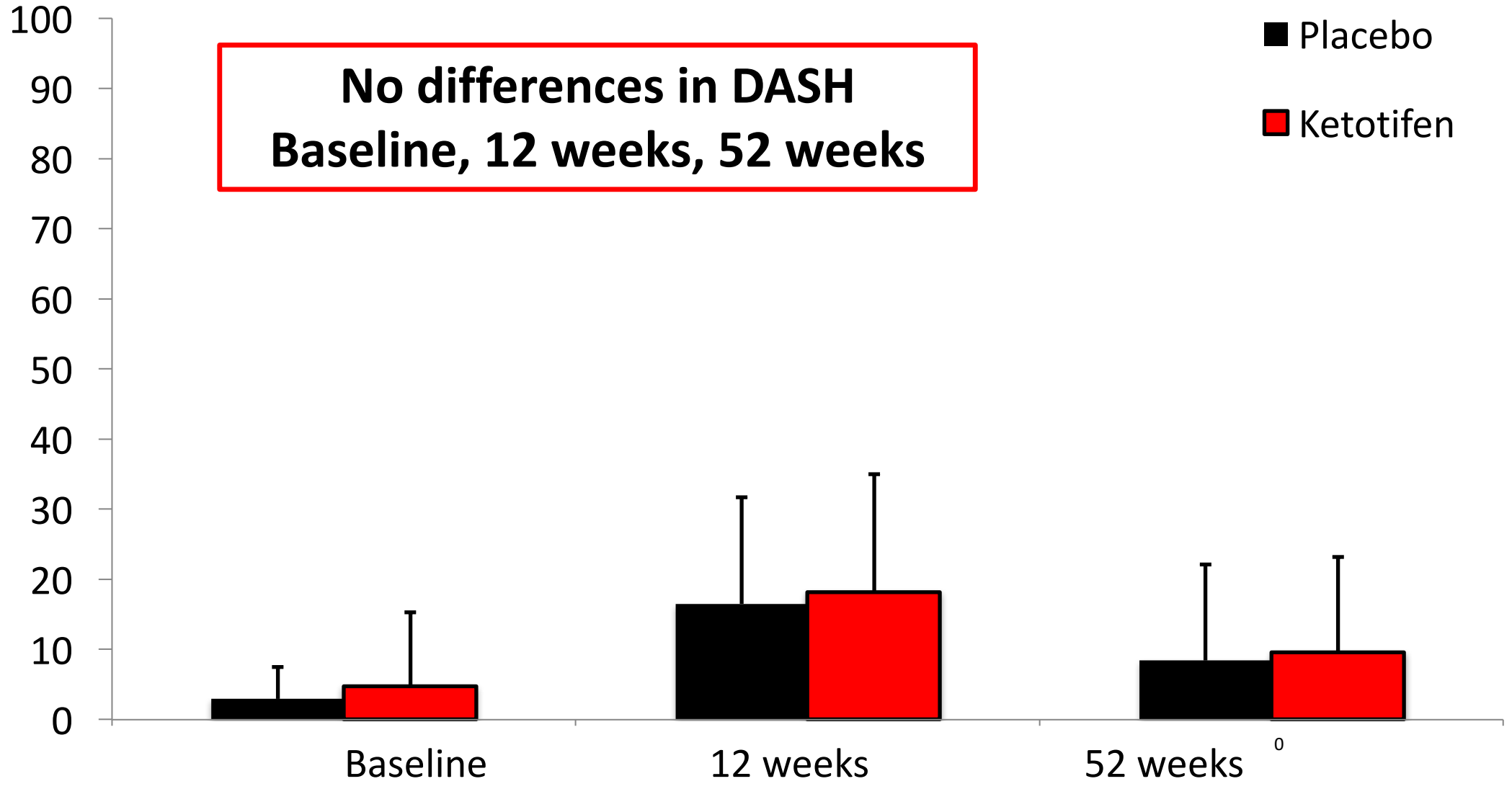
RESULTS

Characteristic	Ketotifen	Placebo
Age, years mean (SD)	46.7 (18.3)	44.4 (13)
Sex, female (%)	41 (55)	29 (45)
Side of Injury – right (%)	32 (43)	26 (40)
Hand dominance – right (%)	63 (91)	56 (89)
Work status – employed (%)	56 (89)	52 (93)
Injury to randomization - days, mean (SD)	3.7 (2.1)	3.7 (2.1)
Fracture Type AO/OTA 13:AO/OTA 21	10:51	7:46
Dislocation Type Posterior : Other	12:3	12:1
Operative Treatment (%)	42	42

RESULTS - ROM


Elbow Flexion and Extension
No differences in ROM at
6 weeks, 12 weeks, 52 weeks
Placebo
Ketotifen
180
160
140
120
100
80
60
40
20
0
6 weeks
12 weeks
52 weeks

RESULTS - DASH



SAFETY - SAE

Description	Time Point	Number of Participants	Randomized to
Pulmonary Embolism	Actively on study	1	Ketotifen
Bilateral lower leg dermatitis	Actively on study	1	Ketotifen
Nonunion	Follow up	1	Placebo
Extreme drowsiness & system wide joint pain/swelling	Actively on study	1	Ketotifen
Deep Vein Thrombosis	Follow up	1	Placebo
Hardware Removal	Follow up	6	2 = Ketotifen 4 = Placebo
Rash, fever, headache, nausea, vomiting	Actively on study	1	Ketotifen
Extreme drowsiness	Actively on study	3	2 = Ketotifen 1 = Placebo
Dizziness & nausea	Actively on study	1	1 = Ketotifen
Re-operation	Follow up	1	1 = Ketotifen

- On Medication – 8 SAE
  - 7 on ketotifen
- Off Medication – 8 SAE (re)operation
  - 3 on ketotifen

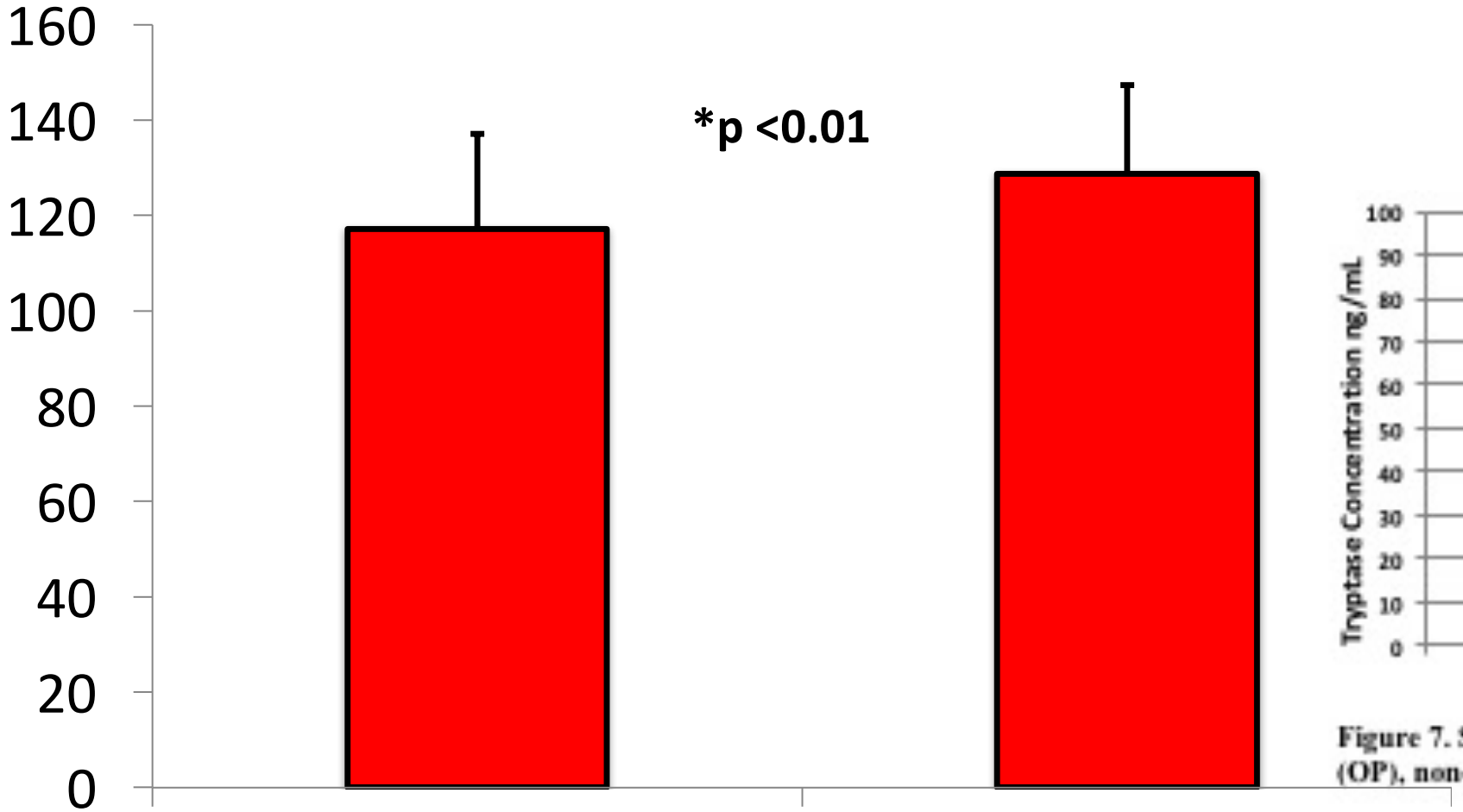
SAFETY - NONUNION

- 1 Nonunion operation – Placebo group
- Rate of Union similar between both groups
  - 48% at 12 weeks
  - Full analysis not complete
- Antihistamine – only article delayed fracture healing at 5 weeks evaluation in rabbit model
  - Gebhard et al JHS 1993 18A:1080
- Cromolyn – HO prophylaxis
  - Mast cell stabilizer, not antihistamine
  - Animal model – Salisbury J Cellular Biochem 2011 112:2748

LIMIT TO OPERATIVE CASES

- No consensus on injury severity for elbow fractures
- In PERK, Op cases greater loss ROM at 12 weeks vs Nonop
- First 41 cases of PERK, Serum Mast Cell Tryptase higher in Op vs nonop and normal control
- Need to operate is a marker for injury severity

LIMIT TO OPERATIVE CASES



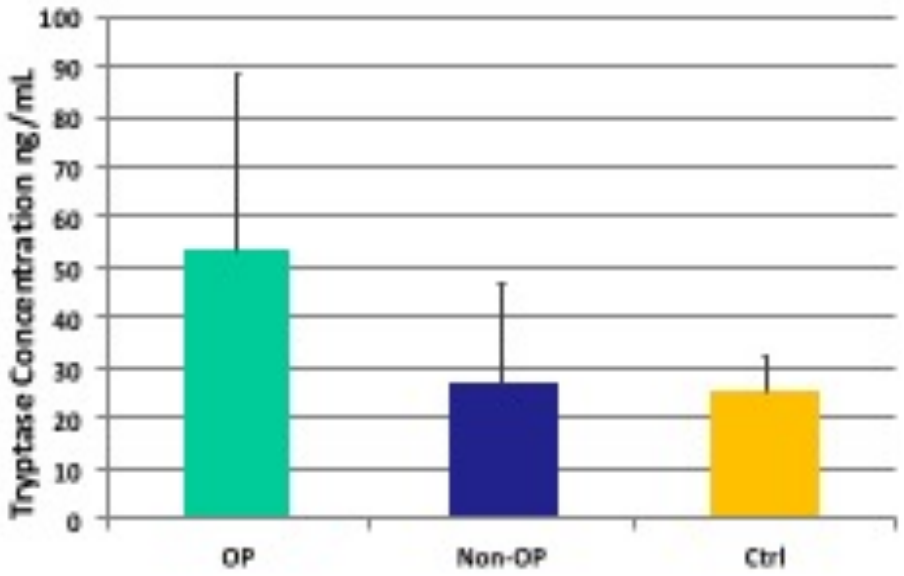


Figure 7. Serum mast cell tryptase levels in the operative (OP), non-operative (Non-OP), and control (Ctrl) groups.

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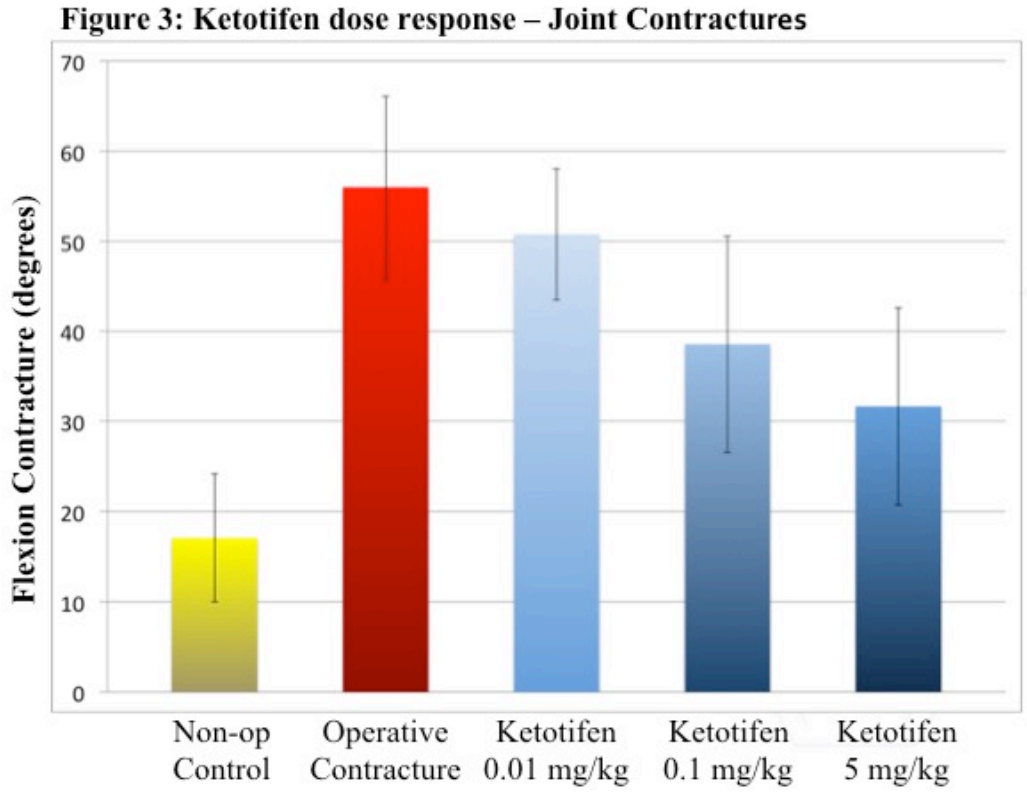
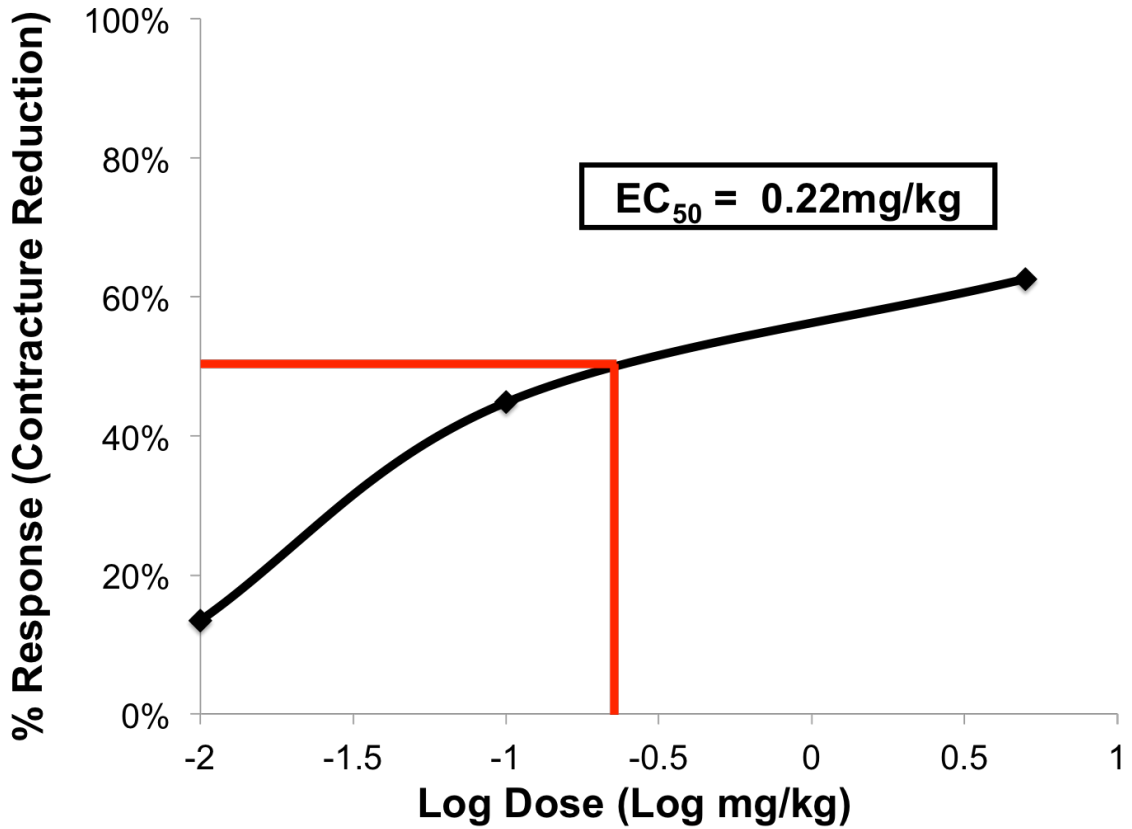
MULTICENTRE

- Using ROM data at 12 weeks, 632 participants total. 11% dropout = 702 participants total, 234 per treatment arm
- Power for DASH 99% using MCID = 10
- Power of 98% for detecting 20% difference in proportion of participants reaching functional ROM between ketotifen and placebo

MULTIDOSE

- Rabbit studies – Dose effect
- SAE with 5 mg





PERK I → PERK II

- Larger sample size – type II error, 2 doses (Multicentre)
- More severe injuries – Operative elbow fractures
- 2 doses – larger dose, one closer to asthma doses

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FOR BONE AND JOINT HEALTH

PrEvention of post-traumatic contractuRes with Ketotifen II (PERK II): Trial Overview & Design

Kevin A. Hildebrand, MD, FRCSC
Chief, Orthopaedic Surgery
Professor, Department of Surgery
Deputy Director, McCaig Institute for Bone and Joint Health
Cumming School of Medicine
University of Calgary

Mobility for Life.

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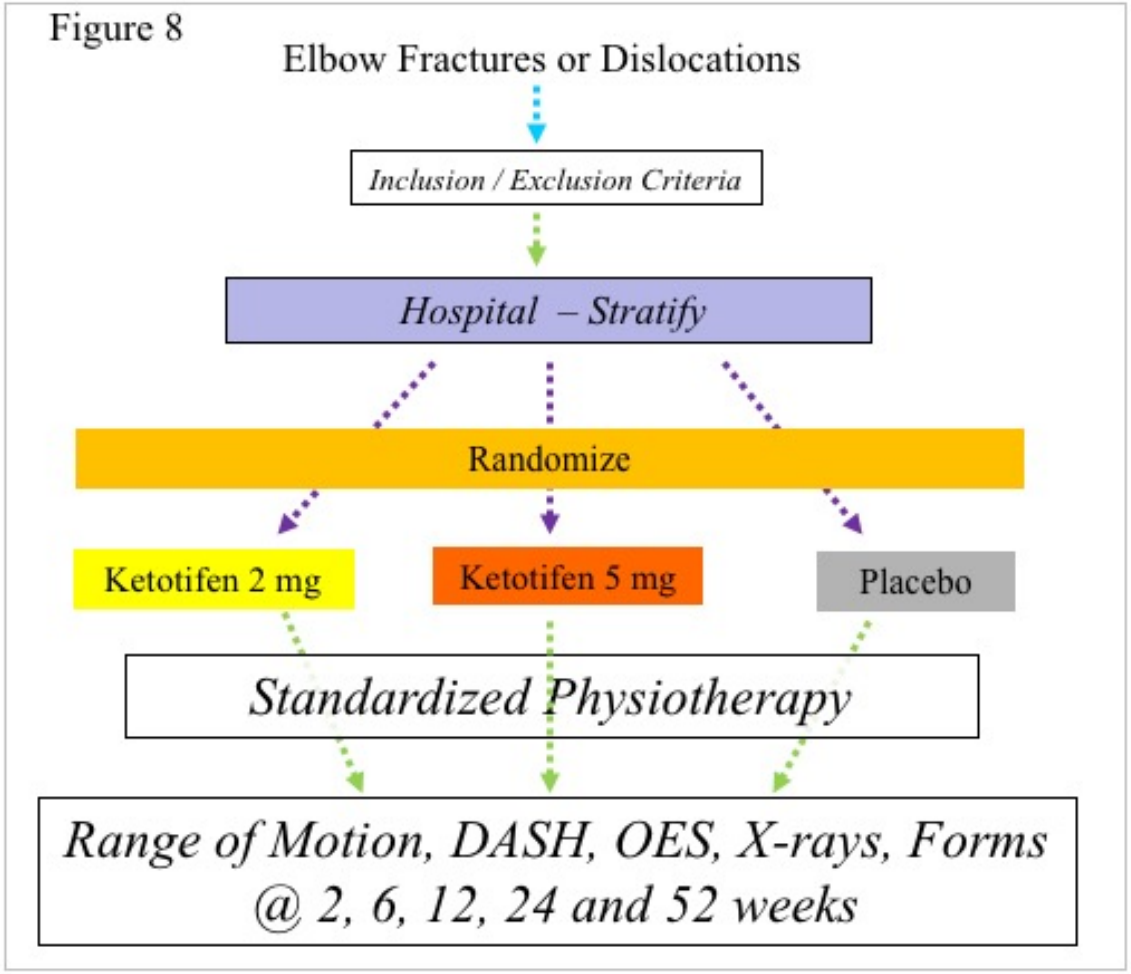
UNIVERSITY OF CALGARY

PERK II

Trial Introduction

RESEARCH HYPOTHESIS:
Ketotifen is superior to a lactose placebo in reducing joint contracture severity in adult participants with isolated elbow fractures or dislocations.



PERK II

Trial Objectives

- Primary Objective

  To determine if Ketotifen given within 7 days of injury can reduce post-traumatic elbow joint contractures when compared to placebo, by measuring elbow range of motion (ROM) at 12 weeks.

PERK II

Trial Objectives

- Secondary Objectives

  1) to ascertain the optimal dose of Ketotifen

  2) to compare adverse events in Ketotifen and placebo groups

PERK II

Trial Design

- Phase III
- Randomized, controlled, double-blinded trial
- 3 parallel groups: placebo, ketotifen 2 mg, ketotifen 5 mg
- All capsules are over encapsulated
- Administered orally, twice daily for 6 weeks

PERK II

Trial Objectives

- Primary Outcome Measure
  - ROM at 12 weeks

PERK II

Trial Objectives

- Secondary Outcome Measures
  - ROM at 2w, 6w, 24w, 52w
  - Disability of the Arm, Shoulder, and Hand (DASH) questionnaire
  - Oxford Elbow Score (OES)
  - standardized case report forms (CRFs)
  - Radiographs
  - SAEs

PERK II

Trial Design: Inclusion and Exclusion Criteria

Inclusion Criteria

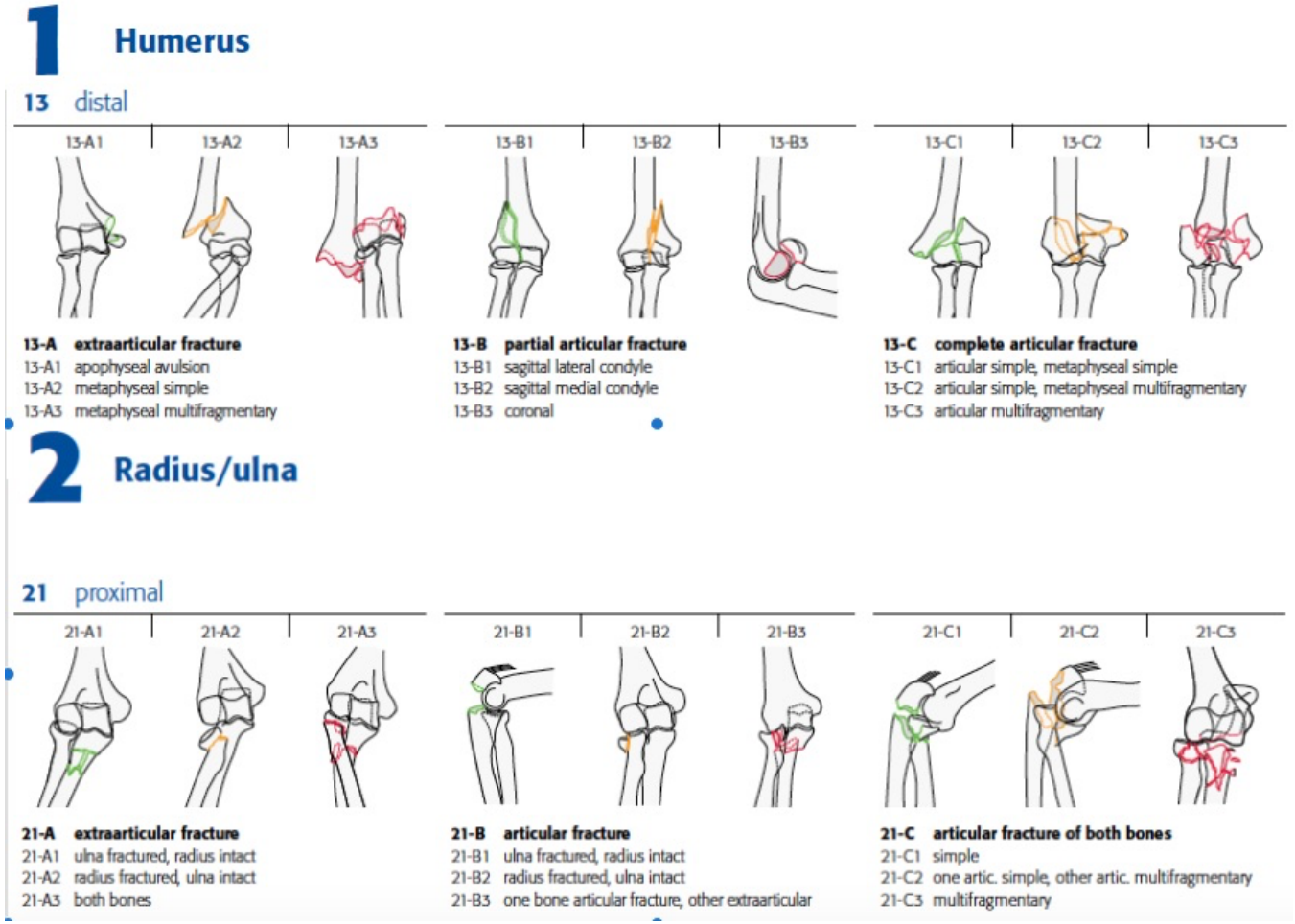
- Age ≥ 18 years old
- Injury isolated to the elbow, with any of the following:
  - Isolated distal humerus (AO/OTA type 13)
  - proximal ulna fractures (AO/OTA type 21)
  - proximal radius fractures (AO/OTA type 21)
  - elbow dislocations
- open fractures with or without nerve injury
- Operative treatment of the elbow fracture or dislocation
- Subject presents within 7 days or less between injury and study recruitment
- Able to give informed consent
- Able to comply with protocol and follow up

Exclusion Criteria

- Pre-existing elbow contracture
- Elbow arthritis (osteoarthritis, inflammatory arthritis, or nonspecific monoarticular arthritis)
- Inability to mobilize elbow within 3 weeks of injury
- Oral hypoglycemic medications
- History of epilepsy
- Lactose intolerance
- Has cognitive impairment or language difficulties that would impede the valid completion of questionnaires
- Any woman who is pregnant or nursing or planning to become pregnant
- Severe renal impairment
- Severe hepatic impairment

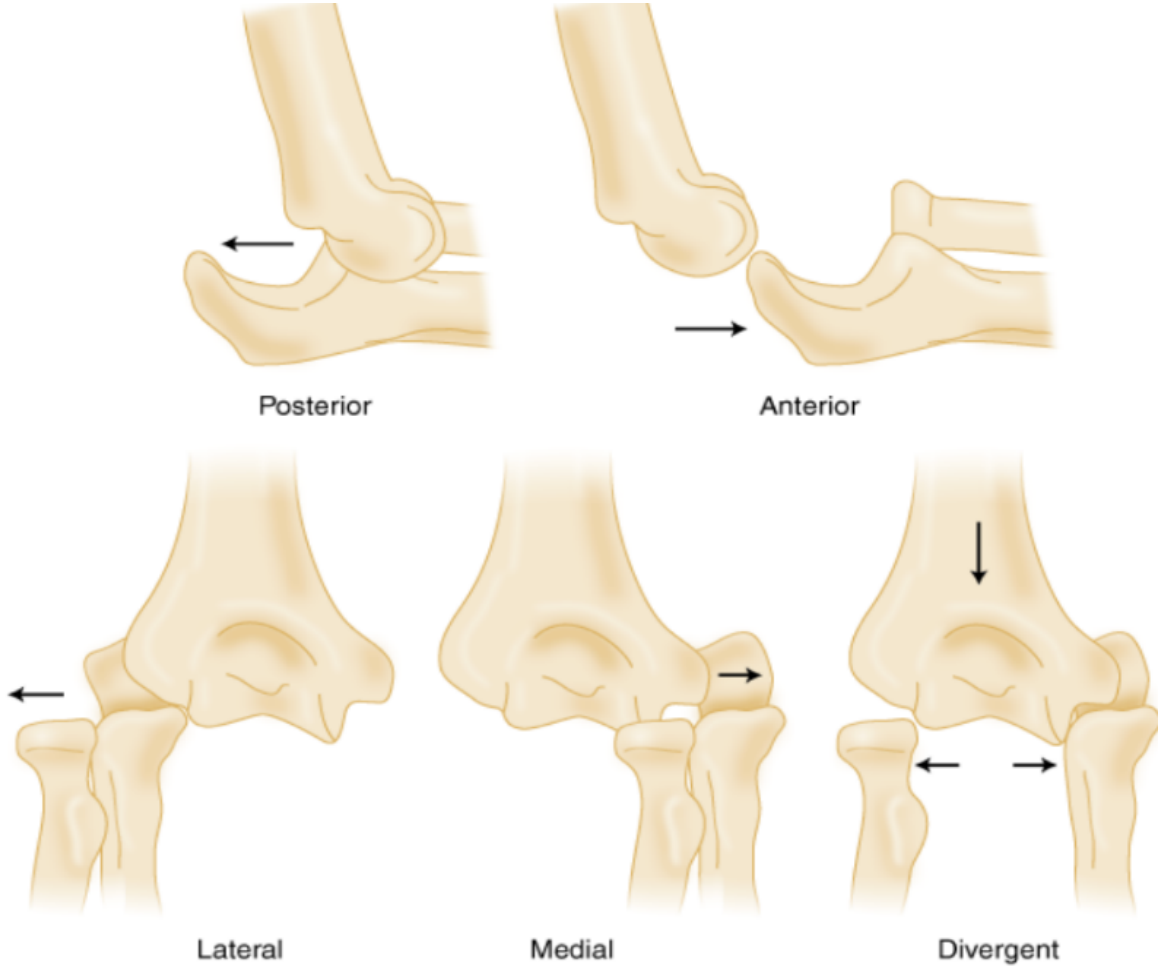
PERK II

OTA Injury Classifications



PERK II

Dislocation Classification



PERK II

Trial Sites

- 13 Canadian sites
- 3 American sites

- Calgary, Alberta
  - Four University of Calgary sites
  - Lead site: Peter Lougheed Centre
  - South Health Campus, Foothills Medical Centre, Rockyview General Hospital
- St. Albert, Alberta
  - Sturgeon Community Hospital

PERK II

Trial Sites

- Vancouver, British Columbia
  - St. Paul's Hospital
- Montreal, Quebec
  - McGill University Health Centre
- London, Ontario
  - St. Joseph's Hospital

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McGill University Health Centre

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PERK II

Trial Sites

- Toronto, Ontario
  - Two sites:
  - St. Michael's Hospital
  - Sunnybrook Health Sciences Centre
- Ottawa, Ontario
  - Two sites:
  - The Ottawa Hospital: Civic and General Campus

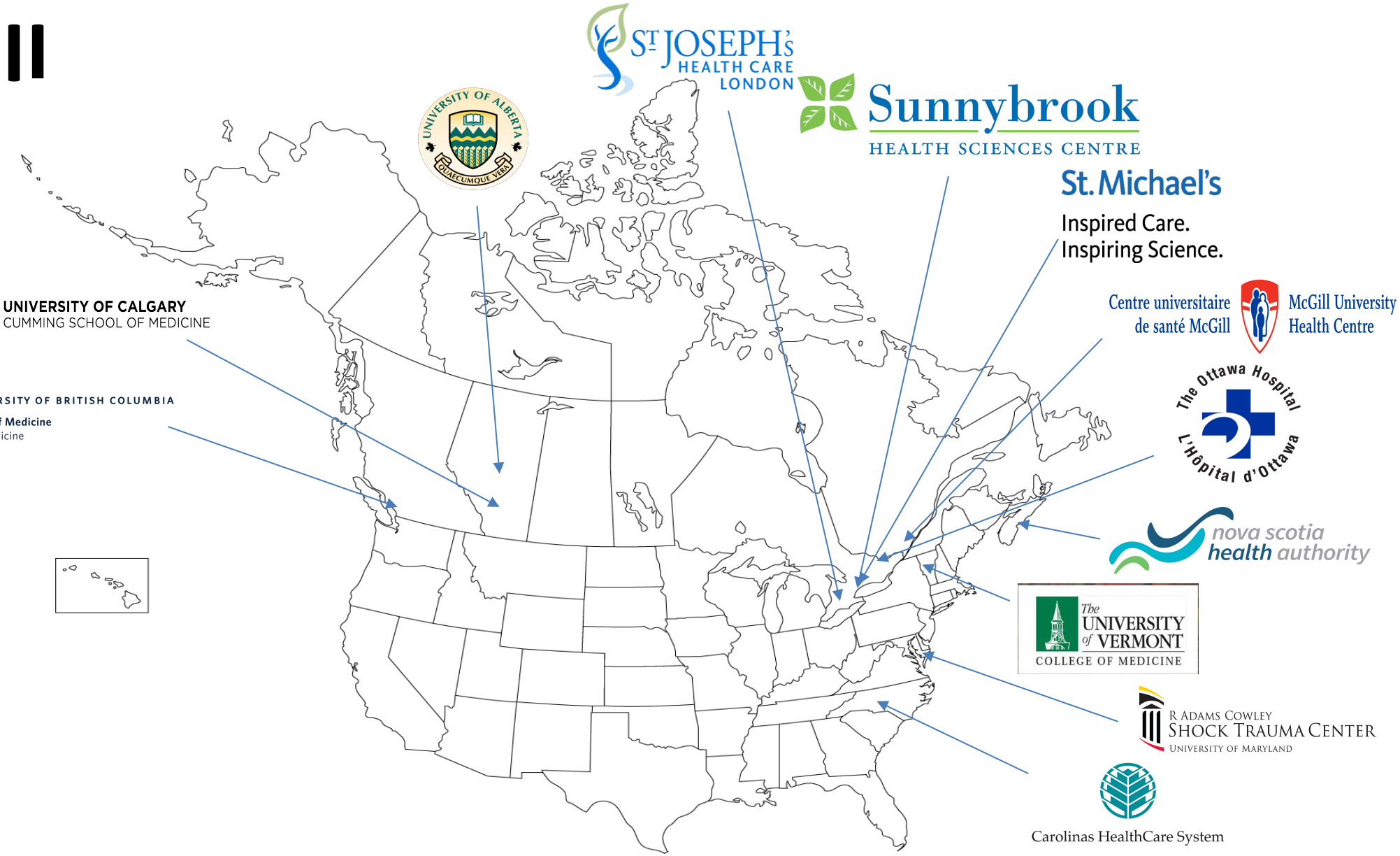
PERK II

Trial Sites

- Halifax, Nova Scotia
  - Queen Elizabeth II Health Science Centre
- Burlington, Vermont
  - University of Vermont Medical Centre
- Charlotte, North Carolina
  - Carolinas Medical Centre
- Baltimore, Maryland
  - University of Maryland Medical Centre

PERK II

Trial Sites



PERK II Recruitment targets

	Year 1				Year 2				Year 3				Site Total
Target Enrollment	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
PLC	0	0	9	13	13	13	14	14	14	14	14	14	132
FMC	0	0	5	7	7	8	8	8	8	8	8	8	75
SHC	0	0	5	7	7	8	8	8	8	8	8	8	75
RGH	0	0	3	4	5	6	7	8	8	7	6	6	60
SCH	0	0	2	3	4	3	3	3	3	3	3	3	30
UVMC	0	0	2	3	4	3	3	3	3	3	3	3	30
CMC	0	0	2	3	4	3	3	3	3	3	3	3	30
MUHC	0	0	2	3	4	3	3	3	3	3	3	3	30
SJH	0	0	2	3	3	4	3	3	3	3	3	3	30
SMH	0	0	2	3	3	3	4	3	3	3	3	3	30
SHSC	0	0	2	3	3	3	3	4	3	3	3	3	30
UMMC	0	0	2	3	3	3	3	3	4	3	3	3	30
TOHC	0	0	2	3	3	3	3	3	3	4	3	3	30
TOHG	0	0	2	3	3	3	3	3	3	3	4	3	30
QHSC	0	0	2	3	3	3	3	3	3	3	4	3	30
SPH	0	0	2	3	3	3	3	3	3	3	3	4	30
Target Enrollment (quarterly)	0	0	46	67	72	72	74	75	75	74	74	73	
Target Enrollment (cumulative)	0	0	46	113	185	257	331	406	481	555	629	702	702

Abbreviations: PLC = Peter Lougheed Centre; FMC = Foothill Medical Centre; SHC = South Health Campus; RGH = Rockyview General Hospital; SCH = Sturgeon Community Hospital; UVMC = University of Vermont Medical Center; CMC = Carolina Medical Center; MUHC = McGill University Health Centre; SJH = St. Joseph's Hospital; SMH = St. Michael's Hospital; SHSC = Sunnybrook Health Sciences Centre; UMMC = University of Maryland Medical Center; TOHC = The Ottawa Hospital, Civic Campus; TOHG = The Ottawa Hospital, General Campus; QHSC = QEII Health Sciences Centre; SPH = St. Paul's Hospital

PERK II

Site Budget – Canadian Dollars

- Payment Schedule
  - Enrolment: $675.00
  - 12 week: $300.00
  - 52 week: $300.00

  Total: $1,275.00* per participant

  *indirect costs will be added

- Start up fee

  Total: $1,900.00^

  ^indirect costs are part of the total
- Pharmacy fees

  Start up, closeout

  Dispensing, Maintenance
- Xray Acquisition fees

  No Budget

PERK II

Budget – Covered by Coordinating Center

- Medication manufacture, distribution (BARL)
- Data and Study Management (CRU)
- Image storage and interpretation (CIPAC)
- Insurance
- Study Monitoring

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PrEvention of post-traumatic contractuRes with Ketotifen II (PERK II): Trial Conduct

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PERK II

	STUDY 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:													
Pill counts					X				X				
ROM					X				X	X	X	X	
DASH	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	*	*	

PERK II

Screening / Enrolling

- Outpatient Clinic / Cast Clinic
- Inpatient Unit
  - Emergency Department
  - Day Surgery
  - Other long-term admitting unit
- Screen
  - Record all exclusion criteria
- Enroll
  - Randomization

PERK II

Randomization

- Clinical Research Unit (CRU) at the University of Calgary
- Medication start after randomization
- Start can be before or after OR, within 7 days injury
  - Logistics around NPO and OR

PERK II

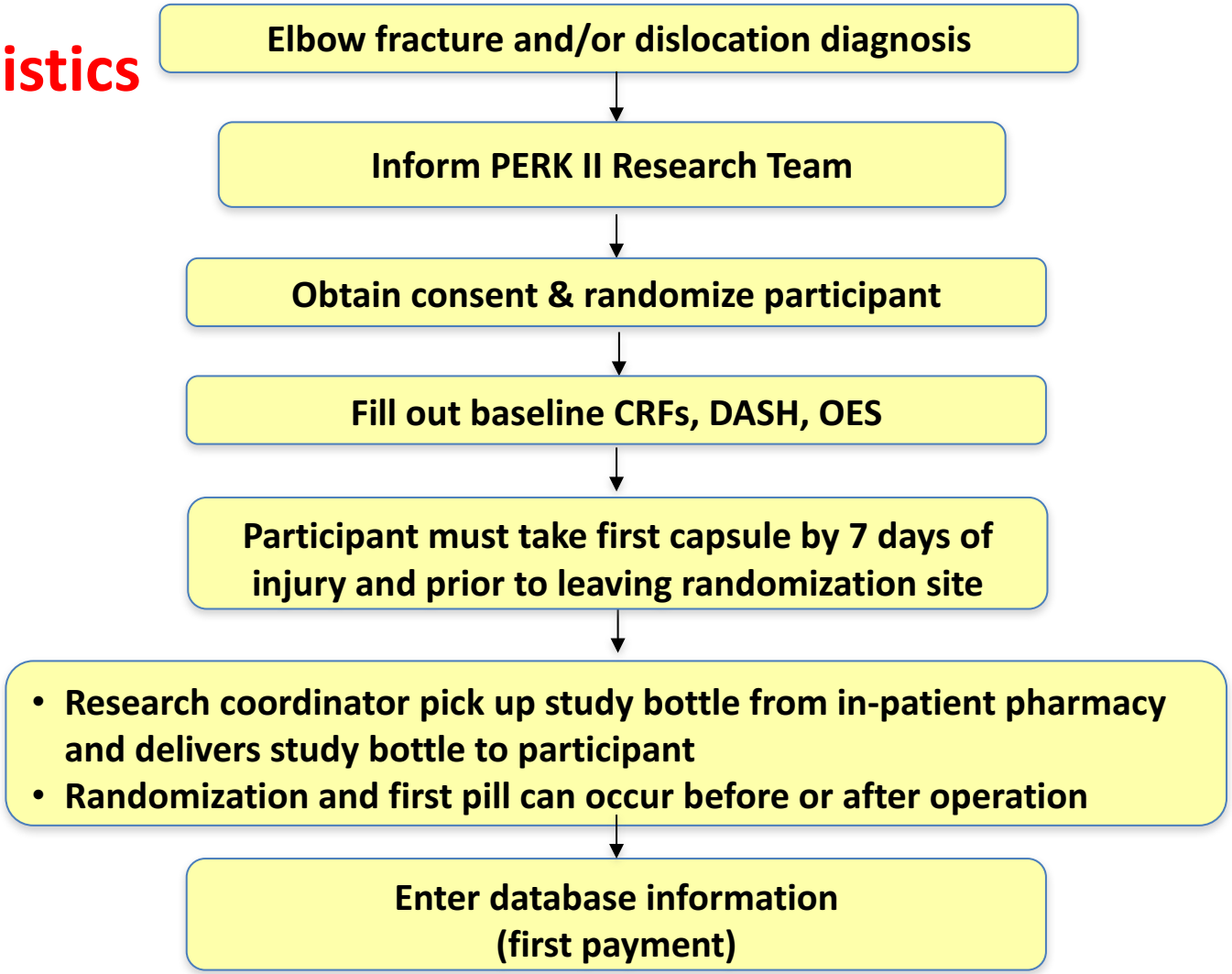
Data and Study Management (Still in Development)

- Clinical Research Unit (CRU) at the University of Calgary
- Electronic Data Capture (EDC):
  - REDCap Cloud
    - US FDA 21 CFR Part 11 compliant
    - GCP compliant
- StudyManager
  - Notices, Pharmacy, Finances, etc

PERK II

Sample Site Logistics

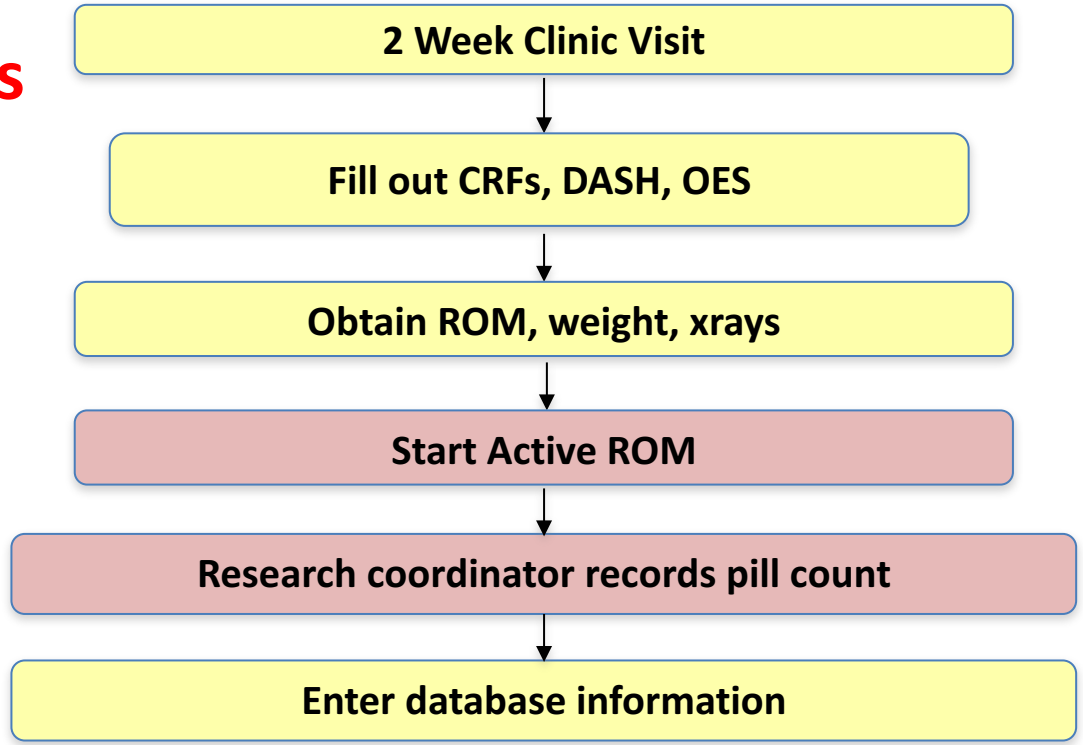
Enrolment & Randomization



PERK II

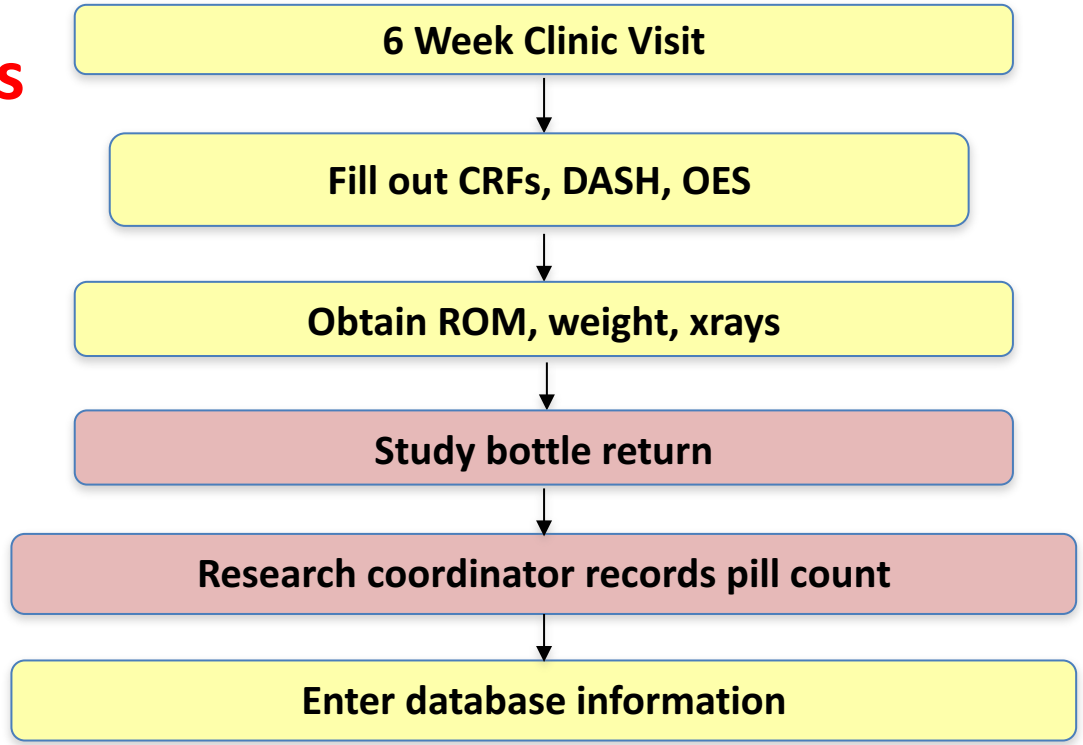
Sample Site Logistics

Post Randomization



PERK II

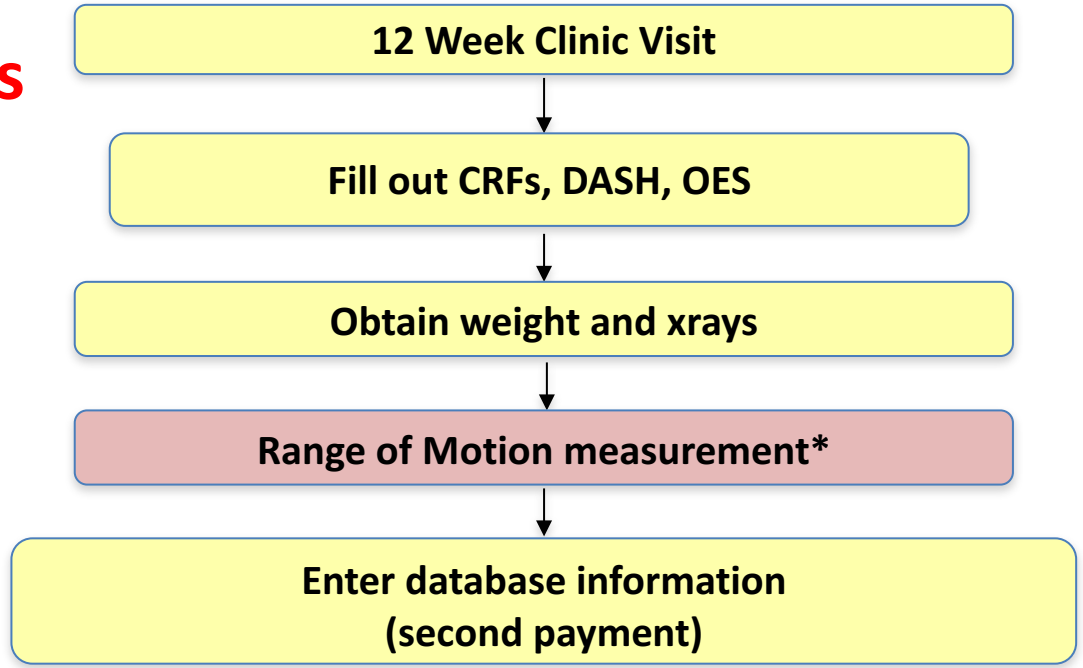
Sample Site Logistics
Post Randomization



PERK II

Sample Site Logistics

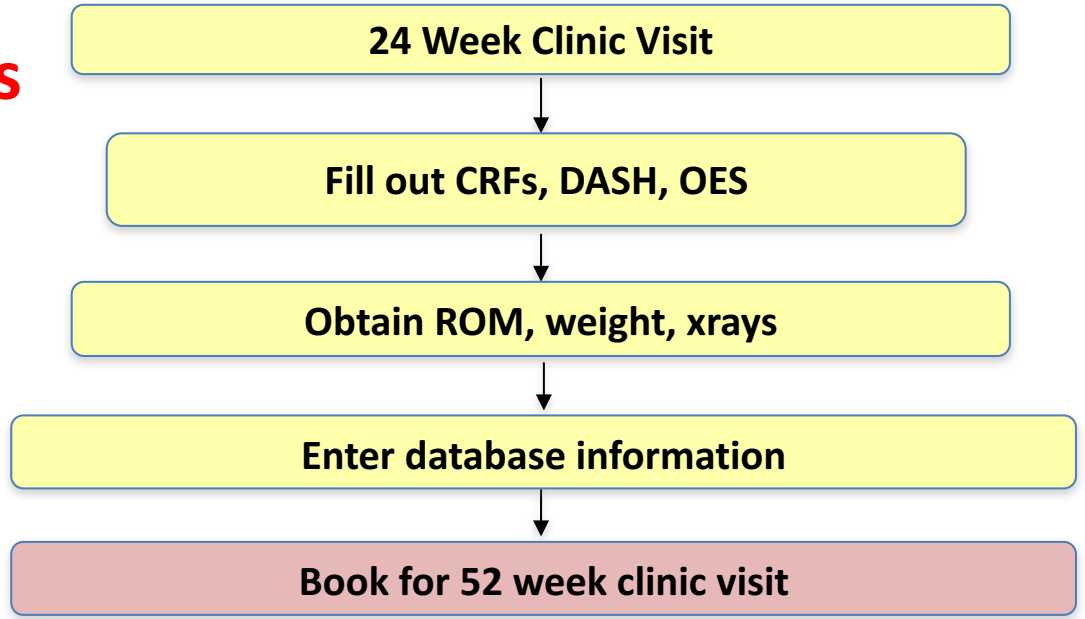
Post Randomization



PERK II

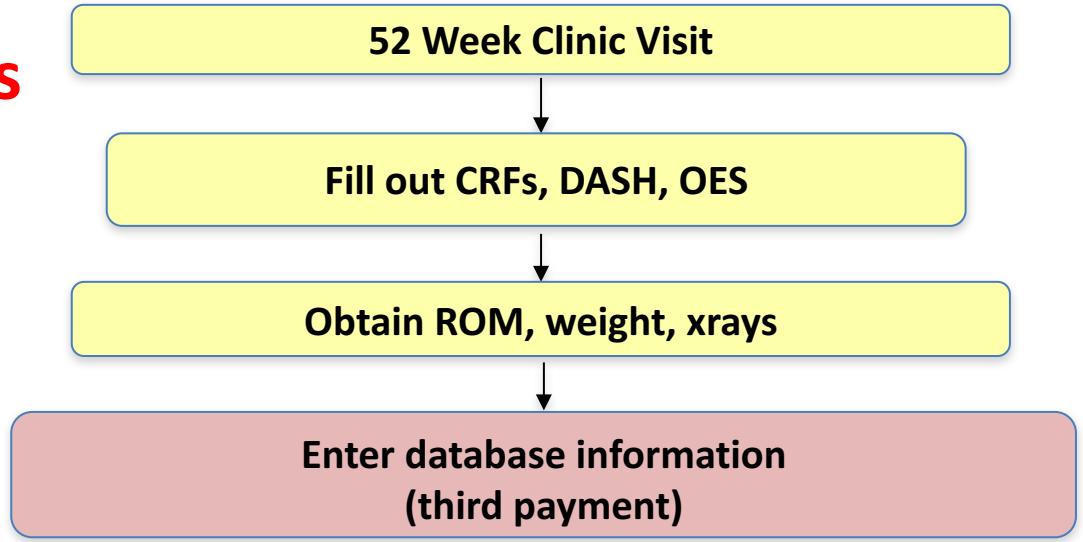
Sample Site Logistics

Post Randomization



PERK II

Sample Site Logistics Post Randomization



PERK II

Case Report Forms (CRFs)

- Research Coordinators with Participants Most
- Treating Surgeon will define mechanism and classify injuries on CRFs

PERK II

Early Mobilization

- standardized home therapy program for all groups that will consist of active ROM exercises for elbow extension-flexion arc and forearm pronation-supination arc performed 3x/day with 20 repetitions.
- Visits to the physiotherapist every 2 weeks will monitor progress and reinforce adherence to home therapy.
- Stretching splints are instituted once it is clear that physiotherapy alone is insufficient, which occurs a minimum of 12 weeks post-randomization.

PERK II

Withdrawal of Participants

- May withdraw consent at any time
- If within the first 6 weeks, study bottle must be returned

PERK II

Ketotifen and Placebo

- Bay Area Research Logistics (BARL) – Hamilton, ON
- TEVA source of Meds
- BARL Overencapsulation
- Capsules are self-administered
- Discontinuation of capsules if excessive drowsiness or skin rash occurs
- No rescue medications

PERK II

Safety

- Participants will be provided with laminated wallet cards
- Common expected side effects: weight gain, drowsiness
- Radiographs will be assessed for non-union and to detect HO
- Other adverse events will be defined as the occurrence of fatigue, rash, headache, trouble sleeping, respiratory or flu-like symptoms, abdominal pain, increased appetite, anxiety or increased nervousness, or diarrhea.

PERK II

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 II

Diagnostic Imaging

- Central Storage with Calgary Image Processing and Analysis Centre (CIPAC)
- Local sites to provide images to CIPAC
- Local processes and CIPAC processes TBD

PERK II

Safety

- Medical Monitor will review each AE
- Adverse Event Committee (AEC)
  - meet monthly
- Trial Steering Committee
- Data Safety Monitoring Board
  - Meet annually

PERK II

Timelines

- Contracts
  - Need site Legal/Contract contacts
- FDA
  - Approval November 13, 2017
- Local Ethics (CHREB)
  - Approved September 11, 2017
  - Amendments based on FDA non-hold items (protocol & ICF)
    - Approved November 21, 2017

PERK II

Timelines

- Health Canada
  - December 2017
- Trial Sites
  - Submit local REB
- Human Research Protections Office (HRPO)
  - December 2017

PERK II

Implementation

- Training session
    - via videoconference March 2018
- Site initiation visit
    - April - June 2018
- Enrolment start date
    - April 2018

PERK II

Communication

- Dropbox
  - Trial documents to be uploaded week of December 4th, 2017
- Switch to Study Manager when trial is live

PERK II

Study Preparation Activities

- Training (PI & Coordinator)
  - TCPS2
  - GCP
  - Health Canada Division 5
- Legal contact for contract negotiation
- Pharmacy contact and delivery address

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PrEvention of post-traumatic contractuRes with Ketotifen II (PERK II): Breakout Sessions

Kevin A. Hildebrand, MD, FRCSC
Chief, Orthopaedic Surgery
Professor, Department of Surgery
Deputy Director, McCaig Institute for Bone and Joint Health
Cumming School of Medicine
University of Calgary

Mobility for Life.

Alberta Health Services

UNIVERSITY OF CALGARY

PERK II

Breakout Session

- Investigators
- Coordinators

Thank You

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Alberta Health Services ("AHS") and The Governors of the University of Alberta ("University") at Suite 400, 8215 – 112 Street, Edmonton, Alberta, Canada T6G 2C8 (hereinafter AHS and University will be collectively referred to as the "Vendor" however the rights and obligations of each of AHS and University shall remain several and not joint) and Dr. Robert Chan ("Investigator") at 6-110 CSB, University of Alberta, Edmonton, Alberta, T6G 2C3

Dear Dr. Robert Chan,

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by the Investigator and Vendor to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or

ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

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

If to the INVESTIGATOR:

Dr. Robert Chan c/o Anelise Silveira
6-110 Clinical Science Building
University of Alberta
Edmonton, Alberta, Canada, T6G 2C3
Phone: 780-492-2398
Email: anelise.silveira@albertahealthservices.ca

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: _____
SEP 04 2018

September 04/ 2018

Agreed to this ---------- day of ~~August 2018~~

ALBERTA HEALTH SERVICES

By: _____
Name: Ronald Welch
Title: Research Administration
Date: 28 Aug 2018

ALBERTA HEALTH SERVICES

By: _____
Name: Chris Wing
Title: Finance and Administration
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Dr. David Williams
Title: Academic Department Chair
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Julaine Herst
Title: Research Services Office
Date: _____

INVESTIGATOR

By: _____
Name: Dr. Robert Chan
Title: Investigator
Date: _____

By: _____
Name: Ronald Welch
Title: Research Administration
Date: _____

ALBERTA HEALTH SERVICES

By: _____
Name: Chris Wing
Title: Finance and Administration
Date: August 27/2018

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Dr. David Williams
Title: Academic Department Chair
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Julaine Herst
Title: Research Services Office
Date: _____

INVESTIGATOR

By: _____
Name: Dr. Robert Chan
Title: Investigator
Date: _____

By: _____
Name: Ronald Welch
Title: Research Administration
Date: _____

ALBERTA HEALTH SERVICES

By: _____
Name: Chris Wing
Title: Finance and Administration
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Dr. David Williams
Title: Academic Department Chair
Date: August 10/18

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Julaine Herst
Title: Research Services Office
Date: _____

INVESTIGATOR

By: _____
Name: Dr. Robert Chan
Title: Investigator
Date: _____

By: _____
Name: Ronald Welch
Title: Research Administration
Date: _____

ALBERTA HEALTH SERVICES

By: _____
Name: Chris Wing
Title: Finance and Administration
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Dr. David Williams
Title: Academic Department Chair
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

JULIE L. STEPHENS
Assistant Director
Research Facilitation & Strategic Initiatives
RESEARCH SERVICES OFFICE
The University of Alberta

By: _____
Name: Julaine Herst
Title: Research Services Office
Date: AUG - 9 2018

Julaine Herst
Assistant Director, Contracts & Agreements
RESEARCH SERVICES OFFICE
The University of Alberta

INVESTIGATOR

By: _____
Name: Dr. Robert Chan
Title: Investigator
Date: _____

By: _____
Name: Ronald Welch
Title: Research Administration
Date: _____

ALBERTA HEALTH SERVICES

By: _____
Name: Chris Wing
Title: Finance and Administration
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Dr. David Williams
Title: Academic Department Chair
Date: _____

THE GOVERNORS OF THE UNIVERSITY OF ALBERTA

By: _____
Name: Julaine Herst
Title: Research Services Office
Date: _____

INVESTIGATOR

By: _____
Name: Dr. Robert Chan
Title: Investigator
Date: August 10, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

Payee Name: Alberta Health Services
Payee Address: Dr. Robert Chan c/o Anelise Silveira, Project#35558
6-110 Clinical Science Building
University of Alberta
Edmonton, Alberta, Canada, T6G 2C3
Phone: 780-492-2398
Email: anelise.silveira@albertahealthservices.ca

UofA GST/HST Account Number: 10810 2831 RT0001

The Research Study is subject to an ethics review fee of $4,000.00 CAD (Overhead Exempt). Upon execution of Agreement and upon receipt of an invoice from the Vendor, UCalgary shall issue a separate cheque/electronic money transfer payable to the Payee at the Payee Address above. This $4,000 REB submission fee is listed in the table above.

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Foothills Medical Centre
McCaig Tower
3134 Hospital Drive NW
Calgary, Alberta, Canada T2N 5A1
Email: psschnei@ucalgary.ca

Dear Dr. Schneider:

RE: Early Start Letter ("Letter Agreement") – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") between Dr. Kevin Hildebrand ("Principal Investigator"), Dr. Prism Schneider ("Site PI") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary, Principal Investigator and Site PI are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This Letter Agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this Letter Agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

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(c) Fundamental Terms: The parties acknowledge that the: (i) scope, type or description of the Research (as applicable) to be supplied or provided, and (ii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Invoice: Site PI shall provide the Principal Investigator with a sufficiently detailed invoice on the Deliverables in accordance with Schedule A. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
CANADA
Attention: Alexandra Garven
Phone: (403) 943 - 5556
Pager: 08802
Email: Alexandra.Garven@albertahealthservices.ca

(f) Upon the termination or expiry of this Letter Agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this Letter Agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this Letter Agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(g) This Letter Agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(h) This Letter Agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this Letter Agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This Letter Agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This Letter Agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to Site PI:

Dr. Prism Schneider
Foothills Medical Centre
McCaig Tower, 3134 Hospital Drive NW
Calgary, Alberta, Canada T2N 5A1
Tel: 403-944-4518

If to Principal Investigator:

Dr. Kevin Hildebrand
University of Calgary
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6

If to UCalgary:

The Governors of the University of Calgary
Legal, Research Services – CSM Legal
Office G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager, CSM Legal
Tel: (403) 210-7813

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: JUN 28 2018

Agreed to this July 5, 2018

Principal Investigator

By: _____
Name: Dr. Kevin Hildebrand

Agreed to this July 9, 2018

Site PI

By: _____
Name: Dr. Prism Schneider

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

University of Maryland, Baltimore
Sponsored Programs Administration
620 West Lexington Street, 4th Floor
Baltimore, MD 21201
ctoalepai@umaryland.edu

Dear Vendor,

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by University of Maryland, Baltimore (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

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(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation. Subject to the limitations contained in this paragraph and to the extent allowed by Maryland law, Vendor agrees to indemnify and hold harmless UCalgary, and any officers, directors, employees, or agents thereof from and against any and all damages, claims, and reasonable out-of-pocket costs and expenses relating thereto and arising out of the negligent acts or omissions of Vendor under this Agreement. Indemnification shall be contingent upon an adequate appropriation by the Maryland General Assembly to Vendor specifically for the purpose contemplated in this paragraph at the time an event which may give rise to Vendor's obligation to indemnify or save harmless occurs. To the extent that a tortious claim is involved, Vendor's obligation to indemnify shall not be greater than the liability that might be determined under the Maryland Tort Claims Act, Section 12-101 et seq., State Government Article, Maryland Annotated Code (the "Act"), if the claim had been asserted against Vendor or the State of Maryland directly pursuant to the Act. The Vendor does not represent that there is, or will be an appropriation for making payments pursuant to this paragraph.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

University of Maryland, Baltimore
Office of Research and Development
Sponsored Programs Administration
620 West Lexington Street, 4th Floor
Baltimore, MD 21201
(410)706-1101
TAX ID # 52-6002033

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: JUN 18 2018

Agreed to this 4th day of June, 2018
University of Maryland , Baltimore

(LT) By: _____
Name: Danielle Brown
Title: Director, Sponsored Programs Admin.
Date: 06/08/2018

SCHEDULE "A"

SERVICES AND FEES

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$3,082.28 USD	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$770.78 USD (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER AGREEMENT – NEW AGREEMENT

Delivered via Email *June 27, 2018*

Ottawa Hospital Research Institute
501 Smyth Road
Ottawa, ON K1H 8L6
Attn: Marisa Akow
Director Research Program Administration
Email: makow@ohri.ca

Dr. J. Whitcomb Pollock
The Ottawa Hospital
501 Smyth Road, CCW 1644
Ottawa, ON K1H 8L6
Email: jpollock@toh.ca

Dear Ms. Akow and Dr. Pollock;

RE: Early Start Letter of Agreement – New Agreement – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "**Research**") between Ottawa Hospital Research Institute and Dr. J. Whitcomb Pollock (collectively, the "**Site**") " and The Governors of the University of Calgary ("**UCalgary**")

UCalgary and the Site are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "**Research**").

In this respect, the parties agree as follows:

(a) Interim Period: This Letter Agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:
   i. the New Agreement being executed, or
   ii. the date which is 90 calendar days following the Commencement Date;
   (the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If the New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this Letter Agreement in all respects, including with respect to the preliminary Research activities during the Interim Period, and this Letter Agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date. The New Agreement shall name both Dr. J. Whitcomb Pollock and Dr. Steven Papp as Site's co-investigators, as the Research will be conducted by each of them at The Ottawa Hospital's General and Civic Campuses, respectively. Dr. J. Whitcomb Pollock shall be identified as the Qualified Investigator for the Site.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be conducted by the Site, and (iii) the Research budget, each being as set out in Schedule A hereto, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the Site through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period Dr. J. Whitcomb Pollock shall provide to UCalgary the deliverables in return for the fees as set out in the attached Schedule "A".

(e) Invoices should be sent to the following address:

University of Calgary
RE: PERK 2 Trial, Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
CANADA
Attention: Alexandra Garven
Phone: (403) 943 - 5556
Pager: 08802
Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the Research at the Site unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this Letter Agreement, no party shall have any liability to the other parties other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this Letter Agreement. No party shall be liable to the other parties for any, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this Letter Agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This Letter Agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This Letter Agreement shall be governed by and construed in accordance with the laws of the Province of Ontario and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and execution of this Letter Agreement and the New Agreement including all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This Letter Agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This Letter Agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this Letter Agreement by email to the following UCalgary address: csmlegal@ucalgary.ca

NOTICE PROVISIONS:

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 email or other means of recorded electronic communication;

If to the SITE:

Ottawa Hospital Research Institute
501 Smyth Road, ORCC 4Th Floor, Box 411,
Ottawa, ON K1H 8L6
Attn: Marisa Akow

Email: makow@ohri.ca
T: 613-737-8899 Ext. 78642
Fax: 613-737-8803

and to:

Dr. J. Whitcomb Pollock
The Ottawa Hospital (General Campus)
Division of Orthopedic Surgery
501 Smyth Road, CCW 1644
Ottawa, ON K1H 8L6

Email: jpollock@toh.ca
T: 613-737-8899 ext. 73031
Fax: 613-737-8837

If to UCALGARY:
The Governors of the University of Calgary
Legal, Research Services – CSM Legal
Office G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager, CSM Legal
Tel: (403) 210-7813
Fax: (403) 210-6677
Email: csmlegal@ucalgary.ca

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: JUN 2 8 2018

Agreed to by: **Ottawa Hospital Research Institute**

By: _____
Name: Marisa Akow
Title: Director, Research Program Administration
Date: _____

Dr. J. Whitcomb Pollock

_____

Date: _____

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: _____

Agreed to by: **Ottawa Hospital Research Institute**

By: _____
Name: Marisa Akow
Title: Director, Research Program Administration
Date: 29 June 18

Debra Lynkowski
Chief Operating Officer
Ottawa Hospital Research Institute

Dr. J. Whitcomb Pollock

_____

Date: 2018/6/29

SCHEDULE "A"

SERVICES AND FEES (all fees in Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local REB submission,)	$4,000	**September 1, 2018** Quarterly Update report to UCalgary
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Quarterly Update report to UCalgary

EARLY START LETTER – NEW CONTRACT

Delivered via Email

The Research Institute of the McGill University Health Centre
2155 Guy Street, Suite 500
Montreal, Quebec, Canada H3H 2R9
Attention: Costas N. Karatzas, M.Sc., Ph.D.
Director – Business Development & Contracts Office

Dear Dr. Karatzas:

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by The Research Institute of the McGill University Health Centre with a principal place of business at 2155 Guy Street, Suite 500, Montreal, Quebec, Canada H3H 2R9 (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:
i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;
(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of the defending party and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

Cinzia Raponi CPA, CMA
Director, Administration
The Research Institute of the McGill University Health Centre
2155 Guy Street, Suite 500
Montreal, Quebec, H3H 2R9 Canada
Tel: 514-934-1934, ext. 44515

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: 5/July/18

Agreed to this 4th day of July 2018

The Research Institute of the McGill University Health Centre

By: _____
Name: Costas N. Karatzas, M.Sc., Ph.D.
Title: Director – Business Development & Contracts Office
Date: July 4th, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

335 – 401 9 Ave SW
Calgary, Alberta, Canada T2P 3C5
Email: kdjohnst@ucalgary.ca

Dear Dr. Johnston:

RE: Early Start Letter ("Letter Agreement") – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") between Dr. Kevin Hildebrand ("Principal Investigator"), Dr. Kelly Johnston ("Site PI") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary, Principal Investigator and Site PI are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This Letter Agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this Letter Agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this Letter Agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this Letter Agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) scope, type or description of the Research (as applicable) to be supplied or provided, and (ii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Invoice: Site PI shall provide the Principal Investigator with a sufficiently detailed invoice on the Deliverables in accordance with Schedule A. Invoices should be sent to the following address:

University of Calgary
RE: PERK 2 Trial, Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
CANADA
Attention: Alexandra Garven
Phone: (403) 943 - 5556
Pager: 08802
Email: Alexandra.Garven@albertahealthservices.ca

(f) Upon the termination or expiry of this Letter Agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this Letter Agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this Letter Agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(g) This Letter Agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(h) This Letter Agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this Letter Agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This Letter Agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This Letter Agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to Site PI:

Dr. Kelly Johnston
335 – 401 9 Ave SW
Calgary, Alberta, Canada T2P 3C5
Tel: 403-265-4885

If to Principal Investigator:

Dr. Kevin Hildebrand
University of Calgary
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6

If to UCalgary:

The Governors of the University of Calgary
Legal, Research Services – CSM Legal
Office G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager, CSM Legal
Tel: (403) 210-7813

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: _____

JUN 28 2018

Agreed to this _____, 2018

Principal Investigator

By: _____
Name: Dr. Kevin Hildebrand
Date: June 28, 2018

Agreed to this June 27, 2018

Site PI

By: _____
Name: Dr. Kelly Johnston
Date: June 27, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

University of Vermont and State Agricultural College
85, S Prospect St
217 Waterman
Burlington, VT 05405-0160
Sonya Stern
spa@uvm.edu

Dear Ms. Stern

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by University of Vermont and State Agricultural College (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

University of Vermont and State Agricultural College
85, S Prospect St
217 Waterman
Burlington, VT 05405-0160
Sonya Stern
spa@uvm.edu

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: 29/AUG/18

Agreed to this day of 2018

By: Emily Trantum
Name: Emily Trantum
Title: Team Lead, Award Acceptance
Date: 8/20/2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (U.S. dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$3,014	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$756 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Sunnybrook Research Institute
2075 Bayview Avenue
Toronto, ON, Canada
M4N 3M5
Attention: Office of the President and CEO, Room C-104
Fax: 416-480-6133

And

Diane Nam, M.Sc., MD, FRCS(C)
Associate Scientist
Sunnybrook Health Sciences Centre
2075 Bayview Ave., Room MG 361
Toronto, ON
M4N 3M5
Phone: 416-480-5641
Fax: 416-480-5886
Email: diane.nam@sunnybrook.ca

Dear Dr. Nam and Sunnybrook

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by Sunnybrook Research Institute (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New

Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without

limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

2075 Bayview Avenue
Toronto, ON, Canada
M4N 3M5
Attention: Office of the President and CEO, Room C-104

Fax: 416-480-6133

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: JUL 10 2018

Agreed to this 29th day of June 2018

Sunnybrook Research Institute

By: Michael Julius
Michael Julius (Jul 9, 2018)
Name: Michael Julius

Title: Vice President Research
Date: Jul 9, 2018

By: Rod Engeland
Rod Engeland (Jul 9, 2018)
Name: Rod Engeland
Title: Executive Director Research Finance & Operations
Date: Jul 9, 2018

By: Diane Nam
Diane Nam (Jul 4, 2018)
Name: Diane Nam, MD
Title: Study Investigator
Date: Jul 4, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Providence St. Joseph's and St. Michael's Healthcare
At its St. Michael's site, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8
Dr. Arthur Slutsky, Dr. Aaron Nauth
NauthA@smh.ca

Dear Dr. Arthur Slutsky and Dr. Aaron Nauth:

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the "**Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2)**" (the "Research Study") by Providence St. Joseph's and St. Michael's Healthcare, at its St. Michael's site (the "Subsite"), and Dr. Aaron Nauth, a physician-investigator with a research appointment at the Subsite, (the "Subsite PI") (collectively, the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, the Vendor is intending to conduct the Research Study with the understanding that UCalgary and the Vendor are intending to negotiate in good faith a clinical study agreement (the "**New Agreement**") in respect of the performance of the Research Study. The Vendor has hereby agreed to perform certain preliminary research activities for the Research Study as described in Schedule "A" hereto (the "**Start-Up Activities**"), and UCalgary has committed to reimburse Subsite for these Start-Up Activities via this letter agreement. For clarity, this letter agreement (the "**Letter Agreement**") is made by and between the Vendor and UCalgary.

In this respect, the parties agree as follows:

(a) Interim Period: This Letter Agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this Letter Agreement) (the "**Commencement Date**") and shall expire on the earlier of:
   i. the New Agreement being executed, or
   ii. the date which is 90 calendar days following the Commencement Date;
   (the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this Letter Agreement in all respects, including with respect to the provision of the Research Study (for clarity, specifically ***excluding*** UCalgary's commitment in this Letter Agreement to reimburse Subsite for Start-Up Activities), and this Letter Agreement shall automatically expire.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term of the New Agreement (as defined in paragraph (d) below), (ii) scope, type or description of the certain research activities in the Research Study (as applicable) to be supplied or provided by Subsite or Subsite PI, and (iii) the pricing or fees for the research activities described in subsection (ii) above have been largely agreed to and may be reflected in the New Agreement. UCalgary shall provide funding to the Subsite through this Letter Agreement in order to fund the Start-Up Activities prior to the execution of the New Agreement. Specifically, UCalgary shall

reimburse Subsite for the fees described under Schedule A upon the full execution of this Letter Agreement and upon forty-five (45) days of the receipt of invoices.

Invoices should be sent to the following address:

University of Calgary
RE: PERK 2 Trial, Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
CANADA
Attention: Alexandra Garven
Phone: (403) 943 - 5556
Pager: 08802
Email: Alexandra.Garven@albertahealthservices.ca

For clarity, all payments contemplated under this Letter Agreement shall be made payable to **St. Michael's Hospital,** 30 Bond Street, Toronto, Ontario, Canada M5B 1W8, c/o Dr. Aaron Nauth.

(d) Term: The term of the New Agreement shall be for as long as required in order to complete the overall Research Study at Subsite unless otherwise terminated in accordance with the terms of the New Agreement.

(e) Upon the termination or expiry of this Letter Agreement, no party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this Letter Agreement. No party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this Letter Agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(f) This Letter Agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written of the same subject matter herein.

(g) This Letter Agreement shall be governed by and construed in accordance with the laws of the Province of Ontario and the federal laws of Canada applicable therein.

(h) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this Letter Agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors if applicable.

(i) This Letter Agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(j) This Letter Agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this Letter Agreement by email to the following address: csmlegal@ucalgary.ca

NOTICE PROVISIONS FOR ALL PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

Subsite:

Providence St. Joseph's and St. Michael's Healthcare
At its St. Michael's site
30 Bond Street, Toronto
Ontario, Canada M5B 1W8
Attn: Dalton Charters, Senior Director of Research Operations
Office of Research Administration
Tel: (416) 864-6060 Ext. 2558

Subsite PI:

Dr. Aaron Nauth
St. Michael's Hospital
55 Queen Street East, Suite 800
Toronto, Ontario M5C 1R6
Tel: (416) 864-6017

If to UCALGARY:

The Governors of the University of Calgary
Legal, Research Services – CSM Legal
Office G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager, CSM Legal
Tel: (403) 210-7813

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: AUG 16 2018

Providence St. Joseph's and St. Michael's Healthcare

By: _____
Name: Dr. Arthur Slutsky
Title: Vice President, Research
Date: Aug 10, 2018

Dr. Aaron North

By: 

Title: Subsite PI

Date: 08-Aug-2013

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Roth McFarlane Hand and Upper Limb Clinic
St. Joseph Health Care London DB-222
PO BOX 5557
London ON
N6A 4V2
Attention: Katrina Munro
Email: Katrina.munro@sjhc.london.on.ca

Dear Ms. Joy MacDermid

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by (St. Joseph Health Care London) (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:
   i. the New Agreement being executed, or
   ii. the date which is 90 calendar days following the Commencement Date;
   (the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

Joy MacDermid
Hand and Upper Limb Clinical Research lab
DB-222 PO BOX 5557
London ON
N6A 4V2

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: 25/AUG/18

Agreed to this ---------- day of August 2018

St. Josephs Health Care London

By: _____
Name: Dr. Joy MacDermid
Title: Principal Investigator
Date:

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Fraser Orthopaedic Research Society (FORS)
#608 6th Floor, 260 Sherbrooke Street
New Westminster, BC V3L 3M2
Attention: Dr. Farhad Moola (c/o Mauri Zomar)
E-mail: fmoola@me.com / mauri.zomar@fraserhealth.ca

Dear Dr. Farhad Moola,

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by Dr. Farhad Moola and Fraser Health Authority (collectively, the "**Subsite**") to The Governors of the University of Calgary ("**UCalgary**") (collectively, the "**parties**")

As you are aware, UCalgary and the Subsite are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:
i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;
(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the Subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of British Columbia and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the SUBSITE:

Dr. Farhad Moola (c/o Mauri Zomar)
Fraser Orthopaedic Research Society (FORS)
#608 6th Floor, 260 Sherbrooke Street
New Westminster, BC V3L 3M2
Email: mauri.zomar@fraserhealth.ca

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

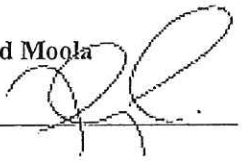
Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: 21/June/18

Agreed to this 14th day of JUNE 2018

FRASER HEALTH AUTHORITY

By: _____
Name: Susan Chunick
Title: Director, Department of Evaluation and Research Services, Fraser Health Authority
Date: June 15/2018

Dr. Farhad Moola

By: 

Title: Principal Investigator
Date: 15 June 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

Nova Scotia Health Authority
5790 University Ave. Halifax, NS B3H 1V7
Jennifer Thurlow
jennifer.thurlow@nshealth.ca
Principal Investigator: Dr. Andrew Trenholm

Dear Dr. Trenholm

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by (the Nova Scotia Health Authority and Dr. Andrew Trenholm (collectively the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) This letter agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(j) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(k) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(l) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

Nova Scotia Health Authority
5790 University Ave.
Halifax, NS B3H 1V7
Attn: Director, Research Services
Tel: 902-473-4069

Dr. Andrew Trenholm
Rm. 4868 – 1796 Summer St.
Halifax, NS B3H 3A6
Tel: 902-473-5311

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: JUN 26 2018

By: _____
Name: Dr. Andrew Trenholm
Title: Staff Orthopedic Surgeon
Date: June 25/18.

By: _____
Name: Lisa Underwood
Title: Director, Research Services
Date: June 25, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

Delivered via Email

The Charlotte-Mecklenburg Hospital Authority d/b/a Carolinas HealthCare System
1000 Blythe Blvd.
Charlotte, NC 28203
SPA.GnC@carolinashealthcare.org

Dear Dr. Mclendon,

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Research Study") by The Charlotte-Mecklenburg Hospital Authority d/b/a Carolinas HealthCare System (the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:

i. the New Agreement being executed, or
ii. the date which is 90 calendar days following the Commencement Date;

(the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: The parties agree to negotiate in good faith the New Agreement and agree that they shall make commercially reasonable efforts to have the New Agreement finalized and executed by the Expiry Date. If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables as UCalgary may require from time to time. The prices and/or fees payable for the Deliverables shall be as set out in the attached Schedule "A".

(e) Purchase Order: Deliverables shall be ordered by way of a purchase order and the terms and conditions attached to each purchase order shall form the terms and conditions of each such

purchase transaction until such time as the New Agreement is executed. Invoices should be sent to the following address:

University of Calgary, RE: PERK 2 Trial, Dr. Kevin Hildebrand

2500 University Drive NW

Calgary, AB T2N 1N4

CANADA

Attention: Alexandra Garven

Phone: (403) 943 - 5556

Pager: 08802

Email: Alexandra.Garven@albertahealthservices.ca

(f) Term: The term of the New Agreement shall be for as long as required in order to complete the overall research initiative unless otherwise terminated in accordance with the terms of the New Agreement.

(g) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(h) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

The Charlotte-Mecklenburg Hospital Authority
d/b/a Carolinas HealthCare System
Sponsored Programs Administration – Grants & Contracts
4828 Airport Center Parkway, Bldg E
Charlotte, NC 28208
Attn: Grants & Contracts Supervisor
Tel: (704) 512-3861

If to UCALGARY:

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

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research
Date: 21 / June / 18

Agreed to:

The Charlotte-Mecklenburg Hospital Authority
d/b/a Carolinas HealthCare System

By: George Mclendon
Name: George Mclendon, PhD
Title: Vice President, Research
Date: 6/14/2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

EARLY START LETTER – NEW CONTRACT

The University of British Columbia
University Liaison Office
103-6190 Agronomy Road
Vancouver, British Columbia
Canada V6T 1Z3
Attn: Michael Matier, Contracts Officer

Providence Health Care Society
Suite 400 – 1190 Hornby Street
Vancouver, British Columbia,
Canada V6Z 2K5
Attn: S.F. Paul Man, MD, FRCPC

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

Delivered via Email

Dear Dr. Goetz, Dr. Man and Mr. Matier,

RE: Early Start Letter – New Contract – Agreement for the Commencement of Preliminary Research Activities relating to the Prevention of posttraumatic joint contractures with Ketotifen 2 (PERK 2) (the "Study") by and The University of British Columbia, a corporation continued under the University Act of British Columbia and having offices at 103 – 6190 Agronomy Road, Vancouver, British Columbia, V6T 1Z3 ("UBC"), Providence Health Care Society, incorporated by the Sisters of Charity of Providence and having its administrative offices at Suite 400 – 1190 Hornby Street, Vancouver, British Columbia, Canada V6Z 2K5 ("PHCS"), and Dr. Thomas Goetz) (UBC PHCS and Dr. Thomas Goetz collectively, the "**Vendor**") to The Governors of the University of Calgary ("UCalgary")

As you are aware, UCalgary and the Vendor are currently in the process of negotiating an agreement (the "**New Agreement**") in respect of the performance of certain research activities in connection with the Study, including those activities described in Schedule "A" hereto (the "Research").

In this respect, the parties agree as follows:

(a) Interim Period: This letter agreement shall commence and be effective on the date that it is accepted and executed by the parties (being the date of execution by the last of the representatives of the parties to execute this letter agreement) (the "**Commencement Date**") and shall expire on the earlier of:
   i. the New Agreement being executed, or
   ii. the date which is 90 calendar days following the Commencement Date;
   (the "**Expiry Date**"). The period of time from the Commencement Date until the Expiry Date is referred to herein as the "**Interim Period**".

(b) New Agreement: If a New Agreement is finalized and executed, the terms and conditions of the New Agreement shall govern and supersede this letter agreement in all respects, including with respect to the provision of the Research Trial during the Interim Period, and this letter agreement shall automatically expire. The parties agree that the New Agreement and its terms and conditions shall take effect on and be dated and deemed effective as of the Commencement Date.

(c) Fundamental Terms: The parties acknowledge that the: (i) Term, (ii) scope, type or description of the Research (as applicable) to be supplied or provided, and (iii) the pricing or fees for the

Protocol, each being as set out herein, have been largely agreed to and shall be reflected in the New Agreement. UCalgary shall provide funding to the subsite through this Letter Agreement in order to fund certain elements of the Research prior to the execution of the New Agreement.

(d) Supply and Pricing: During the Interim Period the Subsite shall supply, provide and deliver to UCalgary the Deliverables. The prices and/or fees payable for the Deliverables and the dates by which they are due shall be as set out in the attached Schedule "A".

(e) Invoice: Vendor shall provide UCalgary with a sufficiently detailed invoice in accordance with the Deliverables specified in Schedule A. Invoices should be sent to the following address:

University of Calgary
RE: PERK 2 Trial, Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
CANADA
Attention: Alexandra Garven
Phone: (403) 943 - 5556
Pager: 08802
Email: Alexandra.Garven@albertahealthservices.ca

Payment shall be due from UCalgary within thirty (30) days of receipt of (i), a Deliverable due in accordance with Schedule A and, (ii) a sufficiently detailed invoice. Payment shall be made by cheque as follows:

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

(f) Upon the termination or expiry of this letter agreement, neither party shall have any liability to the other party other than in respect of any obligations or liabilities which have accrued hereunder prior to the date of termination or expiry or pursuant to any provisions which are, expressly or by implication, intended to survive or to take effect on or after the termination or expiry of this letter agreement. Neither party shall be liable to the other party for any special, incidental, indirect, exemplary, punitive, or consequential losses or damages that may arise as a result of the performance, termination or expiration of this letter agreement, including any loss of profits or anticipated loss of profits, loss of business opportunity, anticipated loss of reputation, and loss of reputation.

(g) This letter agreement constitutes the entire agreement between the parties pertaining to the subject matter hereof, and supersede all prior agreements, understandings, negotiations and discussions, whether oral or written.

(h) This letter agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

(i) Each party will pay its own expenses in respect of the negotiation, preparation and implementation of this letter agreement and the New Agreement including, without limitation, all fees and expenses of their respective legal counsel, accountants and other advisors.

(j) This letter agreement may not be amended except by a written instrument signed by a duly authorized representative of each of the parties.

(k) This letter agreement may be executed by the parties in counterparts and may be executed and delivered by facsimile or other means of electronic transmission and all such counterparts shall together constitute one and the same agreement.

If you are in agreement with the above terms, please confirm your acceptance by signing and returning a copy of this letter by email to the following address:

NOTICE PROVISIONS FOR BOTH PARTIES:

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 email or other means of recorded electronic communication;

If to the VENDOR:

The University of British Columbia
University Liaison Office
103-6190 Agronomy Road
Vancouver, British Columbia, Canada V6T 1Z3
Attn: Contracts Officer
Tel: (605) 822-0892

Providence Health Care Society
S.F. Paul Man, MD, FRCPC
Vice President, Research and Academic Affairs
President, Providence Health Care Research Institute
Suite 400 – 1190 Hornby Street
Vancouver, British Columbia, Canada V6Z 2K5
Tel: (604) 806-9608

Dr. Thomas Goetz
208-1160 Burrard Street
Vancouver, British Columbia
Canada V6Z 2E8
Tel: (604) 689-5101

If to UCALGARY:

The Governors of the University of Calgary
Legal, Research Services – CSM Legal
Office G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager, CSM Legal
Tel: (403) 210-7813

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research

Date: 21 / June / 18

ACCEPTED AND AGREED:

The University of British Columbia

By: _____

Name: MARIO A. KASAPI
Associate Director
Title University - Industry Liaison Office

LEGAL APPROVED TH

Date: June 22, 2018

Providence Health Care Society

By: _____
Name: S.F. Paul Man, MD, FRCPC
Title: Vice President, Research and Academic Affairs
President, Providence Health Care Research Institute

Date: June 28 / 18

Dr. Thomas Goetz

By: _____

Date: _____

Yours truly,

The Governors of the University of Calgary

Per: _____
Name: Dr. Marcello Tonelli
Title: Senior Associate Dean, Health Research

Date: 21 / June / 18

ACCEPTED AND AGREED:

The University of British Columbia

By: _____

Name: MARIO A. KASAPI
Associate Director

Title University - Industry Liaison Office

LEGAL APPROVED IH

Date: June 22, 2018

Providence Health Care Society

By: _____
Name: S.F. Paul Man, MD, FRCPC
Title: Vice President, Research and Academic Affairs
President, Providence Health Care Research Institute

Date: _____

Dr. Thomas Goetz

By: Thomas Goetz Thomas Goetz

Date: June 27, 2018

SCHEDULE "A"

SERVICES AND FEES (all fees in (Canadian dollars)

Description of Services	Fees	Deliverables
Site Start Up Fee (Local IRB/REB submission, Department of Defense Human Research Protections Office (HRPO) submissions)	$4,000	**September 1, 2018** Update report to lead site
Informed Consent Form (ICF) Translation (site dependent)	$1,000 (if applicable)	**December 1, 2018** Update report to lead site

Alexandra Garven

From:	Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) <kimberly.l.odam.civ@mail.mil>
Sent:	Thursday, August 30, 2018 7:30 AM
To:	hildebrk@ucalgary.ca
Cc:	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); Daphtary, Maithili M CTR USARMY MEDCOM USAMRMC (US); Kiwanuka, Jacqueline N CTR USARMY MEDCOM USAMRMC (US)
Subject:	A-20465.a and A-20465.b1, HRPO Approval Memorandum (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 Kevin A. Hildebrand, MD University of Calgary, Calgary, Alberta, in Support of the Proposal, "Prevention of Post-Traumatic Contractures With Ketotifen II (PERK II)," Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Numbers A-20465.a (University of Calgary) and A-20465.b1 (Peter Lougheed Centre)

1. The subject protocol (version 4.0/dated 31 July 2018) was approved by the Conjoint Health Research Ethics Board (CHREB) initially on 11 September 2017 and most recently on 15 August 2018. The Peter Lougheed Centre is relying on the review provided by the CHREB. 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 125 adults with elbow fracture or dislocation injuries at the Peter Lougheed Centre.

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 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 11 September 2018. 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 is Maithili Daphtary, PhD, Human Subjects Protection Scientist, at 301-619-7838, DSN 343-7838, or maithili.m.daphtary.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.
CLASSIFICATION: UNCLASSIFIED

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 136411

REMOVE FULL CLINICAL HOLD

Kevin A. Hildebrand, MD
c/o Dr. Michael Bosse
P.O. Box 32861
Charlotte, NC 28232

Dear Dr. Hildebrand:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ketotifen fumarate.

We also refer to your amendment dated October 27, 2017, which provides a complete response to our September 7, 2017, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed our review of your amendment and, as communicated to you by Linda Ebonine of this Division on November 13, 2017, have concluded that you may proceed with your proposed clinical investigation.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

  - you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the most recent date when clinical studies were permitted to begin) [21 CFR 312.33]. If your IND previously had an harmonized annual report due date, it is no longer valid and therefore you will need to submit a new request.

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, please call Linda Ebonine, Regulatory Health Project Manager, at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA EBONINE
11/15/2017

BADRUL A CHOWDHURY
11/15/2017

Health Canada / Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator # 3105A
OTTAWA, Ontario
K1A 0K9

AUG 0 9 2018

Alexandra Garven
Clinical Research Coordinator
University of Calgary
3280 Hospital Drive NW,
Health Research Innovation Centre
CALGARY, Alberta
T2N 4Z6
(403) 943-5556

Your file Votre référence
HC6-24-c218219
Our file Notre référence

No Objection Letter RE: Protocol # PERK2_KAH (Version 3.0)

Dear Ms. Garven:

I am pleased to inform you that the information and material to support your Clinical Trial Application for **KETOTIFEN**, control number **218219**, received on July 12, 2018, have been reviewed and we have no objection to your proposed study. I would remind you of the necessity of complying with the *Food and Drug Regulations,* Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice.*

Please note that Health Canada has implemented electronic reporting of adverse drug reactions and is currently in pilots with some sponsors. Those sponsors who have an established electronic connection with Canada Vigilance Production stream should submit their reports using the distribution rules provided to them by Health Canada, and reporting to multiple directorates is no longer required. For the sponsors who have not yet established this connection, they should continue submitting their reports to the applicable directorate by fax or by courier. The following website provides further clarification on Health Canada's adverse drug reactions reporting requirements for clinical trials:
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.pdf

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Yours sincerely,

Roxana Alexa, MD
Clinical Manager
Office of Clinical Trials

RA/jl

Canada

Subject: RE: Dr. Kevin Hildebrand: ISS Prevention of Posttraumatic Contractures with Ketotifen (PERK II)
Date: Monday, October 16, 2017 at 11:49:02 AM Mountain Daylight Time
From: Brandon Kearnan
To: Kevin A. Hildebrand
CC: Martin Sergerie, Reni Caccamo
Attachments: image003.jpg, image004.png, image005.jpg, image006.png

Hi Kevin,
I have confirmed that we have BARL set up in our system as a ship to.
Can you please confirm if there is someone specific there that you have been working with that we can begin the conversations of shipment quantities and timing?

With this being a 3 year program we can set up a schedule and quantities to help plan our inventory.

Thanks,
Brandon

Brandon Kearnan
Demand Planning Analyst

brandon.kearnan@tevacanada.com

T 1.416.291.8888 x1255455
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9

From: Kevin A. Hildebrand (External) [mailto:hildebrk@ucalgary.ca]
Sent: Thursday, September 28, 2017 10:42 AM
To: Brandon Kearnan
Cc: Martin Sergerie; Reni Caccamo; Alex Garven
Subject: Re: Dr. Kevin Hildebrand: ISS Prevention of Posttraumatic Contractures with Ketotifen (PERK II)

Hi Brandon,

These estimates remain unchanged.

We have engaged the Bay Area Research Logistics (BARL) in Hamilton to acquire, package, and distribute the medication.

Thank you for your support of our project!

Kevin Hildebrand

From: Brandon Kearnan <Brandon.Kearnan@tevacanada.com>
Date: Wednesday, September 27, 2017 at 12:25 PM
To: Kevin Hildebrand <hildebrk@ucalgary.ca>
Cc: Martin Sergerie <Martin.Sergerie@tevapharm.com>, Reni Caccamo <Reni.Caccamo@tevacanada.com>
Subject: RE:Dr. Kevin Hildebrand: ISS Prevention of Posttraumatic Contractures with Ketotifen (PERK II)

Hello Dr. Hildebrand,

I have been forwarded your request for supply of our Ketotifen for your study. I am hoping that you can provide some clarity on a few items below in order to determine the feasibility of Teva supplying the product.

Teva only supplies Ketotifen in 1mg Tablets in 100 bottles. Please confirm if the estimated demand provided of 137,592 tablets for the 3 years is sufficient based on our format for this molecule. If not, what would the new demand be?

The information I received mentions that the study is expected to start in the first quarter of 2018 is this still on track?
As for shipping and receiving of the product is there a desired location for product to ship to?

The Alberta pricing for this product is $172.45 per bottle (100 tablets).

Look forward to working together.

Thanks,
Brandon

Brandon Kearnan
Demand Planning Analyst

brandon.kearnan@tevacanada.com

T 1.416.291.8888 x1255455
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9

This message is intended solely for the designated recipient(s). It may contain confidential or proprietary information and may be subject to attorney-client privilege or other confidentiality protections. If you are not a designated recipient you may not review, copy or distribute this message. If you receive this in error, please notify the sender by reply e-mail and delete this message. Thank you.

Teva Pharmaceuticals

Teva Pharmaceuticals
41 Moores Rd | Frazer, PA 19355

ISS Decline Letter

July 7th, 2017

Dr. Kevin Hildebrand, MD
Professor
McCaig Institute for Bone and Joint Health
Cumming School of Medicine
University of Calgary
HRIC 3A08, 3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6

RE: ISS Protocol /Concept Entitled "Prevention of Posttraumatic Contractures with Ketotifen (PERK II) "

Dear Dr. Hildebrand,

We would like to thank you for your interest in Teva's Investigator Sponsored Study (ISS) Program. The Investigational Review Committee recently considered your study referenced above. Although we recognize the importance of this research to University of Calgary unfortunately, we are not able to support this study financially.

Teva receives many requests for Investigator sponsored research projects and unfortunately is not able to support all of these requests.

Once again, thank you for your interest in Teva's ISS Program and do not hesitate to submit other proposals in the future should you have other research interests.

Sincerely,

Martin Sergerie, PhD, DESS
Associate Director, Medical Affairs

Canada Innovation

MEDISCA®

YOUR TRUSTED PARTNER IN COMPOUNDING

CERTIFICATE OF ANALYSIS

METHYLCELLULOSE, USP (1500 mPa•s)

Batch/Lot Number : 611027

Manufacturing Date : 12/17/2015

Expiration Date : 11/30/2019

Retest Date : NOT APPLICABLE

† All dates in this document are in format mm/dd/yyyy unless otherwise specified

TESTS	SPECIFICATIONS	RESULTS
ASSAY ON DRIED BASIS	26.0 - 33.0 % of methoxy (-OCH3) groups.	29.9 %
DESCRIPTION	White, fibrous powder or granules.	CONFORMS
SOLUBILITY	It swells in water and produces a clear to opalescent, viscous, colloidal suspension. Insoluble in alcohol, ether and chloroform; soluble in glacial acetic acid and a mixture of alcohol and chloroform	CONFORMS
IDENTIFICATION A*	The powdered material aggregates on the surface.	POSITIVE
IDENTIFICATION B*	A clear or slightly turbid solution occurs with its thickness dependent on the viscosity grade.	POSITIVE
IDENTIFICATION C	A red color develops immediately, and it does not change to purple within 100 min.	POSITIVE
IDENTIFICATION D	A coherent, clear film forms on the glass slide.	POSITIVE
IDENTIFICATION E	The flocculation temperature is higher than 50°C	POSITIVE
VISCOSITY <911><912>	1125 - 2100 mPa.s	1436 mPa.s
LOSS ON DRYING <731>	<= 5.0 %	2.1 %
RESIDUE ON IGNITION <281>	<= 1.5 %	0.6 %
HEAVY METALS <231>III	<= 20 ppm	<= 20 ppm
pH	5.0 - 8.0	6.9
RESIDUAL SOLVENTS <467>	Meets the requirements.	CONFORMS
LABELING	Label it to indicate its nominal viscosity type [viscosity of a solution (1 in 50)] in milli-Pascal second (mPa·s).	
PACKAGING AND STORAGE	Preserve in well-closed containers.	

*TESTED ON 01/26/2016

Lot number has been changed from 131344 to 611027

S. Kuj

01Dec2016

The above mentioned product conforms to the specifications of USP.

The above test results are a direct transcription of information provided to Medisca Inc. from the Certificate of Analysis provided by the manufacturer / supplier. Additional testing conducted by Medisca Inc. is represented by an asterisk.

Dated: 1/27/2016

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CERTIFICATE OF ANALYSIS

LACTOSE, NF (Monohydrate)

Batch/Lot Number : 609891

Manufacturing Date : 05/01/2016

Expiration Date : 04/30/2020

Retest Date : NOT APPLICABLE

† All dates in this document are in format mm/dd/yyyy unless otherwise specified

TESTS	SPECIFICATIONS	RESULTS
DESCRIPTION	White, free-flowing powder.	CONFORMS
SOLUBILITY	Freely but slowly soluble in water; practically insoluble in alcohol.	CONFORMS
CLARITY AND COLOR OF SOLUTION	The absorbance divided by the path length in cm is <= 0.04.	0.01 ; CONFORMS
IDENTIFICATION A: <197K>*	IR: Reference to standard spectrum.	POSITIVE
IDENTIFICATION B: <201>	TLC: Reference to standard chromatogram.	POSITIVE
SPECIFIC ROTATION <781>	+54.4 ° to +55.9 °	+55.4 °
MICROBIAL LIMITS <61>	<= 100 cfu per g (Total aerobic microbial count) <= 50 cfu per g (Total combined yeast and mold count)	4 cfu per g < 1 cfu per g
ABSENCE OF SPECIFIED MICROORGANISMS <62>	Meets the requirements for the absence of Escherichia coli.	CONFORMS
ACIDITY OR ALKALINITY	The solution is colorless, and <= 0.4 mL of 0.1 N NaOH is required to produce a pink or red color.	0.1 mL ; CONFORMS
LOSS ON DRYING <731>	<= 1.0 %	0.1 %
WATER <921>I	4.5 - 5.5 %	4.9 %
RESIDUE ON IGNITION <281>	<= 0.1 %	0.02 %
HEAVY METALS <231>	<= 5 µg/g	<= 5 µg/g
PROTEIN AND LIGHT ABSORBING IMPURITIES <851>	<= 0.25 in the range of 210 - 220 nm. <= 0.07 in the range of 270 - 300 nm.	0.01 0.00
RESIDUAL SOLVENTS <467>	Meets the requirements	CONFORMS
LABELING	Where the labeling states the particle size distribution, it also indicates the d10, d50, and d90 values and the range for each. For modified Lactose Monohydrate, also label it to indicate the method of modification.	
PACKAGING AND STORAGE	Preserve in tight containers.	

*TESTED ON 07/01/2016

Lot number has been changed from 135619 to 609891

S. K
01 Dec 2016

The above mentioned product conforms to the specifications of NF.

The above test results are a direct transcription of information provided to Medisca Inc. from the Certificate of Analysis provided by the manufacturer / supplier. Additional testing conducted by Medisca Inc. is represented by an asterisk.

Dated: 7/5/2016

Lactose NF monohydrate

Adresse : 6090 Henri-Bourassa Ouest, Saint-Laurent, QC H4R 3A6 CAN
Sans Frais : 1.800.665.6334 | Télécopie : 514.338.1693
Site Web : www.medisca.com

MEDISCA®
YOUR TRUSTED PARTNER IN COMPOUNDING

May 25, 2016

Dear valued customer,

Medisca packages products with all relevant government regulations, including Good Manufacturing Practices, as appropriate for Active Pharmaceutical Ingredient suppliers. Medisca follows the international Conference on Harmonization Guideline Q7; *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.*

LACTOSE, NF (Anhydrous) and LACTOSE, NF (Monohydrate) are produced using bovine milk derived raw materials and the product is 100% weight/weight. To the best of our knowledge LACTOSE is not genetically modified or manufactured with genetically modified materials. The manufacturer nor Medisca do not perform PCR analysis for the demonstration of GMO status of the materials.

Certificate of Origin: This is to certify that, to the best of our knowledge and belief, all of the bovine milk raw materials used in the manufacture of LACTOSE have originated solely from the United States of America. According to The Code of Federal Regulations of the USDA [9CFR94.18 (a)(1)]. The milk material used is classified as Category C "Tissues with no detectable infectivity".

BSE/TSE: Section 6.6 Milk and Milk Derivatives of the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 3) states: *"Milk derivatives manufactured according to the conditions below are unlikely to present any TSE risk and shall therefore be considered compliant with this note for guidance.*
1. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption, and
2. No other ruminant materials, with the exception of calf rennet, are used in the preparation of such derivates (e.g. pancreatic enzyme digests of casein)." LACTOSE meets the aforementioned conditions, and therefore, do not require a Certificate of Suitability. Although acceptable according to the guidance excerpt above, animal enzymes, including calf rennet, were not used in the manufacture.

Specified Risk Material Statement: It is certified to the best of our knowledge that the above-named product does not contain and is not derived from: (a) as regards to bovine animals: i.e. the skull excluding the mandible and including the brain and eyes, and the spinal cord of animals aged over 12 months; ii. the vertebral column excluding the vertebrae of the tail, the spinous and the transverse processes of the cervical, thoracic and lumbar vertebrae and the median sacral crest and wings of the sacrum, but including the dorsal root ganglia of animals aged over 30 months; and iii. the tonsils, the intestines form the duodenum to the rectum and the mesentery of animals of all ages. (b) as regards ovine and caprine animals: i. the skull including the brain and eyes, the tonsils, and the spinal cord of animals aged over 12 months or which have a permanent incisor erupted through the gum, and ii. the spleen and ileum of animals of all ages. (c) or mechanically separated meat obtained from bones of bovine, ovine or caprine animals; (d) the animals from which this animal by-product is derived, have not been slaughtered after stunning by means of gas injected into the cranial cavity or killed by the same method or slaughtered by laceration of the central nervous tissue by means of an elongated rod-shaped instrument introduced into the cranial cavity.

Adresse : 6090 Henri-Bourassa Ouest, Saint-Laurent, QC H4R 3A6 CAN
Sans Frais : 1.800.665.6334 | Télécopie : 514.338.1693
Site Web : www.medisca.com

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Latex is not used as a raw material component or as a material of construction of any equipment utilized to manufacture.

Lactose by definition is a sugar derived from milk. This disaccharide consists of one molecule of galactose and one molecule of glucose. Lactose does not contain sucrose.

With regards to allergens, the best of our knowledge the LACTOSE does not contain:

- Cereals containing gluten (i.e. wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and products thereof
- Crustaceans and products thereof
- Eggs and products thereof
- Fish and products thereof
- Peanuts and products thereof
- Soybeans and products thereof
- Nuts i.e. Almond (*Amygdalus communis L.*), Hazelnut (*Corylus avellana*), Walnut (*Juglans regia*), Cashew (*Anacardium occidentale*), Pecan nut (*Carya illinoiesis (Wangenh.) K. Koch*), Brazil nut (*Bertholletia excelsa*), Pistachio nut (*Pistacia vera*), Macadamia nut and Queensland nut (*Macadamia ternifolia*) and products thereof
- Celery and products thereof
- Mustard and products thereof
- Sesame seeds and products thereof
- Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/L expressed as SO2
- Lupin and products thereof
- Molluscs and products thereof
- Dyes

Please be advised that Medisca has not tested for the presence of the above stated allergens. Therefore, this statement is provided for informational purposes only, as instructed to Medisca by the manufacturer, and is not meant to be a guarantee of absence of the above stated allergens.

Please note that above statements issued are based on information provided by the manufacturer and that these statements are to the best of our knowledge accurate.

Salutations,
The MEDISCA Team

Henrietta Wetzler, B.Sc
Document Control Team Leader

MEDISCA®
YOUR TRUSTED PARTNER IN COMPOUNDING

Address : 661 Route 3, Unit C, Plattsburgh, New York 12901 USA
Toll Free : 1.800.932.1039 | Fax : 1.855.850.5855
Website : www.medisca.com

Methylcellulose USP

November 30, 2015

Dear valued customer,

As per the manufacturer and to the best of our knowledge, METHYLCELLULOSE, USP (1500 mPa.s) - lot 128026, 124243, 121967 are derived from petroleum, plant an inorganic sources. The manufacturing facilities are dedicated for that purpose and no other product lines are produced on the same production lines. The product is Kosher certified. Based on examination of the ingredients and sources, the product is free from known allergy stimulating food substances and has not been exposed to environments where they were present.

There are no raw materials used, including additives that have origin in:

- Buckwheat
- Peanuts or peanut products (butter, oil, flour)
- Tree nuts (almonds, pecans, walnuts, Brazil nuts, cashew, chestnuts, etc.)
- Plant derivates, including nuts and seeds (except for highly purified cellulose)
- Eggs or egg products (whites, yolks, meringue, mayonnaise, etc.)
- Fish (cod, flounder, salmon, trout, tuna, etc.)
- Shellfish (crustaceans and mollusks)
- Celery (root, leaves, stalk, not seeds)
- Dairy or dairy derivatives
- Cereals containing gluten
- Wheat or wheat products
- Corn or corn derivatives
- Soybean or soy products (soy derived vegetable protein, tofu, etc.)
- Sulfites (not added or expected to be formed, test method used has a detectable limit of 10 ppm)
- FD&C Yellow #5 and #6 or any artificial or natural colors
- Preservatives and antioxidants
- Umbelliferae (carrot or parsley family)
- Flavors/enhancers
- Nitrites/nitrates

Therefore based on our knowledge of the manufacturing process and the raw materials used to produce these products, there is no potential for the materials listed above to be present in these products.

Please be advised that Medisca has not tested for the presence of the above stated allergens. Therefore, this statement is provided for informational purposes only, as instructed to Medisca by the manufacturer, and is not meant to be a guarantee of absence of the above stated allergens.

Salutations
The MEDISCA Team

Alex Dombrovsky
Quality Assurance Specialist

Subject: RE: Zaditen Packaging Expiry Date
Date: Wednesday, August 29, 2018 at 1:03:59 PM Mountain Daylight Time
From: Puzzo Rebecca
To: Kevin A. Hildebrand, Alexandra Garven
CC: Kolendowicz Roxanne
Attachments: image001.png

Hello there Kevin,

Thank you for your reply. I just wanted to update you based on the expiration date. After investigating the materials needed for our operation. The Medisca filler we have on hand at the moment is 30NOV2019 so therefore that is the expiry date we need to use for the packaged drug. We are in the process of ordering more filler but in the mean time for this production run, I wanted to check with you to make sure that date was OK. For the future production runs we will use the 18 month expiration date. To update your team as well, we will be finishing the over encapsulating and bottling tomorrow and label the bottles next Tuesday. We will be good to ship the product by the end of next week.

Thank you,

-Rebecca

From: Kevin A. Hildebrand <hildebrk@ucalgary.ca>
Sent: Wednesday, August 29, 2018 12:23 AM
To: Puzzo Rebecca <puzzoreb@barl.ca>; Alexandra Garven <Alexandra.Garven@albertahealthservices.ca>
Cc: Salehi Salah <salehis@barl.ca>; Kianpour, Sussan <kianpour@barl.ca>; Kolendowicz Roxanne <kolendowr@barl.ca>
Subject: Re: Zaditen Packaging Expiry Date

Hi Rebecca,

Continue with the 18 months.

Kevin Hildebrand

From: Puzzo Rebecca <puzzoreb@barl.ca>
Date: Tuesday, August 28, 2018 at 1:44 PM
To: Alex Garven <Alexandra.Garven@albertahealthservices.ca>, Kevin Hildebrand <hildebrk@ucalgary.ca>
Cc: Salehi Salah <salehis@barl.ca>, "Kianpour, Sussan" <kianpour@barl.ca>, Kolendowicz Roxanne <kolendowr@barl.ca>
Subject: Zaditen Packaging Expiry Date

Hello there,

We have begun packaging and over encapsulation of the Zaditen. During this time it was discussed with our Quality Control Staff the expiry date of the drug. Our SOP's state that we assign an expiry date of maximum 12 months to drug that we are over encapsulating and bottling. As the drug expiration date is up to your team as this is packaged for your needs, it is your decision. Our QC staff just wanted you to be aware of our

recommendations and procedures beforehand. Do you want to continue with the 18 months as the drug expiration date and use 29 FEB 2020. Or use the recommended date of 12 months?

Let us know as soon as you can.

Thank you,

Rebecca Puzzo
Clinical Trial Coordinator
Bay Area Research Logistics
Tel: 905-527-1938 ext#58 Fax: 905-527-1196
puzzoreb@barl.ca www.bayarearesearchlogistics.com

Regulatory Information & Documents

> **Subject** – Regulatory Declarations – BSE safety

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is pharmaceutical grade, and in full compliance with all pharmaceutical regulatory statutes. Specifically, Capsugel fully complies with the following where applicable:

- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), which is published by the European Commission following Commission Directive 2003/63/EC, (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), Annex I, Part I, paragraph 3.2.2.4. Control of excipients.
  These Directives require that applicants for Marketing Authorisation must demonstrate that medicinal products are manufactured in accordance with the latest version of this Note for Guidance and compliance is demonstrated by the "Certificate of Suitability" issued to the manufacturer of the bovine gelatin by the European Directorate for the Quality of Medicines (EDQM).
- Regulation (EC) No 853/2004 of the European Parliament and of the Council laying down specific hygiene rules for food of animal origin.
- Regulation No 999/2001, amended by Regulation (EC) No 1923/2006, and as regards specified risk material, amended by Commission Regulation (EC) No 722/2007.

- United States Food and Drug Administration's September 1997 Guidance for Industry for "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA -regulated Products for Human Use".
- United States Food and Drug Administration - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 – "Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants - Proposed Rule" January 12, 2007.
- United States Food and Drug Administration - 21 CFR Parts 189 and 700 – "Use of Materials Derived From Cattle in Human Food and Cosmetics; and Recordkeeping Requirements for Human Food and Cosmetics Manufactured From, Processed With, or Otherwise Containing, Material From Cattle; Final Rule and Proposed Rule"

- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", Chapter 2, Article 7 and Article 10 "Specifications and Standards for Food or additives" revised and announced by No. 10 in MHLW notification on January 16, 2004.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of the MHLW issued on May 20, 2003 and the latest version by Notification No. 343 of MHLW, issued on July 01, 2009.

- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Colmar, FRANCE
10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Bornem, BELGIUM
Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

Greenwood, USA
535 North Emerald Road
SC-29646 Greenwood
T (888) 783 6361
F (888) 783 6360

Puebla, MEXICO
Paseo de los Tamarindos 60.
1er. piso.
Col. Bosques de las Lomas
05120 México, D.F. México
T (5255) 91715948-9, 91715831
F (01) 8001126000

Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

- Rousselot SAS R1-CEP 2000-027
- Rousselot SAS R1-CEP 2001-332
- PB Gelatins R1-CEP 2002-110
- PB Leiner R1-CEP 2004-022
- Gelita Group R1-CEP 2003-172
- Sterling Gelatin R1-CEP 2001-211
- Nitta Gelatin R1-CEP 2000-344
- Nitta Gelatin R1-CEP 2004-247
- Nitta Gelatin R1-CEP 2004-320
- Nitta Gelatin R1-CEP 2005-217

Capsugel continuously monitors all regulatory activities, please let us know if there are further questions or clarification needed.

For further information, please consult your customer service representative.

Last updated
August, 2012

Colmar, FRANCE
10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Bornem, BELGIUM
Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

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European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2000-027-Rev 02

Name of the substance:
GELATIN
Limed bone gelatin
India, Argentina, New Zealand and Australia origin

Name of holder:
ROUSSELOT
Kanaaldijk Noord 20-21
The Netherlands-5691 NM Son

Site(s) of production:
ROUSSELOT SAS
Chemin Moulins Premiers
France-84800 Isle-Sur-La-Sorgue

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2000-027-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- country(ies) of origin of source materials:	Argentina, India, New Zealand and Australia
- nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
- manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001, GMP and HACCP, and in accordance with the dossier submitted.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

afaq ISO 9001 Quality

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **22 June 2005** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 27 July 2012

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

ROUSSELOT, as holder of the certificate of suitability

R1-CEP 2000-027-Rev 02 for GELATIN

hereby authorises Amy Pharmaceutical Company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:
August 6, 2012

Véronique FABIEN-SOULE
Regulatory Affairs Director
ROUSSELOT
Kanaaldijk Noord 20-21
NL-5691 NM SON
P.O. Box 9 NL - 5690 AA SON
The Netherlands

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

afaq ISO 9001 Quality

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2001-332-Rev 02

Name of the substance:
GELATIN
Alkaline Hide Gelatin

Name of holder:
ROUSSELOT
Kanaaldijk Noord 20-21
The Netherlands-5691 NM Son

Site(s) of production:
ROUSSELOT ARGENTINA SA
Avda Gobernador Vergara 2532
Villa Tesei
Argentina-1688 Hurlingham

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2001-332-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- countries of origin of source materials:	Argentina, Brazil, Uruguay and Paraguay
- nature of animal tissues used in manufacture:	Bovine hide splits
- manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

afaq ISO 9001 Quality

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **28 June 2007** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 20 July 2012

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

ROUSSELOT, as holder of the certificate of suitability

R1-CEP 2001-332-Rev 02 for GELATIN

hereby authorises Any Pharmaceutical Company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

Véronique FABIEN-SOULE
Regulatory Affairs Director
ROUSSELOT
Kanaaldijk Noord 20-21
NL-5691 NM SON
P.O. Box 9 NL - 5690 AA SON
The Netherlands

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: July 23, 2012
Véronique Fabien-Soulé
Regulatory Affairs Director

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

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European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2002-110-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
PB GELATINS
Marius Duché Straat 260
Belgium-1800 Vilvoorde

Site(s) of production:
PB GELATINS GMBH
Grosse Drakenburgerstrasse 43
Germany-31582 Nienburg

PB GELATINS LTD
Treforest
United Kingdom-CF37 5SU Pontypridd

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2002-110-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– country (ies) of origin of source materials:	India
– nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
– manufacturing process:	Alkaline process

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **13 December 2007** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM & HealthCare

Strasbourg, 26 November 2007

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

PB Gelatins, as holder of the certificate of suitability

R1-CEP 2002-110-Rev 00 for GELATIN

hereby authorises any of its pharmaceutical customers
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*
Products containing gelatin supplied by PB Gelatins

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: 26.11.2007

Michel Van den Berghe
Sales Director

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the
Quality of Medicines & HealthCare

Certification of Substances Division

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certificate of suitability
No. R1-CEP 2004-022-Rev 00

Name of the substance:
GELATIN
Sodium Hydroxide Hide Gelatin

Name of holder:
PB LEINER ARGENTINA S.A.
Parque Industrial Sauce Viejo
Santo Tomé
Argentina-S 3017 Sauce Viejo

Site(s) of production:
PB LEINER ARGENTINA
Parque Industrial Sauce Viejo, Ruta 11 km 455
Santo Tomé
Argentina-S 3017 Sauce Viejo

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2004-022-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

— countries of origin of source materials:	Argentina, Paraguay and Uruguay
— nature of animal tissues used in manufacture:	Bovine hides
— manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP, and in accordance with the dossier submitted.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **16 June 2009** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 5 June 2009

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

PB Leiner Argentina S.A., as holder of the certificate of suitability

R1-CEP 2004-022-Rev 00 for GELATIN
ANY OF ITS PHARMACEUTICAL CUSTOMERS

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

PRODUCTS CONTAINING GELATIN SUPPLIED BY PB LEINER ARGENTINA SA

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: Marisa Santiago
Quality, Research & Applications Manager

October 6 , 2009

PB Leiner Argentina S.A.
MARISA SANTIAGO
QUALITY ASSURANCE
MANAGER

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2003-172-Rev 00

Name of the substance:
GELATIN
Alkaline Hide Gelatin

Name of holder:
GELITA GROUP
Uferstrasse 7
Germany-69412 Eberbach

Site(s) of production:
GELITA DO BRASIL — MARINGA PLANT
Rod. Maringa — Iguaraçu-Pr 317
Km 09 Gleba Ribeirao
Brazil-87001-970 Maringa, PR

GELITA DO BRASIL — ESTANCIA VELHA PLANT
2070, R. Campo Grande
Brazil-93600-000 Estancia Velha, RS

GELITA DO BRASIL - MOCOCA PLANT
Av. Tiradentes s/no.
Brazil-13733-400 Mococa, SP

GELITA DO BRASIL-COTIA PLANT
Rua Phillip Leiner 200
Km 28.3 Rodovia Raposo Tavares
Brazil-06714-285 Cotia, SP

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2003-172-REV 03

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- countries of origin of source materials: Argentina, Brazil and Uruguay
- nature of animal tissues used in manufacture: Bovine hides
- manufacturing process: Alkaline process

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **25 July 2008** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM & HealthCare

Strasbourg, 15 July 2008

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

GELITA Group , as holder of the certificate of suitability

R1-CEP 2003-172-Rev 00 for GELATIN

hereby authorises ..... any pharmaceutical company .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: July, 18, 2008 Bernhard Münzing
Manager New Business Projects / Product Marketing
GELITA Deutschland GmbH
Uferstraße 7
69412 Eberbach

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2001-211-Rev 01

Name of the substance:
GELATIN
Limed Bone Gelatin

Name of holder:
STERLING BIOTECH LIMITED
Division - Sterling Gelatin
ECP Road, Village Karakhadi
Taluka Padra
India-391 450 Vadodara, Gujarat

Site(s) of production:
STERLING BIOTECH LIMITED
Division - Sterling Gelatin
ECP Road, Village Karakhadi
Taluka Padra
India-391 450 Vadodara, Gujarat

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2001-211-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– country(ies) of origin of source materials:	India
– nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
– manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP standards, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **17 May 2007** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 10 November 2010

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

STERLING BIOTECH LIMITED, as holder of the certificate of suitability

R1-CEP 2001-211-Rev 01 for GELATIN

hereby authorises **Any Pharmaceutical Company**
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

Vikram C. Kale
General Manager (QC/QA)
Date: 01.12.2010

STERLING BIOTECH LIMITED
Division - Sterling Gelatin
ECP Road, Village: Karkhadi - 391450
Ta.: Padra, Dist. Vadodara, Gujarat, India.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability No. R1-CEP 2000-344-Rev 02

Name of the substance:
GELATIN
Limed Bone Gelatin

Name of holder:
NITTA GELATIN INDIA LTD.
Post Box n° 4262, 50/1002 SBT Avenue
Panampilly Nagar
India-682 036 Cochin, Kerala

Site(s) of production:
NITTA GELATIN INDIA LTD.
Gelatin Division, Post Box n° 3109
Kusumagiri, P.O. Kakkanad
India-682 030 Cochin, Kerala

NITTA GELATIN INDIA LTD.
Ossein Division
Kathikudam P.O. Koratty
India-680 308 Trissur, Kerala

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2000-344-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– country of origin of source materials:	India
– nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
– manufacturing process:	Alkaline process

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001, HACCP, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **5 June 2007** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 20 December 2010

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

NITTA GELATIN INDIA LTD., as holder of the certificate of suitability

R1-CEP 2000-344-Rev 02 for GELATIN

Any pharmaceutical company

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

HARD GELATIN CAPSULES

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:
13 JAN 2011

G. SUSEELAN
MANAGING DIRECTOR

NITTA GELATIN INDIA LIMITED COCHIN

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax. 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2004-247-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
NITTA GELATIN INC.
4-4-26 Sakuragawa 4 Chome
Japan-556-0022 Naniwa-Ku, Osaka

Site(s) of production:
NITTA GELATIN INC.
Osaka Plant
22 Futamata 2 Chome
Japan-581-0024 Yao-Shi, Osaka Prefecture

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2004-247-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- country(ies) of origin of source materials:	India
- nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
- manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001, and in accordance with the dossier submitted.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **13 May 2010** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 5 May 2010

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

Nitta Gelatin Inc., as holder of the certificate of suitability

R1-CEP 2004-247-Rev 00 for GELATIN

hereby authorises Any pharmaceutical Company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: Sep 25, 2010

for Masahiro Morimura
Department Manager, Quality Assurance Department
Nitta Gelatin Inc.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2004-320-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
NITTA GELATIN INC.
4-4-26 Sakuragawa 4 Chome
Japan-556-0022 Naniwa-Ku, Osaka

Site(s) of production:
NITTA GELATIN INC.
Osaka Plant
22 Futamata 2 Chome
Japan-581-0024 Yao-Shi, Osaka Prefecture

THAI BONES INDUSTRY CO LTD
Ayuthaya Plant
30 Moo 12 Tambol Utai, Amphur Utai
Thailand-13210 Ayuthaya

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2004-320-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- country(ies) of origin of source materials:	New Zealand
- nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
- manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **13 May 2010** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 5 May 2010

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

Nitta Gelatin Inc., as holder of the certificate of suitability

R1-CEP 2004-320-Rev 00 for GELATIN

hereby authorises Amy Pharmaceutical Company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*: Sep 25, 2010

for Masahiro Morimura
Department Manager, Quality Assurance Department
Nitta Gelatin Inc.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2005-217-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
NITTA GELATIN INC.
4-4-26, Sakuragawa
Japan-556-0022 Naniwa-Ku, Osaka

Site(s) of production:
THAI BONES INDUSTRY CO., LTD. (key intermediate)
Ayuthaya Plant
30 Moo 12 Tambol Utai, Amphur Utai
Thailand-13210 Ayuthaya

NITTA GELATIN INC. (final substance)
Osaka Plant
2-22, Futamata
Japan-581-0024 Yao-Shi, Osaka Prefecture

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2005-217-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– country(ies) of origin of source materials:	Argentina
– nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
– manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001, GMP, HACCP, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **30 March 2011** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 16 March 2011

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

Nitta Gelatin Inc., as holder of the certificate of suitability

R1-CEP 2005-217-Rev 00 for GELATIN

hereby authorises Any pharmaceutical company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

March 23, 2011 NITTA GELATIN INC. MANAGER/IKUO OKUMURA

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

PERK II 2018-09-25 Meeting notes

Date

25 Sep 2018

Attendees

- qiao.zhang@ucalgary.ca
- Dr. Hildebrand

Goals

- To clarify about unblinding process (Skype call)

Discussion items

	Item	Notes

1	Discuss options for unblinding process	• CRU unblinding service: price is not acceptable
		• BARL
		  • unblinding service: they will have the right permission in SM to support them to do unblinding. Needs to find out the price.
		  • BARL to add the drug content into their shipping info. Send the drug content together with the drugs to the sites. Then the site will only have access of the unblinded info of the drugs at their sites. The site staff who receives the drugs needs to be unblinded. SOP may be needed.
		• Study Manager updates: with cost and timeline influence.
		• Share the full drug list of 999 drug IDs and drug content with all sites: hard to manage and all sites will have access to all unblinded info.

2	No updates on SM	• No updates on Study Manager about the unblinding info access to site pharmacy, stick to the existing plan
3	Timeline update	• EDC is about to be ready to go live • needs user role definition • SM is during deployment phase

Action items

- [ ]

PERK II Study Manager Drug Management Requirements

Document status	**FINAL**
Document owner	qiao.zhang@ucalgary.ca
Study PI	Dr. Kevin Hildebrand
Study PI Signature	PERK 2 SM Drug Management 20180511 Signed.pdf KETOCT17-PERKIIStudyManagerDrugManagementRequirements-150518-2000.pdf
Date	11 May 2018

Workflow

	Process	Details	Drug Location	Drug Status
1	Package	• generate a list of drug with content; • needs re-pack every 6 months: whenever needed, go to SM to start packing	• BARL	• Ready to pack • Packed (ready for shipment creation)
2	Create shipment	• initial number of drugs per shipment/site • field to enter shipment tracking number		
3	Receive shipment at site	• Drug shipment will be received by pharmacists at site. • Location of drug is pharmacy after shipment received.	• In-patient Pharmacy (site)	• Available
4	Stock Clinic	• Drug will be available for Rmd when the location is treatment room and status is available.	• Clinic (Site)	• Available (for Rmd)
5	Randomization			• Allocated
6	Re-allocation			• Allocated

Drug Info

	Item	Details	Notes
1	Drug Status	• Ready to pack • Packed • Available • Allocated • Quarantine • Permanently Unavailable • Expired • Disposed	• When drug is expired or Permanently Unavailable, site will dispose of the drug and change the status to Disposed. • Reason/Notes
2	Drug Location	• BARL • In-patient Pharmacy (site) • Clinic (Site)	
3	Drug bottle ID	• 5 digits	

	Drug content	• 2mg • 5mg • lactose placebo	
4	Expiration	• 18 months for both groups after packing	• 12 weeks before the expiration date of drug: triggers notification • 6 weeks before the expiration date of drug: auto update to "expired" status in SM
5	Temperature	• No need to track in Study Manager • Only monitor during shipment	

Numbers

	Item	Details
1	**Randomization threshold**	• Can't randomize if reaching the threshold • 1:1:1
2	Packaging	• default: 10, 10, 10 • changable • the 3 numbers can be different
3	Package Theshold	• to get the notification • 15: 15: 15
4	~~Shipment~~	• ~~default: 4:4:4~~ • ~~changeable~~
5	Re-shipment threshold per site (pharmacy threshold)	• default for all sites: 3:3:3 • To trigger a notification to central drug manager
6	Re-shipment goal	• Parmacists decide based on status showing in SM • No auto-calculation needed • Show a not of the site pharmacy current drug status.
7	Clinic threshold	• default for all sites: 2:2:2 • To trigger a notification
8	Stock clinic goal	• Coordinators decide based on status showing in SM • No auto-calculation needed • Always first balance the 3 groups
9	Drug bottles	• 999 Bottles total with 33% split of allocation among 3 groups

Questions

	Item	Details

1	Site and sub-sites	• 3 situations: Drug workflow_situations.jpg
		  • BARL ship to A, and can randomize at A
		  • A's In-patient Pharmacy receives shipment and stock clinic
		  • This scenario will happen the most.
		  • BARL ship to B, B has clinic C and D, can randomize at B, C, D
		  • B, C, D is seperate site in SM
		  • BARL creates shipment separately.
		  • **Site Pharmacist permission can be assigned to multiple sites.**
		  • BARL ship to E, E distributes to clinic F, G, H, can randomize at F, G, H
		  • F, G, H is seperate site in SM
		  • BARL creates shipment separately.
		  • **Site Pharmacist permission can be assigned to multiple sites.**
		• "Site"
		  • Each location which the randomization happens with the same randomization pool is considered as a site in EDC and SM

2	Re-shipment from one site to another site	• move drug IDs from CRU back end based on request
		  • move drug IDs to BARL, BARL creates a new shipment to the new site.
		  • move drug IDs from one site to another site (most likely)

3	Re-allocation	• if patient lost the drug and come back in a few days. • if drug has some issue after randomization and new drug is needed.

Case Report Forms Approval

Project Details	
Project Name	PERK 2
Project Platform(s)	DataFax

☑ ***The project instruments/data collection forms are all present.***
☑ ***Comments/changes requested during CRFs creation and validation have been addressed/corrected.***
☑ ***v1.5 of CRFs will be uploaded and used in iDataFax database.***

Project Approval (Project Lead)		
	Qiao Zhang	

Project Approval (PI)		
September 11, 2018	Dr. Kevin Hildebrand	

Project Acceptance (Director)		
	Andrea Hanley	
Date (dd/mmm/yyyy)	*Name, Role*	*Signature*

Item	Details
PERK 2 CRFs v1.1	CRFs v1.1 for PERK 2 (May 2018) to be uploaded and used in iDataFax database. Changes: • New form: “Medications” • New forms: “DASH, PCS, Oxford Elbow Score forms” for Interim Visit • Plate 22-25: barcodes (added new visits) • Plate 45: deleted.
PERK 2 CRFs v1.2	CRFs v1.2 for PERK 2 (May 2018) to be uploaded and used in iDataFax database. Changes: • Plate 4: moved the question “Data of injury” from plate 3 to 4 • Plate 16: re-ordered question options; Added plate number info to question options and re-formatted it.

	• Plate 19: revised the question for “Adverse Event”. • Plate 22-28: added to visit “Allocation” in the barcode.
PERK 2 CRFs V1.3	• Plate 41: added 2 options at the bottom.
PERK 2 CRFs V1.4	• Plate 006: remove "ft" from the height-unit • Plate 010: o remove check box in front of "Dislocation Type" o add "Not Applicable" check box below "Dislocation Type" o update to "closed", "open" option in the cell of "Not Applicable" • Plate 011: o remove check box in front of "Fracture" o add "Not Applicable" check box below "Fracture" • Plate 009, 032, 055 (Medication forms) o add "QID" before "PRN" as an option for frequency • Plate 018: add "-" signs for Pronation and Supination, both right and left (4 places) • Plate 019: remove "radiographics assessment" table • Plate 020 and 046: add one question "None" on the top • Plate 044: add "-" signs for Pronation and Supination, both right and left (4 places) • Plate 055: add "frequency" wording. • Plate 056, 057: New plate
PERK 2 CRFs V1.5	• Plate 001: add one inclusion criteria • Plate 015 and 034: add one field and re-order questions • Plate 009, 032 and 055: modify the number fields for dose

Any and all requests for change(s) requested after the date of approval below, and which fall outside the scope of the original contract, are considered new work and will be subject to a new service agreement and the costs associated.

CRU #042 PERK 2 Plate #001 Enrollment

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

SCREENING FORM *(page 1 of 2)*

INCLUSION CRITERIA (Must answer "**Yes**" to all below questions for study enrolment)		
1. Age 18 years or older and skeletally mature	☐ Yes	☐ No
2. 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)	☐ Yes	☐ No
3. Injury within 7 days or less	☐ Yes	☐ No
4. Operative treatment of the elbow fracture or dislocation	☐ Yes	☐ No
5. Subject has negative urine pregnancy test	☐ Yes	☐ No

EXCLUSION CRITERIA (Must answer "**No**" to all below questions for study enrolment)		
1. Pre-existing elbow contracture	☐ Yes	☐ No
2. Pre-existing osteoarthritis, inflammatory arthritis, gout or nonspecific monoarticular arthritis of the injured elbow	☐ Yes	☐ No
3. Inability to mobilize injured elbow within 21 days of injury	☐ Yes	☐ No
4. Concomitant musculoskeletal or visceral injuries that prevent post-operative elbow physiotherapy	☐ Yes	☐ No
5. Prior injury or surgery to the affected elbow	☐ Yes	☐ No
6. Total elbow replacement is the planned treatment for the injury	☐ Yes	☐ No
7. Current use of oral hypoglycemic medication	☐ Yes	☐ No
8. History of lactose intolerance	☐ Yes	☐ No
9. Severe renal impairment	☐ Yes	☐ No
10. Severe hepatic impairment	☐ Yes	☐ No
11. History of epilepsy	☐ Yes	☐ No
12. Male or female of reproductive age unwilling to use two effective methods of contraception	☐ Yes	☐ No
13. Female who is pregnant or nursing	☐ Yes	☐ No
14. Subject who has language or cognitive difficulties that prevents reliable completion of questionnaires	☐ Yes	☐ No

CRU #042 PERK 2 Plate #002 Enrollment

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

SCREENING FORM *(page 2 of 2)*

EXCLUSION CRITERIA (Continued) (Must answer "**No**" to all below questions for study enrolment)	
15. Unlikely to maintain follow up (no fixed address, plans to move out of town in the next year, states unable to comply with protocol, etc...)	☐ Yes ☐ No
16. Unwilling or unable to provide written informed consent for trial participation	☐ Yes ☐ No

Eligible for study?	☐ Yes ☐ No
Consented for study?	☐ Yes ☐ No

What is the reason for declining the study?
_____

Signature of investigator confirms data are complete : _____

e-signature
iDataFax use only

☐☐ : ☐☐ ☐☐☐☐ ☐☐ ☐☐ (hh : mm / yyyy / mm / dd)

CRU #042 PERK 2 Plate #004 Allocation

Subject ID: Centre Subject ID **Date:** y y y y m m d d

RANDOMIZATION

Randomization Details	
Date of Injury:	y y y y m m d d
Date of Randomization:	y y y y m m d d
Date of Surgery:	y y y y m m d d
Instructions Given:	☐ Yes ☐ No
Study bottle delivered to patient by:	_____
Date & Time of First Dose Administration:	y y y y m m d d @ h h : m m (24hr)
Number of supervised doses taken at trial site?	
Allocated Drug ID:	
Re-allocated Drug ID:	

Comments:
_____
_____
_____
_____
_____

CRU #042 PERK 2 Plate #005 Allocation

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID)

Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

PARTICIPANT DEMOGRAPHICS

Age:	☐☐
Gender:	☐ Female ☐ Male ☐ Unspecified
Hand Dominance:	☐ Right ☐ Left
Is this a Workers Compensation claim?	☐ Yes ☐ No

CRU #042 PERK 2 Plate #006 Allocation

Subject ID: ☐☐ ☐☐☐☐ *Centre* *Subject ID*

Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

PARTICIPANT BASELINE CHARACTERISTICS *(page 1 of 3)*

DEMOGRAPHICS	
Body Mass Index (BMI):	Height: ☐☐☐.☐ Unit: ☐ in ☐ cm
	Weight: ☐☐☐.☐ Unit: ☐ lbs ☐ kg
Do you consider yourself Latino/Hispanic?	☐ Yes ☐ No
Race: Please select one response based on your strongest ancestral influence	☐ American Indian or Alaska Native A person having origins in any of the original peoples of North and South (including Central America), and who maintains tribal affiliation or community attachment.
	☐ Asian A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
	☐ Black or African American A person having origins in any black racial groups of Africa
	☐ Native Hawaiian or other Pacific Islander A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	☐ White or Caucasian A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
	☐ More than one race Please specify all categories that apply: ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ White or Caucasian

CRU #042 PERK 2 Plate #007 Allocation

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

PARTICIPANT BASELINE CHARACTERISTICS *(page 2 of 3)*

OCCUPATIONAL HISTORY

Pre-Injury Level of Activity:

- ☐ Employed
  - If yes, please specify current role/job title: _____
  - Is this role active or sedentary: ☐ Active ☐ Sedentary
- ☐ Unemployed ☐ Student
- ☐ Disabled ☐ Retired

COMORBIDITIES:

☐ None

- ☐ Blind
- ☐ Visual Impairment
- ☐ Cancer
- ☐ Cardiovascular
  - ☐ CAD ☐ CHF ☐ Arrhythmia
  - ☐ PVD ☐ Other
- ☐ Diabetes
  - ☐ IDDM ☐ NIDDM
- ☐ Gastrointestinal
- ☐ Genitourinary
- ☐ Neurologic
- ☐ Osteoporosis
- ☐ Pulmonary
  - ☐ Asthma ☐ COPD ☐ Other
- ☐ Other: _____

Details:

_____

_____

CRU #042 PERK 2 Plate #008 Allocation

Subject ID: ☐☐ (Centre) ☐☐☐☐ (Subject ID) **Date:** ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

PARTICIPANT BASELINE CHARACTERISTICS *(page 3 of 3)*

SUBSTANCE USE	
ALCOHOL USE:	During the past 30 days, how many days did you have at least one drink of any alcoholic beverage such as beer, wine, a malt beverage or liquor? ☐☐ of 30 days
	During the past 30 days, on the day when you drank, about how many drinks did you drink on the average? ☐ 1 to 3 drinks ☐ 3 to 5 drinks ☐ More than 5 drinks at a time
	Considering all type of alcoholic beverages, how many times during the past 30 days did you have X (X=5 for men, X=4 for women) or more drinks on occasion? ☐☐ of 30 days

TOBACCO USE:	Current tobacco use? ☐ Yes ☐ No If **Yes**, number of uses of tobacco products per day: ☐☐☐
	Past tobacco use? ☐ Yes ☐ No If **Yes**, number of years tobacco products used: ☐☐
	If participant has quit, specify the year they quit: ☐☐☐☐

CRU #042 PERK 2 Plate #003 Allocation

Subject ID: [ ][ ] [ ][ ][ ][ ]
Centre *Subject ID*

Date: [ ][ ][ ][ ] [ ][ ] [ ][ ]
yyyy *mm* *dd*

INJURY INFORMATION

Side of injury:	☐ Right ☐ Left
Surgeon:	Dr. _____

Mechanism of Injury:	☐ Motor vehicle traffic collision (driver/passenger) ☐ Motor vehicle traffic collision (pedestrian) ☐ Motorcycle collision ☐ Ground level fall ☐ Fall from a height ☐ Direct trauma (blunt) ☐ Sport: _____ ☐ Other: _____

Concurrent Injuries:	☐ Yes ☐ No

If yes, please provide details:

_____

_____

CRU #042 PERK 2 Plate #010 Allocation

Subject ID: Centre Subject ID **Date:** y y y y m m d d

INJURY CLASSIFICATION *(page 1 of 4)*

Pre-operative Radiographs:	Date taken: y y y y m m d d ☐ AP ☐ Lateral ☐ Oblique If not obtained pre-operatively, please explain why: _____ _____

TYPE OF INJURY

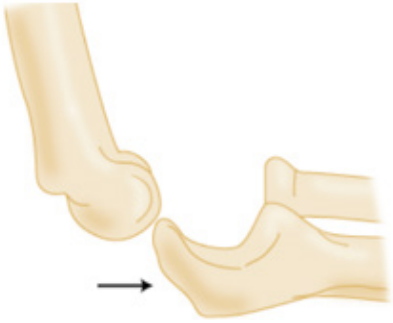
Dislocation Type:
(select all that apply)

☐ Not Applicable

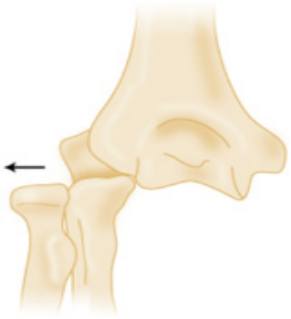
☐ Open

☐ Closed

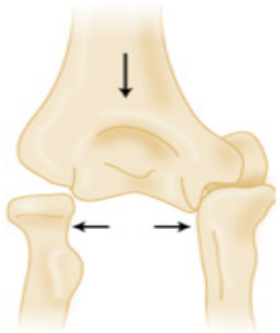
☐ Anterior



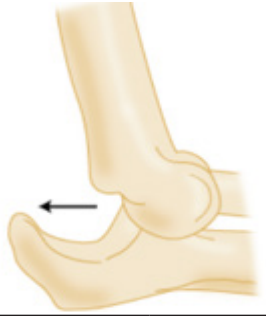
☐ Lateral



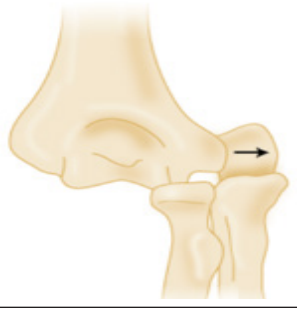
☐ Divergent



☐ Posterior



☐ Medial



INJURY CLASSIFICATION *(page 2 of 4)*

TYPE OF INJURY (Continued)	
Fracture ☐ Not Applicable	☐ Closed
	☐ Open **Gustilo Classification** ☐ I - Low energy, wound less than 1 cm ☐ II - Wound greater than 1 cm with moderate soft tissue damage ☐ IIIA - Adequate soft tissue covers high energy wound greater than 1 cm with extensive soft tissue damage ☐ IIIB - Inadequate soft tissue covers high energy wound greater than 1 cm with extensive soft tissue damage

INJURY CLASSIFICATION *(page 3 of 4)*

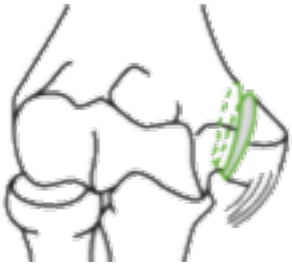
FRACTURE CLASSIFICATION (AO CLASSIFICATION)

DISTAL HUMERUS (TYPE 13)

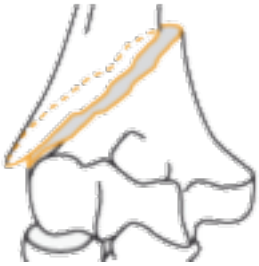
☐ Not Applicable

Extra-Articular:

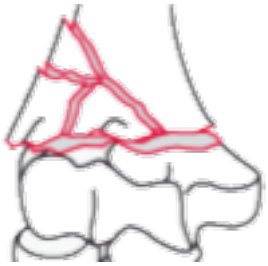
☐ 13-A1: Avulsion



☐ 13-A2: Simple



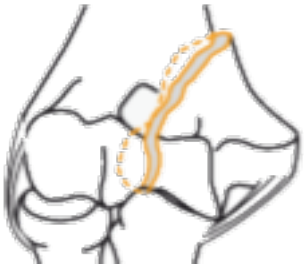
☐ 13-A3: Multi-fragmentary



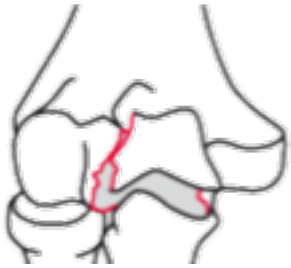
Partial Articular:

☐ 13-B1: Lateral sagittal

☐ 13-B2: Medial sagittal



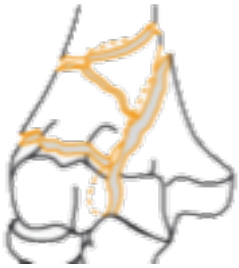
☐ 13-B3: Frontal



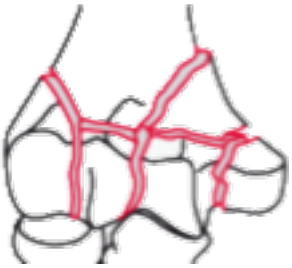
Complete Articular:

☐ 13-C1: Simple

☐ 13-C2: Metaphyseal comminution



☐ 13-C3: Multi-fragmentary



CRU #042 PERK 2 Plate #013 Allocation

Subject ID: Centre Subject ID **Date:** yyyy mm dd

INJURY CLASSIFICATION *(page 4 of 4)*

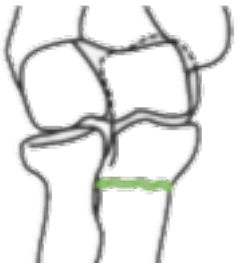
FRACTURE CLASSIFICATION (AO CLASSIFICATION)

PROXIMAL FOREARM (TYPE 21)

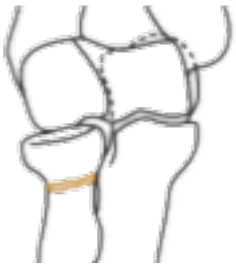
☐ Not Applicable

Extra-Articular:

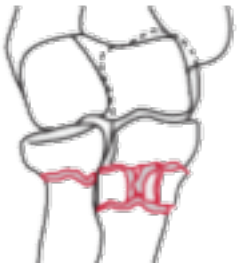
☐ 21-A1: Ulna



☐ 21-A2: Radius

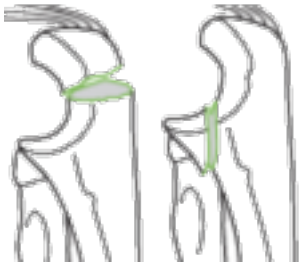


☐ 21-A3: Both Bones

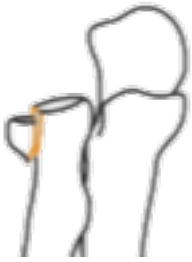


Articular, One bone:

☐ 21-B1: Isolated ulna



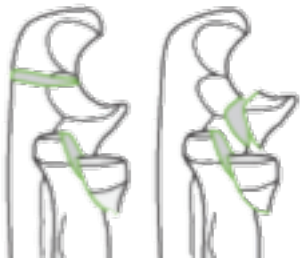
☐ 21-B2: Isolated radius



☐ 21-B3: One articular, other extra-articular

Articular, Both Bones:

☐ 21-C1: Simple



☐ 21-C2: One simple, other multi-fragmentary

☐ 21-C3: Multi-fragmentary

CRU #042 PERK 2 Plate #014 Allocation

Subject ID: Centre Subject ID **Date:** yyyy mm dd

OPERATIVE REPORT *(page 1 of 2)*

Date of Surgery:	yyyy mm dd
Pre-Operative Antibiotics:	☐ None ☐ Cefazolin 2 gram ☐ Other: _____

Type of Anesthesia:	☐ General ☐ Regional Block ☐ Other: _____
Surgical Procedure:	☐ Contracture release elbow
	☐ Excision proximal radius
	☐ Irrigation and debridement of elbow
	☐ Lateral collateral ligament repair or reconstruction
	☐ Medial collateral ligament repair or reconstruction
	☐ ORIF distal humerus
	☐ ORIF proximal radius
	☐ ORIF proximal ulna
	☐ Removal hardware elbow
	☐ Replacement proximal radius
	☐ Ulnar nerve exploration or transposition
	☐ Other: _____
Tourniquet Applied:	☐ Yes ☐ No
Tourniquet Time:	hh : mm
Procedure Time (skin to skin):	hh : mm

CRU #042 PERK 2 Plate #015 Allocation

Subject ID: Centre Subject ID **Date:** y y y y m m d d

OPERATIVE REPORT *(page 2 of 2)*

Post-Operative Antibiotics:	☐ Cefazolin 1 gram TID x 1 day ☐ Other: _____
Immediate Post-Operative Complications:	☐ None
	☐ Vascular
	☐ Systemic ☐ Cardiac ☐ Pulmonary ☐ Other:_____
	☐ Intra-operative fracture
	☐ Implant failure
	☐ Failure to obtain or maintain reduction
	☐ Neurologic
	☐ Other: _____
If any of the above are present, please provide details: _____	

Date of Admission:	y y y y m m d d
Date of Discharge:	y y y y m m d d
Days in Hospital:	

CRU #042 PERK 2 Plate #022

☐ Allocation ☐ Wk 2 ☐ Wk 6
☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ *Centre* *Subject ID*

Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

DASH *(page 1 of 4)*

PLEASE RATE YOUR ABILITY TO DO THE FOLLOWING ACTIVITIES IN THE LAST WEEK BY SELECTING THE APPROPRIATE RESPONSE.					
	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. Open a tight or new jar.	☐	☐	☐	☐	☐
2. Write.	☐	☐	☐	☐	☐
3. Turn a key.	☐	☐	☐	☐	☐
4. Prepare a meal.	☐	☐	☐	☐	☐
5. Push open a heavy door.	☐	☐	☐	☐	☐
6. Place an object on a shelf above your head.	☐	☐	☐	☐	☐
7. Do heavy household chores (e.g., wash walls, wash floors).	☐	☐	☐	☐	☐
8. Garden or do yard work.	☐	☐	☐	☐	☐
9. Make a bed.	☐	☐	☐	☐	☐
10. Carry a shopping bag or briefcase.	☐	☐	☐	☐	☐
11. Carry a heavy object (over 10 lbs).	☐	☐	☐	☐	☐
12. Change a lightbulb overhead.	☐	☐	☐	☐	☐
13. Wash or blow dry your hair.	☐	☐	☐	☐	☐
14. Wash your back.	☐	☐	☐	☐	☐
15. Put on a pullover sweater.	☐	☐	☐	☐	☐
16. Use a knife to cut food.	☐	☐	☐	☐	☐
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	☐	☐	☐	☐	☐
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #023

☐ Allocation ☐ Wk 2 ☐ Wk 6
☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID)

Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

DASH *(page 2 of 4)*

PLEASE RATE YOUR ABILITY TO DO THE FOLLOWING ACTIVITIES IN THE LAST WEEK BY SELECTING THE APPROPRIATE RESPONSE.					
	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	☐	☐	☐	☐	☐
20. Manage transportation needs (getting from one place to another).	☐	☐	☐	☐	☐
21. Sexual activities.	☐	☐	☐	☐	☐

	Not At All	Slightly	Moderately	Quite A Bit	Extremely
22. During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	☐	☐	☐	☐	☐

	Not Limited At All	Slightly Limited	Moderately Limited	Very Limited	Unable
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	☐	☐	☐	☐	☐

PLEASE RATE THE SEVERITY OF THE FOLLOWING SYMPTOMS IN THE LAST WEEK.					
	None	Mild	Moderate	Severe	Extreme
24. Arm, shoulder or hand pain.	☐	☐	☐	☐	☐
25. Arm, shoulder or hand pain when you performed any specific activity.	☐	☐	☐	☐	☐
26. Tingling (pins and needles) in your arm, shoulder or hand.	☐	☐	☐	☐	☐
27. Weakness in your arm, shoulder or hand.	☐	☐	☐	☐	☐
28. Stiffness in your arm, shoulder or hand.	☐	☐	☐	☐	☐

DASH *(page 3 of 4)*

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	So Much Difficulty That I Can't Sleep
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand?	☐	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem.	☐	☐	☐	☐	☐

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is: _____

☐ I do not work. (You may skip this section)

PLEASE SELECT THE BEST RESPONSE THAT DESCRIBES YOUR PHYSICAL ABILITY IN THE PAST WEEK. DID YOU HAVE ANY DIFFICULTY:

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. using your usual technique for your work?	☐	☐	☐	☐	☐
2. doing your usual work because of arm, shoulder or hand pain?	☐	☐	☐	☐	☐
3. doing your work as well as you would like?	☐	☐	☐	☐	☐
4. spending your usual amount of time doing your work?	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #025

☐ Allocation ☐ Wk 2 ☐ Wk 6
☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

DASH *(page 4 of 4)*

SPORT/PERFORMING ARTS MODULE (OPTIONAL)
The following questions relate to the impact of your arm, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.
Please indicate the sport or instrument which is most important to you: _____ ☐ I do not play a sport or an instrument. (You may skip this section.)

PLEASE SELECT THE BEST RESPONSE THAT DESCRIBES YOUR PHYSICAL ABILITY IN THE PAST WEEK. DID YOU HAVE ANY DIFFICULTY:

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. using your usual technique for playing your instrument or sport?	☐	☐	☐	☐	☐
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	☐	☐	☐	☐	☐
3. playing your musical instrument or sport as well as you would like?	☐	☐	☐	☐	☐
4. spending your usual amount of time practising or playing your instrument or sport?	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #026

☐ Allocation ☐ Wk 2 ☐ Wk 6
☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ *Centre* *Subject ID*

Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

PCS

When I'm in pain...					
	Not At All	To A Slight Degree	To A Moderate Degree	To A Great Degree	All The Time
1. I worry all the time about whether the pain will end.	☐	☐	☐	☐	☐
2. I feel I can't go on.	☐	☐	☐	☐	☐
3. It's terrible and I think it's never going to get any better.	☐	☐	☐	☐	☐
4. It's awful and I feel that it overwhelms me.	☐	☐	☐	☐	☐
5.I feel I can't stand it anymore.	☐	☐	☐	☐	☐
6. I become afraid that the pain will get worse.	☐	☐	☐	☐	☐
7. I keep thinking of other painful events.	☐	☐	☐	☐	☐
8. I anxiously want the pain to go away.	☐	☐	☐	☐	☐
9. I can't seem to keep it out of my mind.	☐	☐	☐	☐	☐
10. I keep thinking about how much it hurts.	☐	☐	☐	☐	☐
11. I keep thinking about how badly I want the pain to stop.	☐	☐	☐	☐	☐
12. There's nothing I can do to reduce the intensity of the pain.	☐	☐	☐	☐	☐
13. I wonder whether something serious may happen.	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #027

☐ Allocation ☐ Wk 2 ☐ Wk 6 ☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID)

Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

OXFORD ELBOW SCORE (OES) *(page 1 of 2)*

PLEASE SELECT THE BEST RESPONSE FOR THE FOLLOWING QUESTIONS

1. During the past 4 weeks...

Have you had difficulty lifting things in your home, such as putting out the rubbish, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

2. During the past 4 weeks...

Have you had difficulty carrying bags of shopping, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

3. During the past 4 weeks...

Have you had any difficulty washing yourself all over, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

4. During the past 4 weeks...

Have you had any difficulty dressing yourself, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

5. During the past 4 weeks...

Have you felt that your elbow problem is “controlling your life”?

☐ No, not at all ☐ Occasionally ☐ Some days ☐ Most days ☐ Every day

6. During the past 4 weeks...

How much has your elbow problem been “on your mind”?

☐ Not at all ☐ A little of the time ☐ Some of the time ☐ Most of the time ☐ All of the time

CRU #042 PERK 2 Plate #028

☐ Allocation ☐ Wk 2 ☐ Wk 6 ☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

OXFORD ELBOW SCORE (OES) *(page 2 of 2)*

7. During the past 4 weeks...

Have you been troubled by pain from your elbow in bed at night?

☐ Not at all ☐ 1 or 2 nights ☐ Some nights ☐ Most nights ☐ Every night

8. During the past 4 weeks...

How often has your elbow pain interfered with your sleeping?

☐ Not at all ☐ Occasionally ☐ Some of the time ☐ Most of the time ☐ All of the time

9. During the past 4 weeks...

How much has your elbow problem interfered with your usual work or everyday activities?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Greatly ☐ Totally

10. During the past 4 weeks...

Has your elbow problem limited your ability to take part in leisure activities that you enjoy doing?

☐ No, not at all ☐ Occasionally ☐ Some of the time ☐ Most of the time ☐ All of the time

11. During the past 4 weeks...

How would you describe the worst pain you have from your elbow?

☐ No pain ☐ Mild pain ☐ Moderate pain ☐ Severe pain ☐ Unbearable

12. During the past 4 weeks...

How would you describe the pain you usually have from your elbow?

☐ No pain ☐ Mild pain ☐ Moderate pain ☐ Severe pain ☐ Unbearable

CRU #042 PERK 2 Plate #009

Pg#: ____

Subject ID: __ __ (Centre) __ __ __ __ (Subject ID)

Date: __ __ __ __ (y y y y) __ __ (m m) __ __ (d d)

BASELINE MEDICATIONS

MEDICATION(S)

☐ None

•Please list all medications with the dose and frequency

•Any and all vitamins, minerals, and/or supplements should be included as well

Medication Name: ______________________	Dose: __ __ __ __ __ . __ __ Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt
Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic

Medication Name: ______________________	Dose: __ __ __ __ __ . __ __ Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt
Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic

Medication Name: ______________________	Dose: __ __ __ __ __ . __ __ Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt
Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic

CRU #042 PERK 2 Plate #032

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

DISCHARGE MEDICATIONS

DISCHARGE MEDICATION(S)

Prescribed any discharge medications? ☐ Yes ☐ No

•Please list all medications with the dose and frequency

•Any and all vitamins, minerals, and/or supplements should be included as well

Medication Name: _____

Dose: .

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic
Start Date:	yyyy mm dd

Medication Name: _____

Dose: .

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic
Start Date:	yyyy mm dd

☐ Wk 1 ☐ Wk 3 ☐ Wk 4 ☐ Wk 5

CRU #042 PERK 2 Plate #029

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

PHONE CONTACT *(page 1 of 2)*

☐ Participant Unavailable - Message Left On:

1) ☐☐☐☐ ☐☐ ☐☐ @ ☐☐ : ☐☐ (24hr) (yyyy / mm / dd / hh / mm)

2) ☐☐☐☐ ☐☐ ☐☐ @ ☐☐ : ☐☐ (24hr) (yyyy / mm / dd / hh / mm)

3) ☐☐☐☐ ☐☐ ☐☐ @ ☐☐ : ☐☐ (24hr) (yyyy / mm / dd / hh / mm)

Concomitant Medications	☐ Yes, change to medications (see comments) ☐ No, changes to medications
Adverse Events	☐ New AE/SAE reported (see comments) *(complete Adverse Events and Serious Adverse Events forms)* ☐ Update to previously reported AEs/SAEs ☐ No AEs/SAEs reported
Review Study Medication	☐ Dosage Reviewed ☐ Instructions for use reviewed
Returned to Work	☐ Yes When: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) ☐ No ☐ Student ☐ Retired ☐ Unemployed ☐ Disabled

PHONE CONTACT *(page 2 of 2)*

Reminder of Next Appointment	☐ Yes ☐ No Visit Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) Visit Time: ☐☐ : ☐☐ (24hr) (h h / m m)

Comments

CRU #042 PERK 2 Plate #016

☐ Wk 2 ☐ Wk 6 ☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

VISIT ASSESSMENT *(page 1 of 3)*

Side of Injury	☐ Right ☐ Left
Radiographs of affected limb	☐ AP ☐ Lateral ☐ OBL
Questionnaires	☐ DASH ☐ PCS ☐ OES
Weight	☐☐☐.☐ Unit: ☐ lbs ☐ kg

SINCE THE LAST VISIT
Has the patient had any of the following since the last study visit (please check all that apply and provide details):
☐ Clinic visit
☐ New onset of a medical condition(s)
☐ New medication(s) ***Complete Information on Medications Form (Plate 55)***
☐ Post-operative complications ***Complete Post-Operative Orthopaedic Complications forms (Plate 20 and 21)***
☐ Radiographs
☐ Re-operations and/or additional procedures ***Complete Re-Operative Report forms (Plate 33 and 34)***
☐ Other
☐ Not applicable
Details:
_____
_____

VISIT ASSESSMENT *(page 2 of 3)*

SINCE THE LAST VISIT (Continued)			
Has the participant had:			
Physiotherapy:	☐ Yes	☐ No	
	Number of appointments? ☐☐		
Home Therapy:	☐ Yes	☐ No	
	What is the frequency? ☐ (days per week)		
*Stretching splint:	☐ Yes	☐ No	
	How long? ☐☐ (weeks)		
Hinged Elbow Brace:	☐ Yes	☐ No	
	How long? ☐☐ (weeks)		
NSAID use:	☐ Yes	☐ No	
	Which one? _____		
Pain medication:	☐ Yes	☐ No	
	Which one? _____		
	For how long? ☐☐ (weeks)		
Returned to work?	☐ Yes	☐ No	
	When: ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)		
	☐ Student	☐ Retired	☐ Unemployed ☐ Disabled

CRU #042 PERK 2 Plate #018

☐ Wk 2 ☐ Wk 6 ☐ Wk 12 ☐ Wk 24 ☐ Wk 52

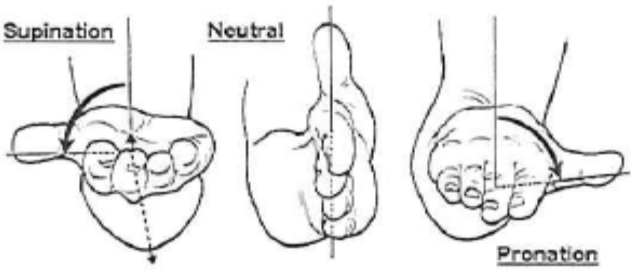
Subject ID: ☐☐ ☐☐☐☐ *Centre* *Subject ID*

Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

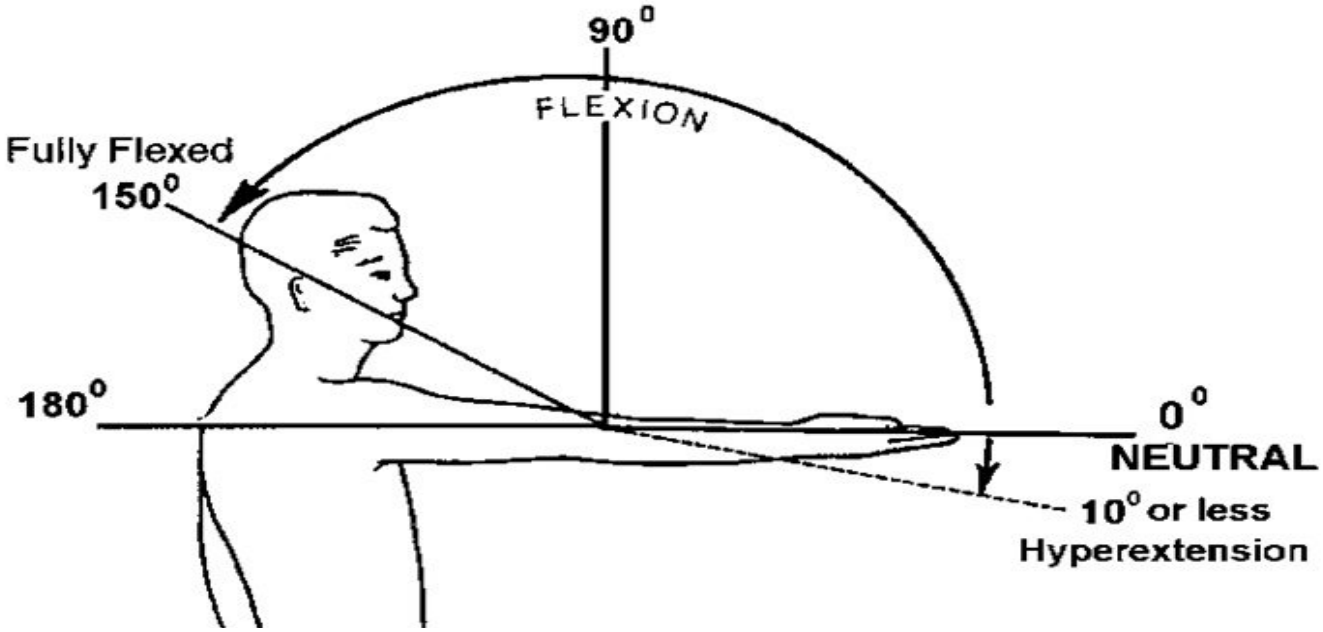
VISIT ASSESSMENT *(page 3 of 3)*

PHYSICAL ASSESSMENT

RIGHT	ACTIVE RANGES OF MOTION (º)	LEFT
(-) ☐ ☐☐☐ deg(º)	Pronation of Forearm	(-) ☐ ☐☐☐ deg(º)
(-) ☐ ☐☐☐ deg(º)	Supination of Forearm	(-) ☐ ☐☐☐ deg(º)



☐☐☐ deg(º)	Elbow Flexion	☐☐☐ deg(º)
(-) ☐ ☐☐☐ deg(º)	Elbow Extension (hyperextension is indicated by a negative sign)	(-) ☐ ☐☐☐ deg(º)



12W obtain ROM for both injured and uninjured sides

CRU #042 PERK 2 Plate #019

☐ Wk 2 ☐ Wk 6

Subject ID: ☐☐ ☐☐☐☐ (*Centre* / *Subject ID*)

Date: ☐☐☐☐ ☐☐ ☐☐ (*yyyy* / *mm* / *dd*)

PILL COUNT (AT 2 & 6 WEEKS FOLLOW-UPS ONLY)

Pill bottle returned?	☐ Yes ☐ No
Counted by research staff?	☐ Yes ☐ No Number of capsules: _____ Capsules intact? ☐ Yes ☐ No
Adverse Event(s)?	☐ Yes *(please fill out AE or SAE form, plate 35 or 37-38)* ☐ No

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID) **Date:** ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

POST-OPERATIVE ORTHOPAEDIC COMPLICATIONS *(page 1 of 2)*

Post-operative complications:	☐ None
PLEASE COMPLETE THE APPROPRIATE SECTION(S)	
Soft Tissue/Wound Healing:	☐ Skin Slough ☐ Hematoma ☐ Wound necrosis ☐ Drainage ☐ Wound dehiscence ☐ Other: _____ ☐ Protrusion of bone through skin
Infection:	☐ Superficial wound infection ☐ Deep wound infection Swab taken: ☐ Yes ☐ No If swab, culture is: ☐ Negative ☐ Positive If positive, specify the bacteria: _____
Bone Abnormality:	☐ Heterotopic Ossification ☐ Collateral ligaments ☐ Intra-muscular ☐ Non-union ☐ Mal-union ☐ Other:_____
Implant Failure or Painful Implant:	☐ Loosening ☐ Local Irritation ☐ Breakage ☐ Other:_____
Other Complications:	_____
First Report of This Event:	☐ Yes ☐ No If no, please record the date of onset: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)
Details:	_____ _____ _____ _____

POST-OPERATIVE ORTHOPAEDIC COMPLICATIONS *(page 2 of 2)*

PLEASE COMPLETE THE APPROPRIATE SECTION(S)	
Treatment, If Any	
Antibiotics Given:	☐ Yes ☐ No Details: _____ _____
Surgical Intervention:	☐ Yes (complete Re-Operative Report forms) ☐ No
Outcome:	☐ Still undergoing treatment ☐ Recovered Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd) ☐ Recovered with sequelae Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

Comments:

_____

_____

_____

_____

_____

Subject ID: ☐☐ (Centre) ☐☐☐☐ (Subject ID) **Date:** ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

PARTICIPANT WITHDRAWAL

Date of withdrawal from study or study discontinuation:	Date: ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)
Reason for withdrawal or study discontinuation:	☐ Death ☐ Unable to locate ☐ Participant withdrew consent ☐ Randomized participant without consent ☐ Other reason: _____

Comments:

_____

_____

_____

Signature of investigator confirms the completion of subject's CRFs: _____

e-signature
iDataFax use only

☐☐ (hh) : ☐☐ (mm) ☐☐☐☐ (yyyy) ☐☐ (mm) ☐☐ (dd)

MEDICATIONS

Has there been a change in participant's medications? ☐ Yes ☐ No

- *Please list all medications with the dose and frequency*
- *Any and all vitamins, minerals, and/or supplements should be included as well*

Medication Name: _____

Dose: .

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic
Start Date:	y y y y m m d d
End Date:	y y y y m m d d

Medication Name: _____

Dose: .

Units: ☐ mg ☐ mcg ☐ mL ☐ cc ☐ IU ☐ mEq ☐ oz ☐ tsp ☐ tbl ☐ gtt

Frequency:	☐ OD ☐ BID ☐ TID ☐ QID ☐ PRN
Routes of Administration:	☐ Oral (PO) ☐ Intramuscular ☐ Intravenous ☐ Subcutaneous ☐ Topical ☐ Ophthalmic
Start Date:	y y y y m m d d
End Date:	y y y y m m d d

Subject ID: Centre Subject ID **Date:** yyyy mm dd

VISIT ASSESSMENT *(page 1 of 3)* - INTERIM

Side of Injury	☐ Right	☐ Left	
Radiographs of affected limb	☐ AP	☐ Lateral	☐ OBL
Questionnaires	☐ DASH	☐ PCS	☐ OES
Weight	☐☐☐.☐	Unit: ☐ lbs	☐ kg

SINCE THE LAST VISIT
Has the patient had any of the following since the last study visit (please check all that apply and provide details):
☐ Clinic visit
☐ New onset of a medical condition(s)
☐ New medication(s) ***Complete Information on Medications Form (Plate 55)***
☐ Post-operative complications ***Complete Post-Operative Orthopaedic Complications forms (Plate 46 and 47)***
☐ Radiographs
☐ Re-operations and/or additional procedures ***Complete Re-Operative Report forms (Plate 33 and 34)***
☐ Other
☐ Not applicable
Details:
_____
_____

CRU #042 PERK 2 Plate #043

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

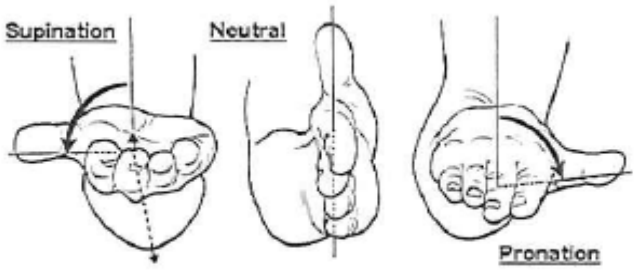
VISIT ASSESSMENT *(page 2 of 3)* - INTERIM

SINCE THE LAST VISIT (Continued)				
Has the participant had:				
Physiotherapy:	☐ Yes	☐ No		
	Number of appointments?			
Home Therapy:	☐ Yes	☐ No		
	What is the frequency?		(days per week)	
*Stretching splint:	☐ Yes	☐ No		
	How long?		(weeks)	
Hinged Elbow Brace:	☐ Yes	☐ No		
	How long?		(weeks)	
NSAID use:	☐ Yes	☐ No		
	Which one? _____			
Pain medication:	☐ Yes	☐ No		
	Which one? _____			
	For how long?		(weeks)	
Returned to work?	☐ Yes	☐ No		
	When: yyyy mm dd			
	☐ Student	☐ Retired	☐ Unemployed	☐ Disabled

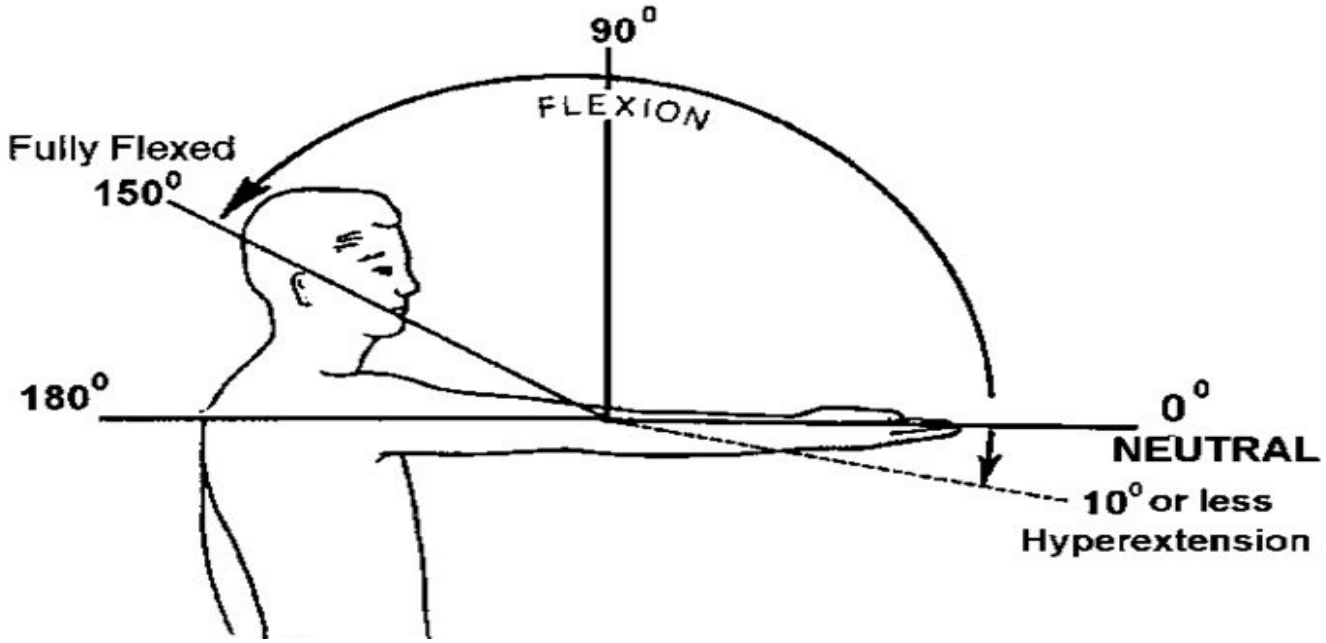
VISIT ASSESSMENT *(page 3 of 3)* - INTERIM

PHYSICAL ASSESSMENT

RIGHT	ACTIVE RANGES OF MOTION (º)	LEFT
(-) deg(º)	Pronation of Forearm	(-) deg(º)
(-) deg(º)	Supination of Forearm	(-) deg(º)



deg(º)	Elbow Flexion	deg(º)
(-) deg(º)	Elbow Extension (hyperextension is indicated by a negative sign)	(-) deg(º)



12W obtain ROM for both injured and uninjured sides

CRU #042 PERK 2 Plate #046

Pg#: ☐☐☐

Subject ID: ☐☐ ☐☐☐☐ (Centre / Subject ID)

Date: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)

POST-OPERATIVE ORTHOPAEDIC COMPLICATIONS *(page 1 of 2)* - INTERIM

Post-operative complications:	☐ None
PLEASE COMPLETE THE APPROPRIATE SECTION(S)	
Soft Tissue/Wound Healing:	☐ Skin Slough ☐ Hematoma ☐ Wound necrosis ☐ Drainage ☐ Wound dehiscence ☐ Other: _____ ☐ Protrusion of bone through skin
Infection:	☐ Superficial wound infection ☐ Deep wound infection Swab taken: ☐ Yes ☐ No If swab, culture is: ☐ Negative ☐ Positive If positive, specify the bacteria: _____
Bone Abnormality:	☐ Heterotopic Ossification ☐ Collateral ligaments ☐ Intra-muscular ☐ Non-union ☐ Mal-union ☐ Other:_____
Implant Failure or Painful Implant:	☐ Loosening ☐ Local Irritation ☐ Breakage ☐ Other:_____
Other Complications:	_____
First Report of This Event:	☐ Yes ☐ No If no, please record the date of onset: ☐☐☐☐ ☐☐ ☐☐ (yyyy / mm / dd)
Details:	_____ _____ _____ _____

CRU #042 PERK 2 Plate #047

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

POST-OPERATIVE ORTHOPAEDIC COMPLICATIONS *(page 2 of 2)* - INTERIM

PLEASE COMPLETE THE APPROPRIATE SECTION(S)	
Treatment, If Any	
Antibiotics Given:	☐ Yes ☐ No Details:
Surgical Intervention:	☐ Yes (complete Re-Operative Report forms) ☐ No
Outcome:	☐ Still undergoing treatment ☐ Recovered Date: yyyy mm dd ☐ Recovered with sequelae Date: yyyy mm dd

Comments:

DASH *(page 1 of 4)* - INTERIM

PLEASE RATE YOUR ABILITY TO DO THE FOLLOWING ACTIVITIES IN THE LAST WEEK BY SELECTING THE APPROPRIATE RESPONSE.					
	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. Open a tight or new jar.	☐	☐	☐	☐	☐
2. Write.	☐	☐	☐	☐	☐
3. Turn a key.	☐	☐	☐	☐	☐
4. Prepare a meal.	☐	☐	☐	☐	☐
5. Push open a heavy door.	☐	☐	☐	☐	☐
6. Place an object on a shelf above your head.	☐	☐	☐	☐	☐
7. Do heavy household chores (e.g., wash walls, wash floors).	☐	☐	☐	☐	☐
8. Garden or do yard work.	☐	☐	☐	☐	☐
9. Make a bed.	☐	☐	☐	☐	☐
10. Carry a shopping bag or briefcase.	☐	☐	☐	☐	☐
11. Carry a heavy object (over 10 lbs).	☐	☐	☐	☐	☐
12. Change a lightbulb overhead.	☐	☐	☐	☐	☐
13. Wash or blow dry your hair.	☐	☐	☐	☐	☐
14. Wash your back.	☐	☐	☐	☐	☐
15. Put on a pullover sweater.	☐	☐	☐	☐	☐
16. Use a knife to cut food.	☐	☐	☐	☐	☐
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	☐	☐	☐	☐	☐
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	☐	☐	☐	☐	☐

DASH *(page 2 of 4)* - INTERIM

PLEASE RATE YOUR ABILITY TO DO THE FOLLOWING ACTIVITIES IN THE LAST WEEK BY SELECTING THE APPROPRIATE RESPONSE.					
	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	☐	☐	☐	☐	☐
20. Manage transportation needs (getting from one place to another).	☐	☐	☐	☐	☐
21. Sexual activities.	☐	☐	☐	☐	☐

	Not At All	Slightly	Moderately	Quite A Bit	Extremely
22. During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	☐	☐	☐	☐	☐

	Not Limited At All	Slightly Limited	Moderately Limited	Very Limited	Unable
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	☐	☐	☐	☐	☐

PLEASE RATE THE SEVERITY OF THE FOLLOWING SYMPTOMS IN THE LAST WEEK.					
	None	Mild	Moderate	Severe	Extreme
24. Arm, shoulder or hand pain.	☐	☐	☐	☐	☐
25. Arm, shoulder or hand pain when you performed any specific activity.	☐	☐	☐	☐	☐
26. Tingling (pins and needles) in your arm, shoulder or hand.	☐	☐	☐	☐	☐
27. Weakness in your arm, shoulder or hand.	☐	☐	☐	☐	☐
28. Stiffness in your arm, shoulder or hand.	☐	☐	☐	☐	☐

DASH *(page 3 of 4)* - INTERIM

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	So Much Difficulty That I Can't Sleep
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand?	☐	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem.	☐	☐	☐	☐	☐

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is: _____

☐ I do not work. (You may skip this section)

PLEASE SELECT THE BEST RESPONSE THAT DESCRIBES YOUR PHYSICAL ABILITY IN THE PAST WEEK. DID YOU HAVE ANY DIFFICULTY:

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. using your usual technique for your work?	☐	☐	☐	☐	☐
2. doing your usual work because of arm, shoulder or hand pain?	☐	☐	☐	☐	☐
3. doing your work as well as you would like?	☐	☐	☐	☐	☐
4. spending your usual amount of time doing your work?	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #051

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

DASH *(page 4 of 4)* - INTERIM

SPORT/PERFORMING ARTS MODULE (OPTIONAL)
The following questions relate to the impact of your arm, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.
Please indicate the sport or instrument which is most important to you: _____ ☐ I do not play a sport or an instrument. (You may skip this section.)

PLEASE SELECT THE BEST RESPONSE THAT DESCRIBES YOUR PHYSICAL ABILITY IN THE PAST WEEK. DID YOU HAVE ANY DIFFICULTY:

	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Unable
1. using your usual technique for playing your instrument or sport?	☐	☐	☐	☐	☐
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	☐	☐	☐	☐	☐
3. playing your musical instrument or sport as well as you would like?	☐	☐	☐	☐	☐
4. spending your usual amount of time practising or playing your instrument or sport?	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #052

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

PCS - INTERIM

When I'm in pain...					
	Not At All	To A Slight Degree	To A Moderate Degree	To A Great Degree	All The Time
1. I worry all the time about whether the pain will end.	☐	☐	☐	☐	☐
2. I feel I can't go on.	☐	☐	☐	☐	☐
3. It's terrible and I think it's never going to get any better.	☐	☐	☐	☐	☐
4. It's awful and I feel that it overwhelms me.	☐	☐	☐	☐	☐
5.I feel I can't stand it anymore.	☐	☐	☐	☐	☐
6. I become afraid that the pain will get worse.	☐	☐	☐	☐	☐
7. I keep thinking of other painful events.	☐	☐	☐	☐	☐
8. I anxiously want the pain to go away.	☐	☐	☐	☐	☐
9. I can't seem to keep it out of my mind.	☐	☐	☐	☐	☐
10. I keep thinking about how much it hurts.	☐	☐	☐	☐	☐
11. I keep thinking about how badly I want the pain to stop.	☐	☐	☐	☐	☐
12. There's nothing I can do to reduce the intensity of the pain.	☐	☐	☐	☐	☐
13. I wonder whether something serious may happen.	☐	☐	☐	☐	☐

CRU #042 PERK 2 Plate #053

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

OXFORD ELBOW SCORE (OES) *(page 1 of 2)* - INTERIM

PLEASE SELECT THE BEST RESPONSE FOR THE FOLLOWING QUESTIONS

1. During the past 4 weeks...

Have you had difficulty lifting things in your home, such as putting out the rubbish, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

2. During the past 4 weeks...

Have you had difficulty carrying bags of shopping, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

3. During the past 4 weeks...

Have you had any difficulty washing yourself all over, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

4. During the past 4 weeks...

Have you had any difficulty dressing yourself, because of your elbow problem?

☐ No Difficulty ☐ A little bit of difficulty ☐ Moderate difficulty ☐ Extreme difficulty ☐ Impossible to do

5. During the past 4 weeks...

Have you felt that your elbow problem is “controlling your life”?

☐ No, not at all ☐ Occasionally ☐ Some days ☐ Most days ☐ Every day

6. During the past 4 weeks...

How much has your elbow problem been “on your mind”?

☐ Not at all ☐ A little of the time ☐ Some of the time ☐ Most of the time ☐ All of the time

CRU #042 PERK 2 Plate #054

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

OXFORD ELBOW SCORE (OES) *(page 2 of 2)* - INTERIM

7. During the past 4 weeks...				
Have you been troubled by pain from your elbow in bed at night?				
☐ Not at all	☐ 1 or 2 nights	☐ Some nights	☐ Most nights	☐ Every night

8. During the past 4 weeks...				
How often has your elbow pain interfered with your sleeping?				
☐ Not at all	☐ Occasionally	☐ Some of the time	☐ Most of the time	☐ All of the time

9. During the past 4 weeks...				
How much has your elbow problem interfered with your usual work or everyday activities?				
☐ Not at all	☐ A little bit	☐ Moderately	☐ Greatly	☐ Totally

10. During the past 4 weeks...				
Has your elbow problem limited your ability to take part in leisure activities that you enjoy doing?				
☐ No, not at all	☐ Occasionally	☐ Some of the time	☐ Most of the time	☐ All of the time

11. During the past 4 weeks...				
How would you describe the <u>worst pain</u> you have from your elbow?				
☐ No pain	☐ Mild pain	☐ Moderate pain	☐ Severe pain	☐ Unbearable

12. During the past 4 weeks...				
How would you describe the pain you <u>usually</u> have from your elbow?				
☐ No pain	☐ Mild pain	☐ Moderate pain	☐ Severe pain	☐ Unbearable

CRU #042 PERK 2 Plate #033

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

RE-OPERATIVE REPORT *(page 1 of 2)*

Date of Surgery:	yyyy mm dd
Pre-Operative Antibiotics:	☐ None ☐ Cefazolin 2 gram ☐ Other: _____

Type of Anesthesia:	☐ General ☐ Regional Block ☐ Other: _____
Surgical Procedure:	☐ Contracture release elbow
	☐ Excision proximal radius
	☐ Irrigation and debridement of elbow
	☐ Lateral collateral ligament repair or reconstruction
	☐ Medial collateral ligament repair or reconstruction
	☐ ORIF distal humerus
	☐ ORIF proximal radius
	☐ ORIF proximal ulna
	☐ Removal hardware elbow
	☐ Replacement proximal radius
	☐ Ulnar nerve exploration or transposition
	☐ Other: _____
Tourniquet Applied:	☐ Yes ☐ No
Tourniquet Time:	hh : mm
Procedure Time (skin to skin):	hh : mm

CRU #042 PERK 2 Plate #034

Pg#:

Subject ID: Centre Subject ID

Date: y y y y m m d d

RE-OPERATIVE REPORT *(page 2 of 2)*

Post-Operative Antibiotics:	☐ Cefazolin 1 gram TID x 1 day ☐ Other: _____
Immediate Post-Operative Complications:	☐ None
	☐ Vascular
	☐ Systemic ☐ Cardiac ☐ Pulmonary ☐ Other:_____
	☐ Intra-operative fracture
	☐ Implant failure
	☐ Failure to obtain or maintain reduction
	☐ Neurologic
	☐ Other: _____
If any of the above are present, please provide details: _____	

Date of Admission	y y y y m m d d
Date of Discharge:	y y y y m m d d
Days in Hospital:	

ADVERSE EVENTS

AE Event #	Adverse Event term _____		
AE Start Date:	yyyy mm dd		
AE End Date (or Continuing):	yyyy mm dd Continuing		
Outcome:	Fatal	Not recovered/ not resolved	Recovered w/sequelae
	Recovered w/o sequelae	Recovering/ resolving	
Severity/Grade:	Mild	Moderate	Severe
Is the Event Serious?	Yes (Complete SAE)	No	
Is the Event Expected?	Yes	No	
AE Treatment:	None	Medication(s)	Non-medication TX
Action Taken with Study Intervention:	None	Interrupted	Discontinued
	Dose reduced	Dose Increased	Not Applicable
Attribution/Relatedness:	Definite	Probable	Possible
	Unlikely	Unrelated	

MedDRA CODING FOR ADVERSE EVENT (AE)

(to be completed by coordinating site)

AE Event #	Site Adverse Event term
	Common sense Adverse Event term
AE Category: (Please look up corresponding AE Category at :https://safetyprofiler-ctep.nci.nih.gov/)	

	Term	Code
System Organ Classes (SOC)		
High Level Group Term (HLGT)		
High Level Term (HLT)		
Preferred Term (PT)		
Lowest Level Term (LLT)		

SERIOUS ADVERSE EVENTS (SAE) *(page 1 of 2)*

SAE Event #	Serious Adverse Event term _____
Report Type	☐ Initial Report ☐ Follow-up Report F/U Report # ☐ Final Report
SAE Classification:	☐ Fatal (resulted in death)
	☐ A life-threatening occurrence
	☐ Requires inpatient hospitalization or prolongation of existing hospitalization
	☐ Results in persistent or significant disability/incapacity
	☐ Results in congenital anomaly/birth defect
	☐ A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.
	☐ Loss of confidentiality that results in criminal or civil liability for participation or damage to financial standing, employability, insurability or reputation of the participant
SAE Start Date:	yyyy mm dd
SAE End Date (or Continuing):	yyyy mm dd ☐ Continuing
Grade:	☐ Mild ☐ Moderate ☐ Severe ☐ Life Threatening ☐ Death (Fatal)
Is the Event Expected?	☐ Yes ☐ No

Subject ID: Centre Subject ID **Date:** yyyy mm dd

SERIOUS ADVERSE EVENTS (SAE) *(page 2 of 2)*

Attribution/Relatedness:	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated
Outcome:	☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving
Lead Site Notified Date:	yyyy mm dd
Local IRB/REB Notified Date:	yyyy mm dd
Narrative/Details:	_____

Signature of investigator confirms the reported SAE : _____

e-signature
iDataFax use only

hh : mm yyyy mm dd

Subject ID: Centre Subject ID

Date: yyyy mm dd

SAFETY ADJUDICATION (SAE)

REPORT INFORMATION	
Serious Adverse Event Name	_____
SAE Start Date	yyyy mm dd
SAE End Date (or Continuing):	yyyy mm dd ☐ Continuing
Report Type	☐ Initial Report ☐ Follow-up Report F/U Report # ☐ ☐ Final Report
Outcome	☐ Fatal ☐ Not recovered/ not resolved ☐ Recovered w/sequelae ☐ Recovered w/o sequelae ☐ Recovering/ resolving

Is the Event		
Serious?	☐ Yes	☐ No
Probably or definitely **Related** to the study drug?	☐ Yes	☐ No
Is the event **expected**?	☐ Yes	☐ No

COMMENTS *(optional)*

Adjudication done by: _____
(Print Name)

Subject ID: Centre Subject ID

Date: yyyy mm dd

PROTOCOL DEVIATION

- ☐ Randomization Error
- ☐ Missed follow up visit:
  - ☐ Clinic ☐ Phone
- ☐ Follow up visit occurred outside of study window
- ☐ Phone visit occurred outside of study window
- ☐ Failure of participant to return study medication
- ☐ Incomplete follow up visit?
  - ☐ ROM measurement
  - ☐ Pill count
  - ☐ Radiographs
  - ☐ Physiotherapy
  - ☐ OES
  - ☐ DASH
  - ☐ PCS
- ☐ Other: _____

Details:

_____

_____

_____

Subject ID: Centre Subject ID

Date: yyyy mm dd

PROTOCOL VIOLATION

- ☐ Enrolment does not comply with Inclusion Criteria
  - If YES, specify Inclusion Criteria: ☐
- ☐ Enrolment does not comply with Exclusion Criteria
  - If YES, specify Exclusion Criteria: ☐☐
- ☐ Failure to obtain Informed Consent
- ☐ Study medication dispensing or dosing error
- ☐ Failure to report a Serious Adverse Event to the local IRB/REB and Sponsor
- ☐ Improper breaking of the blind
- ☐ Incorrect storage of study medication
- ☐ Participant received antihistamine in the first 6 weeks
- ☐ Failure to report unanticipated problem involving the risks to participants or others to the IRB/REB and Sponsor
- ☐ Participant stopped taking medication early
- ☐ Other: _____

CRU #042 PERK 2 Plate #056

☐ Wk 2 ☐ Wk 6 ☐ Wk 12 ☐ Wk 24 ☐ Wk 52

Subject ID: ☐☐ ☐☐☐☐ *Centre* *Subject ID*

Date: ☐☐☐☐ ☐☐ ☐☐ *yyyy* *mm* *dd*

RADIOGRAPHIC ASSESSMENT

HUMERUS	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

ULNA	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

RADIUS	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

CRU #042 PERK 2 Plate #057

Pg#:

Subject ID: Centre Subject ID

Date: yyyy mm dd

RADIOGRAPHIC ASSESSMENT - INTERIM

HUMERUS	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

ULNA	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

RADIUS	☐ Not Applicable	
Fracture line visible on AP?	☐ Yes	☐ No
Fracture line visible on lateral?	☐ Yes	☐ No
Fracture line visible on oblique?	☐ Yes	☐ No

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

August 8, 2017

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:

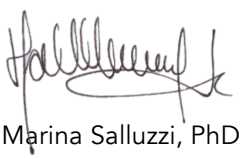
RE: Letter of Support

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. The estimated annual costs for your project are detailed below. 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
6-8 x-ray scans per subject
External Sites: 17
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	$8,870				$8,870
Data Management	$2,085	$4,729	$5,369	$6,949	$19,132
Support	$6,600	$8,633	$8,659	$8,672	$32,564
Administrative	$1,755	$1,336	$1,450	$1,562	$6,104
TOTAL/YEAR	**$19,310**	**$14,699**	**$15,478**	**$17,183**	**$66,670**

Mapi Research Trust

User agreement
Special Terms

Mapi Research Trust, a non-for-profit organisation subject to the terms of the French law of 1st July 1901, registered in Carpentras under number 453 979 346, whose business address is 27 rue de la Villette, 69003 Lyon, France, hereafter referred to as "MRT" and the User, as defined herein, (each referred to singularly as a "Party" and/or collectively as the "Parties"), do hereby agree to the following User Agreement Special and General Terms:

MRT Contact:

Mapi Research Trust
PROVIDE
Address: 27 rue de la Villette, 69003 LYON, France
Telephone: +33 4 72 13 65 75
Fax: +334 72 13 66 82

Recitals

The User acknowledges that it is subject to these Special Terms and to the General Terms of the Agreement, a link to which is included in Appendix 1 to these Special Terms and which are fully incorporated herein by reference. Under the Agreement, the Questionnaire referenced herein is licensed, not sold, to the User by MRT for use only in accordance with the terms and conditions defined herein. MRT reserves all rights not expressly granted to the User.

The Parties, in these Special Terms, intend to detail the special conditions of their partnership.

The Parties intend that all capitalized terms in the Special Terms have the same definitions as those given in article 1 of the General Terms included in Appendix 1.

In this respect, the Parties have agreed as follows:

Article 1. Conditions specific to the User

Section 1.01 Identification of the User

User Name : ***[complete the name of the individual or of the company]*** Dr. Kevin A. Hildebrand

Legal form : ***[individual or company's legal form]***

Address : ***[personal address or address of registered office]*** Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, AB T2N 4Z6

Country : Canada

Name of the contact in charge of the Agreement: Alexandra Garven

Telephone number: 403 - 943 - 5556 ..... Fax number: 403 - 219 - 3095.....

Email address: alexandra.garven@ucalgary.ca .....

If different:

Legal form : ***[individual or company's legal form]***

Address : ***[personal address or address of registered office]***

Country :

Billing address:

VAT number (if applicable): .....

Addressee:

PO number or internal reference (if applicable):

Section 1.02 Identification of the Questionnaire

Title of the Questionnaire:	PCS - Pain Catastrophizing Scale
Author:	Michael Sullivan (Canada)
Owner:	Michael Sullivan (Canada)
Copyright notice:	PCS © 1995 Michael JL Sullivan
References:	Sullivan MJL, Bishop SR and Pivik J. The Pain Catastrophizing Scale: development and validation. Psychological assessment. 1995;7(4):524-532

Article 2. Rights to use

Section 2.01 Context of the Use of the Questionnaire

The User undertakes to only use the Questionnaire in the context of the Study as defined hereafter.
[Tick the box and complete the corresponding fields]

☐ *individual clinical practice (please go directly to section 2.02)*

Planned term of use:
.....

Number of patients expected:
.....
.....
.....

☒ *clinical project or study*

Title:	PrEvention of posttraumatic joint contractures with Ketotifen II (PERK II)
Study/protocol reference:	PERK II v2.0
Disease or condition:	Elbow Dislocations/Fractures
Type of research:	☒clinical trial : ☐Phase II / ☒Phase III ☐ epidemiologic/observational ☐ other: .....
Questionnaire used as primary end point:	☐ yes ☒ no
Number of patients expected:	702
Number of submissions to the Questionnaire for each patient:	5
Term of clinical follow-up for each patient:	52 weeks
Planned term for project:	start (month/year): April 2018 end (month/year): April 2022
Mode of Administration:	☒ paper

☐ electronic

If electronic administration, please indicate mode of data collection:

☐ Hand held device – specify device: .....
☐ Interactive Voice Response (IVR) – specify: .....
☐ Web - specify website: .....
☐ Digital Pen - specify device: .....
☐ Tablet - specify device: .....
☐ other - specify: .....

Use of IT Company (e-vendor):

☒ no
☐ yes – name of IT company and contact:.....

☐ *other project*

Title: .....

Disease or condition: .....

Planned term of use: start (month/year):.....
end (month/year): .....

Description of the project: .....
.....
.....

Presentation format of project: .....

Financing of the Project:

☐ Not funded academic research/project, individual medical practice — *Projects not explicitly funded, but funding comes from overall departmental funds or from the University or individual funds.*

☒ Funded academic research/project — *Projects receiving funding from commerce, government, EU or registered charity.*

Funded academic research– sponsored by industry- fits the "commercial study/project" category.

☐ Commercial study/project — *Industry, CRO, any for-profit companies*

Grants / Sponsoring from (if any) *(name of the governmental/ foundation/company or other funding/sponsoring source):* .....
.....
.....

Section 2.02 Conditions for use

The User undertakes to use the Questionnaire in accordance with the conditions for use defined hereafter.

(a) Rights granted

Acting in the Owner's name, MRT grants the following limited, non-exclusive rights, to the User (the "Limited Rights")

(i) to use the Questionnaire, only as part of the Study; this right is made up exclusively of the right to communicate it to the Beneficiaries only, by any means of communication and by any means of remote distribution known or unknown to date, subject to respecting the conditions for use described hereafter; and

(ii) to reproduce the Questionnaire, only as part of the Study; this right is made up exclusively of the right to physically establish the Questionnaire or to have it physically established, on any paper, electronic, analog or digital medium, and in particular documents, articles, studies, observations, publications, websites whether or not protected by restricted access, CD, DVD, CD-ROM, hard disk, USB flash drive, for the Beneficiaries only and subject to respecting the conditions for use described hereafter; and

(iii) In the context of academic studies, should the Questionnaire not already have been translated into the language requested, the User is entitled to translate the Questionnaire or have it translated in this language, subject to informing MRT of the same beforehand by the signature of a Translation Agreement indicating the terms of it and to providing a copy of the translation thus obtained as soon as possible to MRT.

(iiii) In the context of commercial studies or any project funded by the pharmaceutical industry, the User undertakes to have the Questionnaire translated in this language by Mapi Language Services. Mapi Language Services is the only organization authorized by the Owner to perform linguistic validation/translation work on the Questionnaire.

The User acknowledges and accepts that it is not entitled to amend, modify, condense, adapt, reorganise the Questionnaire on any medium whatsoever, in any way whatsoever, even minor, without MRT's prior specific written consent.

(b) Specific conditions for the Questionnaire

- Use in Individual clinical practice or Research study / project

User shall:

- Cite the reference publications
- never duplicate, transfer or publish the Questionnaire without indicating the Copyright Notice
- Insert the Owner's copyright notice on all pages/screens on which the Questionnaire will be presented
- Mention the following information: "The PCS contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org "
- In case of use of an IT Company (e-vendor), User shall check with Mapi Research Trust that the IT Company has signed the necessary License Agreement with Mapi Research Trust before developing the electronic version of the Questionnaire

In the case of use of an electronic version of the Questionnaire in academic studies, the User undertakes to respect the following special obligations:

- Submit the screenshots of all the Pages where the Questionnaire appears to Mapi Research Trust before release for approval and to check that the above-mentioned requirements have been respected.

In the case of use of an electronic version of the Questionnaire in commercial studies / projects, the User undertakes to respect the following special obligations:

- For the first migration of the Questionnaire (generally the original version) into a specific electronic device
  - Review of screenshots:

    After implementation of the Questionnaire into the device, the user and/or IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user and/or IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.

  - Usability testing:

    Usability testing is a methodology which aims to examine whether respondents are able to use a device and associated software as intended. Major issues of concern in usability testing typically include device complexity, navigation and response selection for example.
    The objective of this investigation is to ensure that the electronic version of the questionnaire as included in the device meets usability criteria, focusing on functional aspects and respondents' understanding of instructions. Usability testing consists in interviews with patients where patients will complete the electronic version of the Questionnaire on the device and comment on their understanding of the instructions, ease of use and handiness of the device. A Usability testing report presenting results will be produced. If any changes are recommended, these will be implemented by the user and/or IT Company. If issues raised by respondents are rated as major, the user and/or IT Company may need to perform additional developments and another round of interviews may be needed.

    The review of screenshots is mandatory. The usability testing is highly recommended by Mapi, however should the User and/or IT Company decide not to perform this step, Mapi Research Trust shall not be held

responsible for any consequence and expense associated with this decision which shall remain the User and/or IT Company's sole liability.

The review of screenshots and usability testing, when and if performed, shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the review of screenshots and usability testing will result in a certification of the electronic device original version of the Questionnaires by Mapi for future licenses.

- For the migration of other language versions of the Questionnaire on an existing certified specific electronic device

    - Update version

After the electronic device original version of the Questionnaire is fully ready, the Questionnaire's language versions developed for paper administration will be updated to reflect the changes in wording of instructions implemented in the electronic device original version of the questionnaire.
Native speakers of the languages will reflect the changes made to the electronic device original version of the Questionnaire and will provide English equivalents of all changes made for Mapi's quality control.

    - Review of screenshots:

After implementation of the Questionnaire into the device, the user and/or IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user and/or IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.

The update of version and review of screenshots are mandatory. These steps shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the update of version and review of screenshots will result in a certification of the electronic device language version of the Questionnaires by Mapi for future licenses.

- Use in a publication or on a website with unrestricted access:

In the case of a publication, article, study or observation on paper or electronic format of the Questionnaire, the User undertakes to respect the following special obligations:

- not to include any full copy of the Questionnaire, but a protected version with the indication "sample copy, do not use without permission"
- to indicate the name and copyright notice of the Owner
- to include the reference publications of the Questionnaire
- to indicate the details of MRT for any information on the Questionnaire as follows: The PCS contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org
- to provide MRT, as soon as possible, with a copy of any publication regarding the Questionnaire, for information purposes
- to submit the screenshots of all the Pages where the Questionnaire appears to MRT before release to check that the above-mentioned requirements have been respected.

- Use for dissemination:

    - On a website with restricted access:

In the case of publication on a website with restricted access, the User may include a clean version of the Questionnaire, subject to this version being protected by a sufficiently secure access to only allow the Beneficiaries to access it.
The User undertakes to also respect the following special obligations:

- to indicate the name and copyright notice of the Owner
- to include the reference publications of the Questionnaire
- to indicate the details of MRT for any information on the Questionnaire as follows: The PCS contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org
- to submit the screenshots of all the Pages where the Questionnaire appears to MRT before release to check that the above-mentioned requirements have been respected.

    - On promotional / marketing documents

In the case of publication on promotional/marketing documents, the User undertakes to respect the following special obligations:

- to indicate the name and copyright notice of the Owner
- to include the reference publications of the Questionnaire
- to indicate the details of MRT for any information on the Questionnaire as follows: The PCS contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org
- to provide MRT, as soon as possible, with a copy of any publication regarding the Questionnaire, for information purposes

- to submit the screenshots of all the Pages where the Questionnaire appears to MRT before release to check that the above-mentioned requirements have been respected.

For any other use not defined herein, please contact MRT for the specific conditions of use and access fees (if applicable).

Article 3. Term

MRT grants the Limited Rights to use the Questionnaire as from the date of delivery of the Questionnaire to the User and for the whole period of the Study as mentioned in section 2.01.

Article 4. Beneficiaries

The Parties agree that the User may communicate the Questionnaire in accordance with the conditions defined above to the Beneficiaries involved in the Study only, in relation to the Study defined in section 2.01.

Article 5. Territories and Languages

MRT grants the Limited Rights to use the Questionnaire on the following territories and in the languages indicated in the table below:

Language:	***For use in the following country***	***Language:***	***For use in the following country***	***Language:***	***For use in the following country***
-French	-Canada				
-Spanish	-USA				

Article 6. Price and payment terms

The User undertakes in relation to MRT to pay the price owed in return for the availability of the Questionnaire, according to the prices set out below, depending on the languages requested and the costs of using the Questionnaire, in accordance with the terms and conditions described in section 6.02 of the General Terms included in Appendix 1.

1. For Individual clinical practice or Research study / project

Transfer of rights to use and reproduce the Questionnaire (Owner's Royalty Fees)	**COMMERCIAL USERS**	COST PER STUDY	1100 Euros*
		COST PER LANGUAGE	550 Euros *
	FUNDED ACADEMIC RESEARCH	COST PER STUDY	n/a
		COST PER LANGUAGE	n/a
MRT's Distribution Costs	**COMMERCIAL USERS**	COST PER STUDY	1 000 Euros*
		COST PER AVAILABLE LANGUAGE	500 Euros*
	FUNDED ACADEMIC USERS	COST PER STUDY	300 Euros*
		COST PER AVAILABLE LANGUAGE	50 Euros*
	NOT FUNDED ACADEMIC USERS	COST PER STUDY	n/a
		COST PER AVAILABLE LANGUAGE	n/a

* excluding VAT

2. For dissemination or marketing purpose (including use in a software or web application)

A - AT THE START OF THE PROJECT

Transfer of rights to use and reproduce the Questionnaire (Owner's Royalty Fees)	**COMMERCIAL USERS**	COST PER STUDY	1100 Euros* (including the delivery of 2 language versions)
		COST PER LANGUAGE	220 Euros*
	FUNDED ACADEMIC RESEARCH	COST PER STUDY	n/a
		COST PER LANGUAGE	n/a
MRT's Distribution Costs	**COMMERCIAL USERS**	COST PER STUDY	1000 Euros* (including the delivery of 2 language versions)
		COST PER AVAILABLE LANGUAGE	500 Euros*
	FUNDED ACADEMIC USERS	COST PER STUDY	n/a
		COST PER AVAILABLE LANGUAGE	n/a
	NOT FUNDED ACADEMIC USERS	COST PER STUDY	n/a
		COST PER AVAILABLE LANGUAGE	n/a

* excluding VAT

B - AT THE END OF THE FIRST YEAR AND EVERY FOLLOWING YEAR IF THE PROJECT IS CONTINUED

(based on the number of actual licenses of the Questionnaire sold by the User during the past year)

Transfer of rights to use and reproduce the Questionnaire (Owner's Royalty Fees)	**COMMERCIAL USERS**	1 to 10 licenses sold	1 100 Euros*
		11 to 20 licenses sold	2 200 Euros*
		21 to 30 licenses sold	3 300 Euros*
		31 to 40 licenses sold	4 400 Euros*
		41 to 50 licenses sold	5 500 Euros*
		over 51 licenses sold	6 600 Euros*
	FUNDED ACADEMIC RESEARCH	COST PER STUDY	n/a
		COST PER LANGUAGE	n/a
MRT's Distribution Costs	**COMMERCIAL USERS**	1 to 10 licenses sold	500 Euros*
		11 to 20 licenses sold	1 000 Euros*
		21 to 30 licenses sold	1 500 Euros*
		31 to 40 licenses sold	2 000 Euros*
		41 to 50 licenses sold	2 500 Euros*
		over 51 licenses sold	3 000 Euros*
	FUNDED ACADEMIC RESEARCH	COST PER STUDY	n/a
		COST PER AVAILABLE LANGUAGE	n/a

* excluding VAT

User-Agreement Special Terms and General Terms are agreed and acknowledged by:

User's name:
Alexandra Garver

User's title:
Clinical Research Assistant

User's Signature **Date**

A Garver 2018/02/12

Appendix 1 to the Special Terms:
User Agreement General Terms

User has read and accepted the MRT's General Terms of the Agreement, which are available on MRT's website: https://eprovide.mapi-trust.org/user-agreement-general-terms

Clinical Outcomes

Clinical Outcomes,
Oxford University Innovation Ltd.,
Buxton Court,
3 West Way
Oxford
OX2 0JB
UK

8th February 2018

Dear Alexandra,

Many thanks for your request for us to quote for the project to translate / adapt the Oxford Elbow Score (OES) into English for USA, English for Canada, Spanish for USA and French for Canada for your study. The table below sets out the project, methods, timelines and prices.

Client	University of Calgary/Peter Lougheed Centre
Project Requirements	Translation and linguistic validation (TLV) of the OES into Spanish for USA and French for Canada Review and Linguistic validation (RLV) of the OES into English for USA and English for Canada
COA	The Oxford Elbow Score (OES)
Language Requirements	English for USA and English for Canada. French for Canada and Spanish for USA.
Methodology	Standard RLV's and TLV's including developer reviews compliant with sector good practices
Population	5 adults awaiting elbow surgery (including but not limited to total elbow replacement) or patients who have had elbow surgery in the past 3 months or patients undergoing physiotherapy for elbow injuries.
Timeline	RLV - 7 weeks (excluding UK bank holidays) TLV – 8 weeks (excluding UK bank holidays)
Budget	RLV - £4,600 per language (x2) TLV - £5,200 per language (x2) £19,600 - TOTAL
Date	8th February 2018

If you have any questions please do not hesitate to ask. If you wish to proceed to commission the work then please let me know and we will draft a full written proposal that doubles in purpose as a contract for the work.

Best wishes

Dr David Churchman

T: +44 (0)1865 614417

M: +44 (0)7393 766153

E: David.Churchman@innovation.ox.ac.uk

Clinical Outcomes

Proposal: Translation and Linguistic Validation of the Oxford Elbow Score (OES) into Spanish for USA and French for Canada. Review and Linguistic validation of the OES into English for USA and English for Canada

8th May 2018
Valid 90 days

Proposal for:	Prepared by:
Kevin Hildebrand	David Churchman
University of Calgary/Peter Lougheed Centre	Clinical Outcomes Oxford University Innovation Limited. Buxton Court, 3 West Way Oxford, OX2 0JB, UK
+1 (403) 220-7282	+44 (0)1865 614417
hildebrk@ucalgary.ca	david.churchman@innovation.ox.ac.uk

This Proposal is made subject to our Standard Terms and Conditions attached and if you accept this Proposal by signing below the contract between us will be formed for the supply of Services and that contract will be subject to our Standard Terms and Conditions. If there is any conflict or inconsistency between this Proposal and our Standard Terms and Conditions, the Proposal will prevail.

To accept this Proposal please send back a countersigned copy to indicate your agreement to these terms.

This Proposal is valid for 90 days.

ON BEHALF OF (University of Calgary/Peter Lougheed Centre)	**ON BEHALF OF OXFORD UNIVERSITY INNOVATION LIMITED:**
NAME: Kevin Hildebrand	NAME: DR PAUL ASHLEY HEAD OF TECHNOLOGY TRANSFER LIFE SCIENCES OXFORD UNIVERSITY INNOVATION LTD
SIGNATURE:	SIGNATURE:
DATE: May 11, 2018	DATE: 15.5.18

Contents

1 Study Requirements

The University of Calgary/Peter Lougheed Centre has requested that the Clinical Outcomes team at Oxford University Innovation Ltd. prepare a proposal for the translation and linguistic validation of the Oxford Elbow Score, a clinical outcome assessment (COA). This proposal will be based on the source file FINAL_OES_English_UK.doc managed under copyright by Oxford University Innovation Ltd and the translation is into Spanish for USA and French for Canada and also English for use in the USA and Canada.

2 Study Methodology

2.1 Review and linguistic validation of the Oxford Elbow Score

The review and linguistic validation methodology that will be employed for the Oxford Elbow Score includes the following steps, which conform to the requirements of both the Oxford Elbow Score developers and copyright holders and the FDA and EMA regulatory agencies. Review and linguistic methodology will be employed for the following language:

- English for USA
- English for Canada

Concept Elaboration	A concept elaboration report already exists for the Oxford Elbow Score. The concept elaboration report clarifies the intended meaning of each item, provides acceptable alternatives for translations if direct translations are not possible, and will be used as a guidance document throughout the study.
In-Country Review	The existing English for UK version of the Oxford Elbow Score will be reviewed by the in-country investigator (any overlapping English for UK text from the Oxford Elbow Score will be retained). If required, the wording will be amended to ensure that it is culturally and grammatically appropriate for use in the target country.
Developer Review	The completed in-country review report will be sent to the developer of the Oxford Elbow Score to obtain their approval of any changes made during the in-country review.
Independent Proofreading	The translation at this stage will be proofread by a medical translator (native target language speaker) who hasn't been involved in the study to date, to ensure complete accuracy and zero errors prior to the cognitive debriefing interviews.
Cognitive Debriefing Interviews	The in-country investigator will recruit and ask 5 patients who are about to or have recently (within last 6 months) undergone elbow surgery to participate in a face-to-face interview. Each participant will firstly complete the Oxford Elbow Score to familiarise themselves with "'the wording. They will then be taken through the Oxford Elbow Score sentence by sentence and asked to comment on whether they understood the instructions, questions, and response options, comment on whether any words or phrases were difficult to understand and if so to suggest alternative wording and finally, to describe in their own words (paraphrase) what the wording in the Oxford Elbow Score means to them. Any issues raised by the participants and any inaccurate paraphrasing will be entered

	into a pilot testing report, this will be reviewed by the project manager and discussed with the in-country investigator to ensure that the final wording is fully acceptable to the patient population the Oxford Elbow Score is designed for.
Professional Formatting	If any changes are made as a result of the cognitive debriefing interviews, the translation will be proofread for a second time to ensure 100% accuracy. Following this step or if no changes were made, the translated text will undergo multilingual typesetting editing, to ensure the translated text is perfectly formatted and the correct fonts for the target language have been used.

2.2 Translation and linguistic validation of the Oxford Elbow Score

The translation and linguistic validation methodology that will be employed for the Oxford Elbow Score includes the following steps, which conform to the requirements of both the Oxford Elbow Score developers and copyright holders and the FDA and EMA regulatory agencies. Translation and linguistic methodology will be employed for the following languages:

- Spanish for USA
- French for Canada

The translation and linguistic validation methodology that will be employed for the Oxford Elbow Score includes the following steps, which conform to the requirements of both the Oxford Elbow Score developer and the FDA and EMA regulatory agencies.

Concept Elaboration	A concept elaboration report already exists for the Oxford Elbow Score. The concept elaboration report clarifies the intended meaning of each item, provides acceptable alternatives for translations if direct translations are not possible, and will be used as a guidance document throughout the study.
Two Forward Translations	The Oxford Elbow Score will be translated twice from English into the target language. The translations will be conducted by professional medical translators (native target language speakers).
Forward Translation Reconciliation	The in-country investigator will reconcile the forward translations to produce a single translation of the highest quality which is both linguistically accurate and culturally relevant to the target country.
Two Back Translations	The reconciled translation will be back translated into English by two professional medical translators (native English speakers) who have not seen the original source text.
Back Translation Review	The project manager will review the back translations against the source text and work with the in-country investigator to resolve any discrepancies in meaning between the translations.
Developer Review	The completed back translation review report will be sent to the developer of the Oxford Elbow Score to obtain their approval of all the decisions made up to that point in the translation study.
Independent Proofreading	The translation at this stage will be proofread by a medical translator (native target language speaker) who hasn't been involved in the study to date, to ensure complete accuracy and zero errors prior to the cognitive debriefing interviews.
Cognitive Debriefing Interviews	The in-country investigator will recruit and ask 5 people who are about to or have recently (within last 6 months) undergone elbow surgery to participate in a face-to-face interview. Each person will firstly complete the Oxford Elbow Score. They will then be taken through the COA sentence by sentence and asked to comment on whether they understood the instructions, questions, and response options,

	comment on whether any words or phrases were difficult to understand and if so to suggest alternative wording and finally, to describe in their own words (paraphrase) what the wording in the Oxford Elbow Score means to them. Any issues raised by the participants and any inaccurate paraphrasing will be entered into a pilot testing report, this will be reviewed by the project manager and discussed with the in-country investigator to ensure that the final wording is fully acceptable to the patient population the Oxford Elbow Score is designed for.
Professional Formatting	If any changes are made as a result of the cognitive debriefing interviews, the translation will be proofread for a second time to ensure 100% accuracy. Following this step or if no changes were made, the translated test will be sent to our partners Graphilingua who are experts in desk top publishing and multilingual typesetting, to ensure the translated text is perfectly formatted and the correct fonts for the target language have been used.

3 Deliverables

Oxford University Innovation Ltd. will provide University of Calgary/Peter Lougheed Centre with the following:

- A weekly project status report
- Final formatted translations in MS Word and PDF
- A certification letter outlining the translation methodology that was undertaken

4 Timeline and Budget

For the purposes of this proposal, one week is based on 5 working days and excludes any public holidays in England.

The following table outlines the timeline for completion of the translation and linguistic validation process:

Language	Country	Methodology	Timeline	Budget
English	USA	Review	7 weeks	£4,600
English	Canada	Review	7 weeks	£4,600
Spanish	USA	Translation	8 weeks	£5,200
French	Canada	Translation	8 weeks	£5,200
		TOTAL TRANSLATION BUDGET		**£19,600**
		TOTAL STUDY BUDGET		**£19,600**

Timeline and budget assumptions:

- The timeline **does not** include the developer's time in reviewing the interview adaptation, concept elaboration report or the back translation review report. Oxford University Innovation Ltd. cannot be held responsible for delays in the project due to the Oxford Elbow Score developer.
- The budget **does** include any fees for the instrument developer.

Invoices: Two invoices will be raised for this project, 50% on project inception and 50% on completion.

5 Appendices

5.1 Study Team

5.1.1 The Clinical Outcomes team at Oxford University Innovation Ltd.

Oxford University Innovation Ltd. (OUI) is the technology transfer company for the University of Oxford. Within OUI is the Clinical Outcomes team dedicated to supporting the use of Clinical Outcomes Assessments (COA), the vast majority being Patient Reported Outcomes (PRO) measures. The Clinical Outcomes team is involved with all aspects of COA management including translation and linguistic validation and eCOA activity, which we are thought leaders in. The Clinical Outcomes team manage a rapidly growing portfolio of high quality COA measures and a library of over 250 translations of the instruments we manage. The Clinical Outcomes team is headed by Dr. David Churchman who has over 10 years' experience in COAs and is an associate of the Health Services Research Unit, Nuffield Department of Population Health at the University of Oxford, and an active member of ISOQOL and ISPOR.

5.1.2 Study Management

Darren Clayson, MSc – Project Manager

Darren is a psychologist and consultant outcomes researcher who has been working closely with Oxford University Innovation Ltd for approaching 10 years. He was also the founder and director of PharmaQuest Ltd., a medical translation company specialising in translation and linguistic validation of COAs until its sale in 2013. Darren has overseen several hundred linguistic validation projects and now works for a number of agencies providing expert advice as well as acting as a project manager and a UK English in-country investigator.

5.1.2 In-Country Investigators

In-country investigators are resident in the target country, native speakers of the target language, fluent in English and have relevant backgrounds, including outcomes research/health/linguistics/medicine/psychology. They have experience of working on translation and linguistic validation projects of COAs for the pharmaceutical industry.

5.1.3 Translators

Forward Translators & Proofreaders

The forward translators and proofreaders are medical translators with at least 3 years' translation experience and a qualification in translation or languages. They are native speakers of the target language and fluent in English.

Back Translators

The back translators are medical translators with at least 3 years' translation experience and a qualification in translation or languages. They are native speakers of English and fluent in the target language.

5.2 Translation Related Publications

Clayson D, Verjee-Lorenz A, Two R, Gerber R, Beaudreuil J. (2011). Translation and linguistic validation – Methodological implications when the source measure is not English. Value in Health 14(3): A154.

Clayson D, Verjee-Lorenz A, Miller F, Two R. (2011). The role of the instrument developer in the translation of patient reported outcome measures. Value in Health 14(7): A432.

Harrington R, Churchman D, Dawson J, Clayson D, Price A, Rees J. (2012). Routine electronic patient reported outcome (ePRO) data collection in an orthopaedic outpatient clinic – Methods used to ensure proper migration of the PRO measure and benefits to the care pathway. Value in Health 15 (4): A43.

Simpson H, Two R, Verjee-Lorenz A, **Clayson D.** (2012). Identification of Culturally Bound Terms in Patient Reported Outcome Measures. Value in Health 15(7): A492.

Two R, Verjee-Lorenz A, **Clayson D,** Dalal M, Grotzinger K, Younossi ZM. (2010). A Methodology for Successfully Producing Global Translations of Patient Reported Outcome Measures for Use in Multiple Countries. Value in Health 13(1): 128-131.

Two R, Verjee-Lorenz A, **Clayson D**, Dalal M, Grotzinger K, Younossi ZM. (2010). Response to the Letter from Ms. Tamzin Furtado. Value in Health 13(4): 508-508.

Verjee-Lorenz A, **Clayson D,** Two R, Giovanaz M. (2010). Concept Elaboration—an essential stage in the translation of PRO measures. Value in Health 13(7): A338.

Verjee-Lorenz A, **Clayson D,** Two R. (2011). Pilot Testing Translations of PRO Measures with Sensitive Populations. Value in Health 14(3): A153.

Verjee-Lorenz A, Two R, **Clayson D,** Miller F. (2011). Comparison of reconciliation and review methodologies for the translation of patient reported outcome (PRO) measures. Value in Health 14(7): A432.

STANDARD TERMS AND CONDITIONS

These Conditions apply to and govern the supply of services by Oxford University Innovation Limited whose registered office is at University Offices, Wellington Square, Oxford OX1 2JD ("OUI").

1. Definitions and Interpretation

1.1 In these Conditions the following words have the following meanings:

the Agreement	means an agreement for the purchase of the Services by the Company from OUI;
the Company	means the company or entity defined on page 2 of the Proposal;
the Company Representative	means the individual named in the Proposal;
the Conditions	means these terms and conditions;
the Contract Period	means the period and Timeline set out in section 4 of the Proposal;
the Contract Price	means the price for the Services set out in section 4 of the Proposal
the Deliverables	means the deliverables identified in section 3 of the Proposal;
the Proposal	means a written proposal issued by OUI specifying the Services to be performed and the cost of the Services and incorporating these terms by reference;
the Questionnaire	means the questionnaire as identified in Section 1, Study Requirements of the Proposal; and
the Services	means the services to be performed by OUI as set out in Section 2 (Methodology) and 3 (Deliverables) of the Proposal.

1.2 OUI and Company are together referred to as "Parties" and individually as "Party".

1.3 The headings in this Agreement shall not affect the interpretation of this Agreement. The singular includes the plural and vice versa and one gender includes the others. Use of the words "includes" and "including" shall be construed as being without limitation. References to statutes and regulations shall be to these as they may be amended or revised from time to time.

2. Services

2.1 In consideration of the Contract Price OUI shall provide the Services to the Company, on a non-exclusive basis and make available the Deliverables to the Company.

2.2 OUI will use reasonable skill and care in carrying out the Services.

2.3 OUI will keep Company Representative informed of progress made on the Services and provide updates on reasonable request by the Company from time to time.

2.4 OUI will use all reasonable endeavours to complete the Services within the Services Period. However, OUI shall have no liability for failing to do so and time shall not be regarded as being of the essence. OUI will notify the Company of any anticipated delays in the Services and use all reasonable endeavours to minimise the delays.

3. Company Materials

3.1 The commencement and completion of the Services is subject to the supply by Company to OUI of any information or materials that OUI reasonably requires in order to properly carry out the Services.

4. Contract Price

4.1 Unless the Proposal states otherwise and subject to OUI providing a VAT invoice, the Contract Price shall be paid in full on delivery of the final translation. All prices are deemed to be expressed exclusive of VAT.

4.2 Interest may be charged by OUI at 2% per month on all overdue payments from the date that payment was due until payment is received by OUI.

5. Intellectual Property

5.1 This Agreement is not intended to result in the transfer or licence of any intellectual property rights by either Party to the other.

5.2 OUI shall have no liability for verifying, procuring or maintain any rights that may be desirable or required for the Company to use the Questionnaire or for OUI to carry out the Services, which shall be the sole responsibility of Company.

6. Confidentiality

6.1 Each Party shall keep confidential and not disclose to any third party information that is marked confidential or apparent by its nature or the manner of its disclosure to be confidential that is received from (or on behalf of) the disclosing Party and will only use that confidential information for the performance of the Services or in connection with this Agreement or its purposes.

6.2 The obligations in clause 6.1 do not apply to information that was already known to the receiving Party; was received by the receiving Party from a third party without breaching a duty of confidentiality; is or becomes publicly known without the fault of the receiving party; is or has been independently developed by the receiving party's

staff who did not have any access to any of the disclosing Party's Confidential Information; or is approved in writing for release by the disclosing Party. Nothing in this Agreement will prevent the recipient from disclosing information where it is required to do so by order of a court of competent jurisdiction or by law (including under the Freedom of Information Act 2000 (FOIA)).

6.3 The obligations of confidentiality in respect of any confidential information in clause 6 shall survive for five years from the date of initial disclosure of that Confidential Information.

7. Liability

7.1 OUI accepts no responsibility for any errors, omissions or other defects in any information, instructions, specifications or materials provided by or on behalf of Company or any consequential errors, omissions or other defects in the Services or the Deliverables and any additional work or Services required to be carried out by OUI as a result shall be charged for accordingly.

7.2 On submission of the final language version(s) of the Questionnaire(s), the Company will have 30 days to raise any queries. Except as expressly stated otherwise in this Agreement, OUI excludes to the fullest extent permitted by law all warranties, conditions or terms, express or implied, statutory or otherwise, including (without limitation) as to the condition, performance, fitness for purpose or satisfactory quality of the Services or the Deliverables.

7.3 Without affecting the generality of clause 7.2, OUI give no implied or express warranty and make no representation that the Deliverables or any questionnaire on which they are based:

7.3.1 will enable specific results to be obtained;

7.3.2 meets a particular specification or is comprehensive within its field;

7.3.3 is suitable for any particular, or the Company's specific, purposes;

7.3.4 does not or will not infringe third party rights.

7.4 The Company will be responsible for obtaining any licence or permissions required from owner of copyright in any third party health outcomes questionnaire to be assessed or otherwise used by OUI for the purposes of the Services and OUI will have no liability in relation to any data obtained by the Company from any such questionnaire.

7.5 Subject to clause 7.6, the liability of either Party for any breach of this Agreement, for any negligence or arising in any other way out of the subject-matter of this Agreement, will not extend to loss of business, profit, revenue, contracts, opportunity, reputation or data (in each case whether direct or indirect), or to any indirect or consequential damages or losses even if they were within the Parties' contemplation at the date of this Agreement.

7.6 Subject to clause 7.6, the maximum liability of OUI to the Company under or in connection with this Agreement whether in contract, tort (including negligence) or otherwise shall not exceed in aggregate the total amount of the Contract Price and

Expenses (excluding VAT or other similar taxes or duties) invoiced by OUI in respect of the Services up to the date of the event or circumstance giving rise to the relevant claim.

7.7 Nothing in this Agreement shall exclude or limit any liability of either Party for (a) fraud or wilful misconduct; and/or; (b) negligence causing personal injury or death.

7.8 Any action by either Party against the other relating to or arising out of the Services must be brought within one (1) year after the aggrieved Party became aware of (or should reasonably have become aware of) the cause of action, failing which the alleged wrongdoer will be discharged of any liability with respect to the claim.

7.9 The Company will not make any claim for damages against any individual employed or engaged by OUI or the University personally except in case of fraud or wilful misconduct.

7.10 The allocations of liability in this Agreement represent the agreed and negotiated understanding of the Parties and OUI's charges for the Services reflect such allocations.

8. Termination

8.1 Either Party may terminate this Agreement immediately if (a) the other Party becomes insolvent or has proceedings commenced against it under insolvency law (including the appointment of an administrator or liquidator) that are not promptly dismissed and (b) if the other Party is in material breach of any term of the Agreement and where the breach is capable of being remedied, fails to remedy the breach after receiving a written notice that specifies the breach and the steps required to remedy it and a reasonable opportunity to remedy the breach.

8.2 If the Company cancels the Services at any point during the Contract Period, OUI will be entitled to charge the Company for the work completed as follows (for each language)

Stage started	Percentage of Contract Price
Project initiation	10%
Forward translation	20%
Forward translation reconciliation	30%
Back translation	40%
Back translation review	50%
Developer/client review	60%
Independent proofreading	70%
Pilot testing	100%

8.3 On termination of this Agreement for any reason, the Company shall immediately pay all outstanding sums to OUI without making any set-off, withholding or deduction.

8.4 Termination of this Agreement shall not affect the accrued rights and liabilities of the Parties and clauses 5, 6, 7, 8.3, 8.4 and 10 inclusive shall survive termination of this Agreement.

9. Force Majeure

If the performance of the Services by OUI is delayed, or prevented by any circumstances

or conditions beyond OUI's control, OUI shall have the right at its option to: a) suspend further performance of the Services until such time as the cause of the delay shall no longer be present or; (b) be discharged from further performance of and liability under this Agreement and if OUI exercises such right Company shall pay that part of the Contract Price and Expenses which relate to the Services already performed.

10. General

10.1 **Assignment** – The Company shall not assign or transfer or purport to assign or transfer any of its rights or obligations under this Agreement.

10.2 **Announcements** - No public announcement or communication (save as may be required by law) concerning the transactions referred to in this Agreement shall be made or dispatched by either Party without the prior written consent of the other Party, not to be unreasonably withheld or delayed.

10.3 **Use of Name** - Neither Party will use the name of the other, or, in the case of the Company, OUI and/or the University, in any marketing, advertising or promotion or to endorse any product or service unless the other Party gives or, in the case of OUI, procures the prior written consent of the other.

10.4 **No Partnership** –Nothing in this Agreement creates, implies or evidences any partnership or joint venture between the Parties or the relationship of principal and agent. Neither Party shall be or hold itself out as being the agent or representative of the other.

10.5 **Entire Agreement** - This Agreement constitutes the entire agreement between the Parties relating to the subject matter of this Agreement and supersedes all previous such agreements. The Company warrants that it has not relied on any representation made by or on behalf of OUI that is not expressly set out in this Agreement and waives all claims for breach of any warranty and all claims for any misrepresentation, (negligent or of any other kind, unless made by us fraudulently) in relation to any representation which is not specifically set out in this Agreement.

10.6 **Variation** - No variation of this Agreement shall be valid unless it is in writing and signed by or on behalf of each of the Parties.

10.7 **Waiver** - The failure to exercise or delay in exercising a right or remedy under this Agreement shall not constitute a waiver of the right or remedy or a waiver of any other rights or remedies and no single or partial exercise of any right or remedy under this Agreement shall prevent any further exercise of the right or remedy or the exercise of any other right or remedy.

10.8 **Notices** – Notices under this Agreement may be validly served by each Party at the other Party's address given at the top of this Agreement, or such other address as either Party may in writing notify to the other for such purpose.

10.9 **Third Party Rights** –Except as provided for the benefit of the employees and appointees of OUI and the University in clause 5.5 above, no third party is intended to benefit from any rights under this Agreement.

10.10 **Governing Law** - English Law governs this Agreement and the Parties submit to the exclusive jurisdiction of the English courts for the resolution of any dispute which may arise out of or in connection with this Agreement

AWARD/CONTRACT

1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700)		RATING	PAGE 1 OF PAGES 17
2. CONTRACT *(Proc. Inst. Ident.)* NO. W81XWH-17-1-0665	3. EFFECTIVE DATE 30 Sep 2017	4. REQUISITION/PURCHASE REQUEST/PROJECT NO. 0011096131	

5. ISSUED BY CODE W81XWH USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST FORT DETRICK MD 21702-5014		6. ADMINISTERED BY *(If other than Item 5)* CODE **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 W91ZSQ FORT DETRICK- CDMRP FORT DETRICK- CDMRP 1120 FORT DETRICK FREDERICK MD 21702		12. PAYMENT WILL BE MADE BY CODE HQ0490 DEFENSE FINANCE AND ACCOUNTING SERVICE DFAS-INDY VP GFEBS 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**

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(X)	SEC.	DESCRIPTION	PAGE(S)	(X)	SEC.	DESCRIPTION	PAGE(S)
		PART I - THE SCHEDULE				**PART II - CONTRACT CLAUSES**	
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	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					
	G	CONTRACT ADMINISTRATION DATA			L	INSTRS., CONDS., AND NOTICES TO OFFERORS	
	H	SPECIAL CONTRACT REQUIREMENTS			M	EVALUATION FACTORS FOR AWARD	

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: See 00800 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.M.ParkerReeser.civ@mail.mil
19B. NAME OF CONTRACTOR / 19C. DATE SIGNED BY _____ Oct 24 2017 *(Signature of person authorized to sign)*	20B. UNITED STATES OF AMERICA / 20C. DATE SIGNED BY _____ 24-Sep-2017 *(Signature of Contracting Officer)*

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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: 0972016201701300001831033337410 R.0002688.6.1 6100.9000021001
COST CODE: A7444
AMOUNT: $1,459,924.16
CIN GFEBS001109613100001: $1,459,924.16

AB: 0972017201801300001831033337410 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 measures 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

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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.

Asthma medication may prevent loss of joint motion following injury

Learn about Kevin Hildebrand's ketotifen research at free forum Oct. 28

2

By Nancy Whelan, McCaig Institute for Bone and Joint Health **October 26, 2017**

Dr. Kevin Hildebrand with patient Jacqueline Burrus, after surgery to repair multiple fractures in the bones that make up her elbow. ***Photo by Don Molyneaux, for the McCaig Institute for Bone and Joint Health***

One cold morning in January 2015, Jacqueline Burrus ran to catch a bus and slipped on the ice. She put her right arm out to break her fall, and in that instant her life was changed forever.

"I hit the ground, got up right away, brushed the snow off my coat and walked on the bus. It wasn't until I sat down that I realized my elbow was killing me." An X-ray and CT scan confirmed she had multiple fractures in the bones that make up the elbow — the radius, humerus and ulna — and she was immediately scheduled for surgery.

The road to recovery has been long for Burrus. "After the surgery my elbow was locked in a 90 degree angle," she says. "I had severe pain and after seven months I still couldn't move my elbow." She was referred to Dr. Kevin Hildebrand for a second surgery to help regain her range of motion, but even after months of physiotherapy her elbow mobility is still severely restricted.

Stiff elbows often occur post-surgery

Loss of joint motion following an injury, otherwise known as a post-traumatic contracture, is a common complication following fractures. "Many people with elbow fractures or dislocations lose elbow motion and 10 to 15 per cent require surgery," says Hildebrand, an orthopedic surgeon and University of Calgary researcher in the Cumming School of Medicine's McCaig Institute for Bone and Joint Health. "People with a joint contracture can have trouble dressing, eating, grooming and reaching. They're simple little things we take for granted but make a huge difference in daily life."

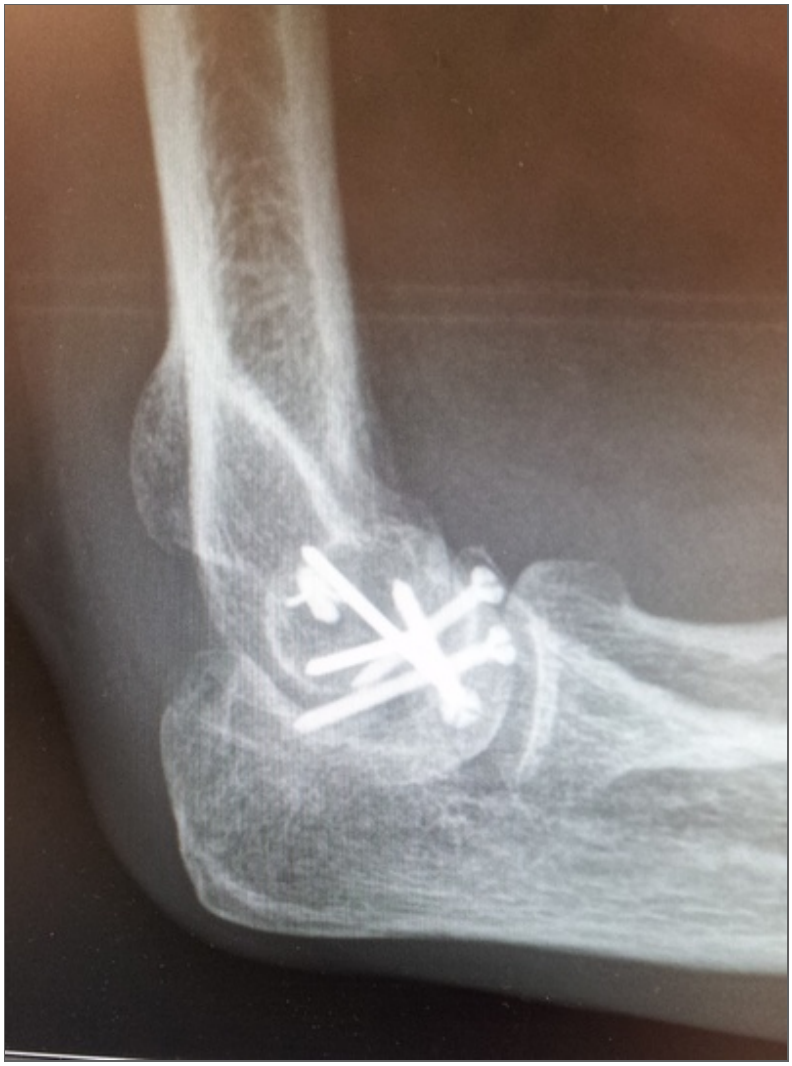
For Burrus, the impact of her injury is significant. "It's been a big challenge to learn how to live like this," she says. "I've had to learn to do everything, including write, with my left hand. All the sports I used to enjoy — swimming, yoga, skiing, volleyball — I can't do anymore. I often have horrendous pain in my shoulder and neck because those muscles do a lot of compensating for my elbow."

Research suggests new purpose for asthma drug

Hildebrand's research focuses on the joint capsule, the critical structure that limits motion after an injury. The joint capsule connects the ends of the bones that form a joint and is made of ligaments and tendons. In an injured joint capsule there is an increased number of mast cells, a cell type associated with inflammation, asthma and excessive scarring.

Hildebrand's research has shown that ketotifen, a medication used to treat asthma for over 40 years, shows promise in preventing post-traumatic contractions. Ketotifen works by inhibiting the activity of mast cells. "The prospects of using this drug to treat contractures is exciting. We know it is safe, it's readily available in pill form and it's inexpensive," says Hildebrand. But before ketotifen can be prescribed for joint injuries, its effectiveness needs to be proven.

With funding from the U.S. Department of Defense, Hildebrand has launched a multi-centre clinical trial in 16 centres across North America. The four-year study, which begins in April 2018, will recruit 702 people who have sustained an elbow injury that requires surgery. Participants will randomly receive either ketotifen or a placebo for six weeks after surgery, and then elbow range of motion will be measured for up to one year after the injury.



X-ray of Jacqueline Burrus's surgically repaired elbow.

Ketotifen offers hope for the future

At this point, Burrus doesn't qualify for the ketotifen study because the drug needs to be given right after surgery, but she sees hope in the new study. "I wouldn't want anyone else to go through what I have, because this has been an interesting adventure," says Burrus. "I do have faith that there is way to resolve this issue somehow."

Hildebrand will be talking about this study at the Wood Forum on Shoulder and Elbow Health, Oct. 28, 10 a.m – noon at the Red and White Club, McMahon Stadium. Find more information or register for the Wood Forum.

Kevin Hildebrand is an orthopaedic surgeon and a professor in the Department of Surgery in the Cumming School of Medicine. He is the deputy director of the McCaig Institute for Bone and Joint Health and the Chief of Orthopaedic Surgery, Alberta Health Services – Calgary Zone. Because joint injuries and subsequent contractures are common in Service members in combat or training exercises, this clinical trial is being funded by the U.S Department of Defense. The Canadian Institutes of Health Research, the American Foundation for Surgery of the Hand, and the Workers' Compensation Board of Alberta funded a prior pilot study.

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Prevention of Post-Traumatic Contractures with Ketotifen
Dr. Kevin Hildebrand, University of Calgary

Recently the military reviewed extremity injuries in war and determined that joint stiffness and contractures were a major complication that limits function. Approximately 200,000 elbow fractures or dislocations occur in adults each year in the United States and up to 30,000 individuals require surgery due to loss of elbow motion. Recent studies have shown that joint contractures result from a myofibroblast-mast cell-neuropeptide axis of fibrosis in the joint capsule, the critical structure limiting joint motion. Dr. Kevin Hildebrand and his research team sought to determine whether Ketotifen, a mast cell stabilizer that has been used in the treatment of chronic asthma for over 30 years, could reduce joint contracture severity. Using a rabbit model of post traumatic contractions, it was determined that Ketotifen prevents growth factor release and decreases contracture severity by 50%. Importantly, decreases in the number of myofibroblasts, mast cells, neuropeptide containing nerve fibers, and measures of fibrosis in the joint capsule were also observed. Based on these findings, and with support from an FY14 PRORP Clinical Trial Development Award, Dr. Hildebrand designed a Phase III multicenter randomized control trial. Dr. Hildebrand and his team built the necessary infrastructure to conduct the trial and report findings. Dr. Hildebrand was then awarded an FY16 PRORP Clinical Trial Award to support the execution of a Phase III clinical trial to determine the optimal dosage and efficacy of Ketotifen in preventing post-traumatic elbow joint contractures. Findings from these studies can aid in the development of a potential new therapy for joint fibrosis and contracture that repurposes an established drug for a new indication.

Subject: RE: [Non-DoD Source] Re: Response Required - CDMRP PRORP Research Highlight
Date: Monday, September 24, 2018 at 5:20:01 AM Mountain Daylight Time
From: Belton, Amy M CTR USARMY MEDCOM CDMRP (US)
To: Kevin A. Hildebrand

Hi,

There is now a final version of the program book that will be posted to the CDMRP website in the coming weeks.

I will send you the link once it is posted.

Amy

-----Original Message-----
From: Kevin A. Hildebrand [mailto:hildebrk@ucalgary.ca]
Sent: Monday, September 24, 2018 4:50 AM
To: Belton, Amy M CTR USARMY MEDCOM CDMRP (US) <amy.m.belton.ctr@mail.mil>
Subject: Re: [Non-DoD Source] Re: Response Required - CDMRP PRORP Research Highlight

Hi Amy,

No further picture updates. When will the next version with this article be published?

Thanks, Kevin Hildebrand

On 2018-08-13, 3:53 PM, "Kevin A. Hildebrand" <hildebrk@ucalgary.ca> wrote:

> Hi Amy,
>
> No team picture yet unfortunately. Maybe Monday August 20 if it is still possible.
>
> This is a recent picture of me.
>
> Kevin Hildebrand
>
> On 2018-08-13, 11:40 AM, "Belton, Amy M CTR USARMY MEDCOM CDMRP (US)" <amy.m.belton.ctr@mail.mil> wrote:
>
>> Sure I can share the link to the program book when it becomes available.
>>
>> Also, can you please provide a picture of yourself or your team to include with the highlight.
>>
>> Amy
>>
>> -----Original Message-----
>> From: Kevin A. Hildebrand [mailto:hildebrk@ucalgary.ca]
>> Sent: Monday, August 13, 2018 12:38 PM
>> To: Belton, Amy M CTR USARMY MEDCOM CDMRP (US) <amy.m.belton.ctr@mail.mil>
>> Cc: Alex Garven <Alexandra.Garven@albertahealthservices.ca>; hildadm <hildadm@ucalgary.ca>
>> Subject: Re: [Non-DoD Source] Re: Response Required - CDMRP PRORP Research Highlight
>>
>> You're welcome Amy. Can you send me a link to the article when it is posted?

Kevin Hildebrand

On 2018-08-13, 10:34 AM, "Belton, Amy M CTR USARMY MEDCOM CDMRP (US)" <amy.m.belton.ctr@mail.mil> wrote:

AWESOME!!! Thanks so much!!!!

-----Original Message-----
From: Kevin A. Hildebrand [mailto:hildebrk@ucalgary.ca]
Sent: Monday, August 13, 2018 12:16 PM
To: Belton, Amy M CTR USARMY MEDCOM CDMRP (US) <amy.m.belton.ctr@mail.mil>
Cc: Alex Garven <Alexandra.Garven@albertahealthservices.ca>; hildadm <hildadm@ucalgary.ca>
Subject: [Non-DoD Source] Re: Response Required - CDMRP PRORP Research Highlight

All active links contained in this email were disabled. Please verify the identity of the sender, and confirm the authenticity of all links contained within the message prior to copying and pasting the address to a Web browser.

Hi Amy,

This is excellent. No changes from me. Thank you!

Kevin Hildebrand

On 2018-08-13, 7:39 AM, "Belton, Amy M CTR USARMY MEDCOM CDMRP (US)" <amy.m.belton.ctr@mail.mil> wrote:

Hello Dr. Hildebrand,

I am reaching out to you regarding the review of the attached highlight. If you could review the attached highlight and get it back to me as soon as possible we would greatly appreciate it.

Thanks,

Amy

-----Original Message-----
From: Shuman Moss, Laurie A CTR USARMY MEDCOM CDMRP (US)
Sent: Wednesday, August 1, 2018 2:47 PM
To: hildebrk@ucalgary.ca
Cc: Belton, Amy M CTR USARMY MEDCOM CDMRP (US) <amy.m.belton.ctr@mail.mil>
Subject: Response Required - CDMRP PRORP Research Highlight

Dear Dr. Hildebrand,

The Congressionally Directed Medical Research Program's (CDMRP) Peer Reviewed Orthopaedic Research Program (PRORP) appreciates your hard work and

support! We would like to feature your research in the PRORP's annual program book and it could also appear on the CDMRP's website and in future annual report pages.

Please see last year's book at

Caution-http://cdmrp.army.mil/prorp/pbks/prorppbk2016.pdf.

I am requesting your approval to use the attached research summary in the upcoming months. If there is any information that you would like to add or change, please feel free to do so. We would like your response and any edits by Friday, August 10th.

Finally, although the Leidos, Inc. graphics department owns generic photos of laboratory equipment and reagents, we would like to brighten the report by adding photographs or graphics related to your specific research. We hope to use as many photos and graphics as space permits to create an eye-pleasing and scientifically interesting program book. Please send a photo of yourself/team and, if possible, a photo representing your research. Please note that by sending us electronic copies of your photographs, you

grant us your permission to use them in conjunction with references to your research.

Thank you so much for your time--I look forward to hearing from you!

All the best,

~Laurie

Laurie Shuman Moss, Ph.D.

Biomedical Life Scientist

5202 Presidents Court, Suite 110

Frederick, MD 21703

Phone: 240-529-0423

Fax: 301-846-0794

BCAHSN
ACADEMIC HEALTH SCIENCE NETWORK

Training Certificate

This is to certify that

Alexandra Garven

Completed 1.25 hours of training on the following BCAHSN training module

Clinical Trials BC Training Series

Regulatory 2018 – Good Documentation Practices - Records

June 20, 2018

Jean E. Smart

Jean Smart, RAC
Regulatory Affairs and Quality Officer
BCAHSN/Clinical Trials BC

June 20, 2018
Date

320

SOCRA

FOR CLINICAL RESEARCH EXCELLENCE

Certificate of Attendance

Alexandra Garven

Has Attended the

FDA Clinical Trial Requirements Regulations Compliance and GCP

May 15 and 16, 2018 Boston, MA, USA

SOCRA designates this educational activity for a maximum of 13.3 Continuing Education Credits for SOCRA CE and Nurse CNE.
SOCRA designates this live activity for a maximum of **13.3** *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

SOCRA Course Code # 18702

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Participants are asked to claim the actual number of CE hours attended. The Ms. Garven has attended _____hours.

SOCRA
530 West Butler Avenue, Ste. 109
Chalfont, PA 18914 U.S.A.
www.SOCRA.org

Director, Course Administrator

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

CUMMING SCHOOL OF MEDICINE
Dr. Kevin A. Hildebrand
Department of Surgery
Section of Orthopaedics
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

Alberta Health Services

March 19, 2018

Juan Rodriguez
USAMRAA Grants Officer
820 Chandler St.
Fort Detrick, MD 21702

RE: W81XWH-15-1-0605 Budget Extension

I request a 3-month extension to June 29, 2018 for the noted contract number. This is necessary to complete the final aspects of the Clinical Trial Development Award (CTDA). We have not received Human Research Protection Office (HRPO) final approval which has domino effects on certain parts of our CTDA. Specifically, we have not been able to send start-up funds to each site to get ethics and subaward contracts moving. A second area of focus is completing database development. Finally, we are working with Oxford University in developing French and Spanish translations of the Oxford Elbow Score (OES), the primary patient reported outcome measure for the trial. Three weeks are scheduled to have these completed.

Yours sincerely,

Dr. Kevin A. Hildebrand, Principal Investigator
Professor, Department of Surgery
Chief, Section of Orthopaedic Surgery
University of Calgary and Alberta Health Services – Calgary Zone

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

CUMMING SCHOOL OF MEDICINE
Dr. Kevin A. Hildebrand
Department of Surgery
Section of Orthopaedics
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

Alberta Health Services

March 19, 2018

Juan Rodriguez
USAMRAA Grants Officer
820 Chandler St.
Fort Detrick, MD 21702

RE: W81XWH-15-1-0605 Budget Redistribution

A request to redistribute the budget to reflect current needs is presented. There are two redistributions – an increase in the amount allocated to sites and translation of patient reported outcome measures. The details are below.

1. Amounts paid to sites – there are three components to this request. First, the number of sites has increased from 15 to 17. Second, the payment per site is increased to reflect more work on the local sites to comply with Human Research Protection Office (HRPO) compliance. Third, 5 sites require translation of consent forms and study protocols. The change is paying each site $4,000 instead of $2,500, and for those sites requiring translation, an additional translation fee of $1,000. Thus, the new total is 17 x $4,000 + 5 x $1,000 = $73,000. Using an exchange rate of C$1.00 = US$0.78, the new site payment total is $73,000 x 0.78 = **US$56,940**. The original Budgeted amount was US$28,500 (See Section F8b).

2. The Oxford Elbow Score (OES) is replacing the SF12 patient reported outcome measure. The OES is an elbow specific score unlike the SF12. It is validated on a United Kingdom English population but not a North American Population. There are no validated French or Spanish translations. Thus, all 3 languages (North American English, French, and Spanish) do not have a validated form of OES. The company can translate and validate the forms to a level that the results of the study could be used to support future applications to regulatory bodies (FDA, Health Canada) to use ketotifen for a new indication, post-traumatic joint contractures. Our goal is to make such an application after the trial results are completed and if a benefit is demonstrated. The quote from the company is 19,600 pounds sterling. Using an exchange rate of £1.00 = US$1.39, the new license fee is £19,600 x 1.39 = **US$27,244**. The original Budgeted amount was US$3,764 (see Section F4 – ADP/Computer Services).

The total to be redistributed is $56,940 - $28,500 **= $28,440** from request 1 and $27,244 - $3,764 = **$23,480** from request 2. $28,440 + $23,480 = **US$51,920** is the total to redistribute. This can be accommodated in Personnel and Travel expenses categories to stay within the total Budget amount.

Yours sincerely,

Dr. Kevin A. Hildebrand, Principal Investigator
Professor, Department of Surgery
Chief, Section of Orthopaedic Surgery
University of Calgary and Alberta Health Services – Calgary Zone

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE	PAGE OF PAGES
S	1 | 29

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO.(If applicable)
P00002	03-May-2018	0010706709	

6. ISSUED BY	CODE	7. ADMINISTERED BY (If other than item 6)	CODE
USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST FORT DETRICK MD 21702-5014	W81XWH	See Item 6	

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)		9A. AMENDMENT OF SOLICITATION NO.
GOVERNORS OF THE UNIVERSITY OF CALGARY, UNIVERSITY OF CALGARY 2500 UNIVERSITY DR NW CALGARY T2N 1N4		9B. DATED (SEE ITEM 11)
	X	10A. MOD. OF CONTRACT/ORDER NO. W81XWH-15-1-0605
CODE 1C344 FACILITY CODE	X	10B. DATED (SEE ITEM 13) 30-Sep-2015

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer ☐ is extended, ☐ is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

☐ A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.

☐ B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).

☐ C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:

X D. OTHER (Specify type of modification and authority)
IAW USAMRAA Terms and Conditions

E. IMPORTANT: Contractor ☒ is not, ☐ is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)
Modification Control Number: jrodrigu182586
Project Title: Prevention of Post traumatic Contractures with Ketotifen
PI: Dr. Kevin Hildebrand
Period of performance: 30 September 2015 to 29 June 2018
Award Amount$238,420.00
Obligated Amount$238,420.00
The purpose of this modification is to incorporate by reference a redistribution of the budget to allocate funds to sites and translation of patient reported outcome measures and, to extend the period of performance by 3 months, at no additional cost to the government, until 29 June 2018 per the recipient's request dated 19 March 2018. A final technical report will be due no later than 28 October 2018. Submission of SF-425 Financial Reports shall continue during the extension period. All other terms and conditions remain unchanged.

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)	16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)
Dr. John Reynolds Associate Vice President (Research)	TERESA PARKER-REESER / GRANTS OFFICER TEL: 301-619-2171 EMAIL: Teresa.M.ParkerReeser.civ@mail.mil
15B. CONTRACTOR/OFFEROR University of Calgary (Signature of person authorized to sign)	15C. DATE SIGNED JUN 07 2018
16B. UNITED STATES OF AMERICA BY (Signature of Contracting Officer)	16C. DATE SIGNED 03-May-2018

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION 00010 - SOLICITATION CONTRACT FORM

DELIVERIES AND PERFORMANCE

The following Delivery Schedule item for CLIN 0001 has been changed from:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
POP 30-SEP-2015 TO 29-MAR-2018	N/A	W03J USA MED RESEARCH MAT CMD W03J USA MED RESEARCH MAT CMD 1077 PATCHEL STREET FORT DETRICK MD 21702-5024 301-619-7416 FOB: Destination	W91ZSQ

To:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
POP 30-SEP-2015 TO 29-JUN-2018	N/A	W03J USA MED RESEARCH MAT CMD W03J USA MED RESEARCH MAT CMD 1077 PATCHEL STREET FORT DETRICK MD 21702-5024 301-619-7416 FOB: Destination	W91ZSQ

SECTION 00800 - SPECIAL CONTRACT REQUIREMENTS

The following have been modified:

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND (USAMRMC)
U. S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY (USAMRAA)

TERMS AND CONDITIONS FOR ASSISTANCE AGREEMENTS
WITH INSTITUTIONS OF HIGHER EDUCATION, HOSPITALS, AND
OTHER NON-PROFIT ORGANIZATIONS

Effective February 2015

AWARD SPECIFIC TERMS AND CONDITIONS

This award is a grant made under the authority of 10 U.S.C. 2358 and 10 U.S.C. 2371. The recipient's revised Statement of Work (SOW) dated 20 August 2015 and the revised budget dated 19 March 2018 for the application

submitted in response to the Fiscal Year 2014 Department of Defense (DoD) Peer Reviewed Orthopaedic Research Program Clinical Trial Development Award Program Announcement (Funding Opportunity Announcement Number W81XWH-14-PRORP-CTDA, which closed 24 October 2014) are incorporated herein by reference.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: 12.420

TERMS AND CONDITIONS INCORPORATED BY REFERENCE

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," (DoDGAR) other than Parts 32 and 33, 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, "Department of Defense FAR Supplement," are incorporated herein by reference, with applicability as stated in those provisions.

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/

ORDER OF PRECEDENCE

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

a. Federal statutes
b. Federal regulations
c. 2 CFR Part 200, as modified and supplemented by DoD's interim implementation found at 2 CFR Part 1103
d. Award-specific terms and conditions

ACCEPTANCE OF AWARD

The recipient is not required to countersign this award. In case of disagreement with any requirements of this award, the recipient shall contact the USAMRAA Grants Officer in order to resolve the issue(s). The recipient shall not assess any costs to the award or accept any payments until the issue(s) is resolved.

RECIPIENT RESPONSIBILITY

In addition to the responsibilities of the recipient as defined in the award or incorporated by reference herein:

a. The recipient will bear primary responsibility for the conduct of the research and will exercise sound judgment within the limits of the award's terms and conditions.

b. The Principal Investigator (PI) specified in the award document will be continuously responsible for the conduct of the research project and will be closely involved with the research effort. The PI, in coordination with the recipient's Office of Sponsored Projects/Business Office, is in the best position to determine the means by which the research may be conducted most effectively.

RESEARCH INTEGRITY AND MISCONDUCT

The recipient shall comply with the requirements of DoD Instruction 3210.7, "Research Integrity and Misconduct," Enclosure 4, "Requirements for Extramural Research Institutions" (available at: http://www.dtic.mil/whs/directives/corres/pdf/321007p.pdf), incorporated herein by reference.

AWARD MODIFICATION

The only method by which this 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.

PRIOR APPROVAL REQUIREMENTS

a. **Administrative Requirements** Prior approvals required by 2 CFR Part 200.308 are waived except those identified below. Recipients shall request prior written approval from the USAMRAA Grants Officer for:

(1) Change in the scope or the objectives of the project as stated in the approved SOW or approved modifications thereto, such as a change in the phenomenon(a) under study, even if there is no associated budget revision.

(2) Change in the PI or change in any key personnel specified in the award document.

(3) The absence for more than 3 months, or a 25 percent reduction in time devoted to the project, by the approved PI or Project Director.

(4) Additional Federal funding for the project.

(5) The transfer of funds allotted for training allowances (direct payment to trainees) to other categories of expense.

(6) The subaward, transfer, or contracting out of any work not approved under the original award. This provision does not apply to the purchase of supplies, materials, equipment, or general support services.

(7) Incurring pre-award costs exceeding 90 calendar days prior to the beginning date of the period of performance.

(8) Incurring pre-award costs prior to the funding of any optional requirements/periods.

(9) Expenditures for individual items of general-purpose equipment and specific-purpose equipment costing $5,000 or more, unless identified in the budget that is incorporated as part of the award.

(10) Charging as direct costs capital expenditures for improvements to equipment that materially increases the equipment's value or useful life.

(11) Making any fund or budget transfers over $25,000 involving alteration or renovation costs, for research projects that provide funds for alterations and renovations.

b. **Cost Principles**. Recipients shall request prior written approval from the USAMRAA Grants Officer for the inclusion of costs that require prior approval in accordance with 2 CFR Part 200 Subpart E, 45 CFR Part 74

Appendix E, and 48 CFR Parts 31 and 231, as applicable. In accordance with those cost principles, the recipient must request prior written approval from the USAMRAA Grants Officer for: (1) those selected items of cost requiring prior approval; and (2) the incurrence of special or unusual costs.

PRE-AWARD COSTS

The recipient may incur pre-award costs up to 90 calendar days prior to the start date of the award agreement in accordance with the 2 CFR 200.308(d)(1) and 200.458. Pre-award costs as incurred by the recipient must be necessary for the effective and economical conduct of the project, and the costs must be otherwise allowable in accordance with the appropriate cost principles. Pre-award costs are made at the recipient's risk. The incurring of pre-award costs by the recipient does not impose any obligation on the Government in the absence of appropriations, if an award is not subsequently made, or if an award is made for a lesser amount than the recipient expected.

CHANGE IN PERFORMANCE PERIOD

In accordance with 2 CFR 200.308(d)(2), the recipient may initiate, without prior approval, a one-time, extension without funds to the expiration date of the award for a period of up to 12 months, as long as the extension without funds does not involve a change in the approved objectives or scope of the project. The recipient shall notify the USAMRAA Grants Officer in writing at least 10 calendar days prior to the expiration date of the award. The notification shall state the additional time needed, the reasons for the extension, and the work to be completed during the extension period. The recipient must be current with all financial and technical reporting requirements and be in compliance with all other terms and conditions of the award. This one-time extension without funds may not be exercised merely for the purpose of using unobligated balances. An official modification to the award document must be issued by the USAMRAA Grants Officer to extend the period of performance.

UNOBLIGATED BALANCES

In accordance with 2 CFR 200.308(d)(3), the recipient is authorized to carry forward unobligated balances to subsequent periods of performance of the award.

MAXIMUM OBLIGATION

The maximum obligation of the Government for support of this award will not exceed the amount specified in the award, as modified. Awards 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, and other costs.

DISALLOWED COSTS

Funds shall not be used for the support of any costs disallowed by the Funding Opportunity Announcement, either as a direct or an indirect cost.

SUPPORTING INFORMATION

Information such as subawards, consultant agreements, vendor quotes, and personnel work agreements may be required in order to support proposed costs or to determine the employment status of personnel. The Government’s receipt of this information does not constitute approval or acceptance of any term or condition included therein.

FINANCIAL INSTABILITY, INSOLVENCY, BANKRUPTCY OR RECEIVERSHIP

a. The recipient shall immediately notify the USAMRAA Grants Officer of the occurrence of the following events: (1) the recipient’s financial instability that would negatively impact performance of this award; (2) the recipient’s or recipient’s parent's filing of a voluntary case seeking liquidation or reorganization under the

Bankruptcy Act; (3) the recipient's consent to the institution of an involuntary case under the Bankruptcy Act against the organization or organization's parent; (4) the filing of any similar proceeding for or against the recipient or recipient's parent, or its consent to, the dissolution, winding-up or readjustment of the recipient's debts, appointment of a receiver, conservator, trustee, or other officer with similar powers over the organization, under any other applicable state or federal law; or (5) the recipient's insolvency due to its inability to pay its debts generally as they become due.

b. Such notification shall be in writing and shall: (1) specifically set out the details of the occurrence of an event referenced in paragraph "a"; (2) provide the facts surrounding that event; and (3) provide the impact such event will have on the project being funded by this award.

c. Upon the occurrence of any of the five events described in paragraph "a" above, the Government reserves the right to conduct a review of this award to determine the recipient's compliance with the required elements of the award (including such items as cost share, progress towards technical project objectives, and submission of required reports). If the USAMRAA Grants Officer's review determines that there are significant deficiencies or concerns with the recipient's performance under the award, the Government reserves the right to impose additional requirements, as needed, including (1) change the payment method; (2) institute payment controls, and (3) require additional reporting requirements.

d. Failure of the recipient to comply with this term may be considered a material failure by the recipient to comply with the terms of this award and may result in termination.

TITLE TO TANGIBLE PERSONAL PROPERTY

Tangible personal property, to include equipment, acquired in whole or in part with award funds is considered to be exempt property in accordance with 2 CFR Parts 200.312 and 200.313. Title to all such exempt property vests in the recipient upon acquisition without further obligation to the Federal Government, except that the USAMRAA Grants Officer may require title be transferred to the Federal Government or to a third party if the project or program for which the equipment was purchased is transferred to a third party.

INTANGIBLE PROPERTY - DATA AND SOFTWARE REQUIREMENTS

All software and data first produced under the award are subject to the Federal Purpose license in accordance with the requirements of 2 CFR Part 200.315. The recipient grants to the Government all necessary and appropriate licenses as a condition of this award.

PATENTS AND INVENTIONS REPORTING REQUIREMENTS

a. iEdison and annual reporting. The recipient shall 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, inventions made during the year shall also be reported annually (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. The form shall be submitted electronically within 90 days of end of the term of award. List all inventions made during the term of the award, or state "none," as applicable. The award will NOT be closed until all reporting requirements have been met.

c. All reports shall be sent electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

FINANCIAL REPORTING REQUIREMENTS

The recipient shall use the Standard Form (SF) 425, "Federal Financial Report," for reporting individual awards. Quarterly and final reports are required for those awards receiving advance payments. Annual and final reports are required for those awards receiving cost reimbursement payments.

The Federal Financial Reporting period end dates fall on the end of the calendar quarter for quarterly reports (3/31, 6/30, 9/30, 12/31), end of the calendar year for annual reports (12/31), and the end date of the term of award for the final report. Quarterly reports shall be submitted no later than 30 days after the end of each quarter. Annual reports shall be submitted no later than 90 days after the end of the calendar year. Final reports shall be submitted no later than 90 days after the end date of the term of award.

Submission Instructions:

a. 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.

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

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

QUARTERLY TECHNICAL REPORTING REQUIREMENTS

For each year of the entire performance period of the award, the PI shall submit a Quarterly Technical Progress Report covering research results (positive and negative data) during each of the first three quarters. A Quarterly Technical Progress Report for the fourth quarter is not required, as the Annual Technical Report shall incorporate all four quarters of progress.

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

The Quarterly Technical Progress Report Format, available on web site https://www.usamraa.army.mil, is required. Each item of the report format shall be completed.

Each report shall 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 below. Name your file with your award number, followed by Year X Quarter Y Report (example: W81XWH-15-1-0000 Year 1 Quarter 1 Report.) If you have questions, contact the GOR.

Grants Specialist E-mail: juan.a.rodriguez236.civ@mail.mil

GOR E-mail: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil

The Quarterly Technical Progress Report shall be brief, factual, and informal, and shall be prepared in accordance with the following:

(1) FRONT COVER:

(a) Award Number:
(b) Log Number:
(c) Project Title:
(d) Principal Investigator Name:
(e) Principal Investigator Organization and Address:
(f) Principal Investigator Phone and Email:
(g) Report Date:

(h) Report Period:

(2) SECTION 1 -- Accomplishments: The PI is reminded that the recipient organization is required to obtain prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.

- What were the major goals of the project?
- What was accomplished under these goals?
- Describe the Regulatory Protocol and Activity Status (if applicable).
- What do you plan to do during the next reporting period to accomplish the goals and objectives?

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.

What was accomplished under these goals?

For this quarterly reporting period only describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided.

Describe the Regulatory Protocol and Activity Status (if applicable).

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state "Nothing to Report."

(a) Human Use Regulatory Protocols

TOTAL PROTOCOL(S): State the total number of human use protocols required to complete this project (e.g., "5 human subject research protocols will be required to complete the Statement of Work"). If not applicable, write "No human subjects research will be performed to complete the Statement of Work."

PROTOCOL(S): List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol _of_ total:
Human Research Protection Office (HRPO) assigned A-number:
Title:
Target required for clinical significance:
Target approved for clinical significance:
Submitted to and Approved by: Provide a bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).
Status: Report on activity status: (i) progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed (ii) amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

"Cadaver" is defined as a deceased person or portion thereof, and is synonymous with the terms "human cadaver" and "post-mortem human subject" or "PMHS." The term includes organs, tissues, eyes, bones, arteries or other specimens obtained from an individual upon or after death. The term "cadaver" does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a "cadaver" under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

TOTAL ACTIVITIES: State the total number of RDT&E, education or training activities that will involve cadavers. If not applicable, write "No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW)."

ACTIVITIES: Provide the following information in a bulleted list for all RDT&E, education or training activities involving human cadavers conducted or supported during the quarter:

- Title of the RDT&E, education or training activity
- SOW task/aim associated with the activity
- Date the activity was conducted
- Identification of the organization's responsible individual (e.g., PI or individual primarily responsible for the activity's conduct)
- Brief description of the use(s) of cadavers in the activity and the total number of cadavers used during the reporting period
- Brief description of the Department of Army organization's involvement in the activity
- Status of document submission and approvals
- Problems encountered in the procurement, inventory, use, storage, transfer, transportation and disposition of cadavers used for RDT&E, education or training. Examples of problems include but are not limited to: loss of confidentiality of cadaveric donors, breach of security, significant deviation from the approved protocol, failure to comply with state laws and/or institutional policies and public relations issues.

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S): State the total number of animal use protocols required to complete this project (e.g., "2 animal use research protocols will be required to complete the Statement of Work"). If not applicable, write "No animal use research will be performed to complete the Statement of Work."

PROTOCOL(S): List the identifier and title for all animal use protocols needed to complete the project. Include information about the approved target number for statistical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol _ of _ total:
Animal Care and Use Review Office (ACURO) assigned Number:
Title:
Target required for statistical significance:
Target approved for statistical significance:
Submitted to and Approved by: Provide a bullet point list of protocol development, submission, amendments, and approvals (include Institutional Animal Care and Use Committee (IACUC) in addition to ACURO).

Status: Provide a bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g., animal use protocol needs revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

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

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives in accordance with the approved SOW.

(3) SECTION 2 – Products: List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- publications, conference papers, and presentations;
- website(s) or other Internet site(s);
- technologies or techniques;
- inventions, patent applications, and/or licenses; and
- other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.

(4) SECTION 3 - Participants & Other Collaborating Organizations

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project. If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g., ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-control and constrained coding

(5) SECTION 4 –Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:

1. **Actual Problems or delays and actions to resolve them**

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

2. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

(6) SECTION 5 – Special Reporting Requirements:

Quad Charts: The Quad Chart (available on https://www.usamraa.army.mil) shall be updated and submitted as an attachment to the Quarterly Technical Report.

ANNUAL/FINAL TECHNICAL REPORTING REQUIREMENTS

Format Requirements:

a. Annual reports shall 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. Annual reports shall 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 shall 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 shall still be submitted within 30 days of the anniversary date of the award. A final report will be due upon completion of the extended performance date that describes the entire research effort.

b. A final report shall also be prepared in accordance with the RPPR and shall be submitted within 90 calendar days of the award performance end date. The report shall summarize the entire research effort, citing data in the annual reports and appended publications.

Although there is no page limitation for the reports, each report shall be of sufficient length to provide a thorough description of the accomplishments with respect to the approved SOW. Reports, in electronic format (PDF or Word file only), shall be submitted to https://ers.amedd.army.mil.

All reports shall have the following elements, in this order:

FRONT COVER:

Sample front cover is provided at http://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting. The Accession Document (AD) Number should remain blank.

Distribution: Reports must include one of two distribution statements:

(1) Unlimited Distribution: If the distribution will be unlimited (i.e., approved for public release), choose the form entitled "Award/Contract Front Cover – Unlimited Distribution A." Results of fundamental research should be public distribution except in rare and exceptional circumstances.

(2) Limited Distribution: If the distribution is to be limited, choose the form entitled "Award/Contract Cover – Limited Distribution B." After report submission, the GOR will review the appropriateness of using this distribution statement. The GOR has the right to challenge the validity of any restrictive markings. Reports that may be eligible for limited distribution may be ones that contain proprietary data that is not to be released to the public. If so, mark the cover page as "Proprietary". DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. The recipient shall maintain records sufficient to justify the validity of any restrictive markings. REPORTS NOT PROPERLY MARKED WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE.

For additional information regarding distribution statements, see DOD Instruction 5230.24 (available at http://www.dtic.mil/whs/directives).

For general information regarding report preparation, access the Research Resources, Technical Reporting, website at https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting.

STANDARD FORM 298: Sample SF 298 is provided at http://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting. The abstract shall be provided in Block 14 and shall state the purpose, scope, and major findings and be an up-to-date report of the progress in terms of results and significance. Abstracts will be submitted to the Defense Technical Information Center (DTIC) and shall not contain proprietary information. Subject terms are keywords that may have been previously assigned to the proposal abstract or are keywords that may be significant to the research.

Pages shall be numbered. The number of pages shall include all pages that have printed data (including the front cover, SF 298, table of contents, and all appendices). Page numbers must match the numbering shown on the Table of Contents.

TABLE OF CONTENTS: Sample table of contents is provided at http://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting.

Example Table of Contents

Page No.

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

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

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

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.

- What were the major goals and objectives of the project?
- What was accomplished under these goals?
- What opportunities for training and professional development did the project provide?
- How were the results disseminated to communities of interest?

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

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Generally, the goals will not change from one reporting period to the next and are unlikely to change during the final reporting period. However, if the awarding agency approved changes to the goals during the reporting period, list the revised goals and objectives. Also explain any significant changes in approach or methods from the agency approved application or plan.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

4. IMPACT: This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period. 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:

- the development of the principal discipline(s) of the project;
- other disciplines;
- technology transfer; or
- society beyond science and technology.

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (*Scientific American style*).

How the field or discipline is defined is not as important as covering the impact the work has had on knowledge and technique. Make the best distinction possible, for example, by using a "field" or "discipline," if appropriate, that corresponds with a single academic department (i.e., physics rather than nuclear physics).

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- improving social, economic, civic, or environmental conditions.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.
- Actual or anticipated problems or delays and actions or plans to resolve them.
- Changes that have a significant impact on expenditures.

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

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

6. PRODUCTS: List any products resulting from the project during the reporting period. Examples of products include:

- publications, conference papers, and presentations;
- website(s) or other Internet site(s);
- technologies or techniques;
- inventions, patent applications, and/or licenses; and
- other products.

If there is nothing to report under a particular item, state "Nothing to Report."

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

Report only the major publication(s) resulting from the work under this award. There is no restriction on the number. However, agencies are interested in only those publications that most reflect the work under this award in the following categories:

> **Journal publications**. List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Include any peer-reviewed publication in the periodically published proceedings of a scientific society, a conference, or the like. A publication in the proceedings of a one-time conference, not part of a series, should be reported under "Books or other non-periodical, one-time publications."
>
> Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).
>
> **Books or other non-periodical, one-time publications**. Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like.

Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Other publications, conference papers, and presentations. Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;
- biospecimen collections;
- audio or video products;
- software;
- models;
- educational aids or curricula;
- instruments or equipment;
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- clinical interventions;
- new business creation; and
- other.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Provide the following information on participants:

- what individuals have worked on the project?
- has there been a change in the other active support of the PD/PI(s) or senior/key personnel since the last reporting period?
- what other organizations have been involved as partners?

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

- Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

  Describe how this person contributed to the project and with what funding support. If information is unchanged from a previous submission, provide the name only and indicate "no change".

  Example:

Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g., ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-control and constrained coding
Funding Support:	The XYZ Foundation (Complete only if the funding support is provided from other than this award.)

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission.

Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."
Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- Financial support;

- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

8. SPECIAL REPORTING REQUIREMENTS:

QUAD CHARTS: N/A

9. APPENDICES: N/A

DELINQUENT REPORTS

If the recipient is delinquent on reporting requirements for other USAMRAA-sponsored awards, payments on this award may be withheld until acceptable delinquent reports have been submitted. No new awards will be issued to the recipient until all delinquent reports are submitted.

MANUSCRIPTS/REPRINTS

Copies of manuscripts or subsequent reprints resulting from the research shall be submitted to usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil.

PUBLICATION, ACKNOWLEDGEMENT, AND PUBLIC RELEASE

Publication. The recipient is encouraged to publish results of the research, unless classified, in appropriate media. One copy of each paper shall be submitted to the GOR simultaneously with its submission for publication. Copies of all publications resulting from the research shall be forwarded 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.

Acknowledgment. The recipient agrees that in the release of information relating to this award such release shall 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.

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

b. "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Orthopaedic Research Program under Award No. W81XWH-15-1-0605. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."

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

d. "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules." (http://www.nih.gov)

e. "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." (http://www.cdc.gov/biosafety)

Public release. Prior to release to the public, the recipient shall notify the USAMRAA Grants Officer and the GOR of the following: planned news releases, planned publicity, advertising material concerning grant/cooperative agreement 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.

SITE VISITS

The USAMRAA Grants Officer, or authorized representative, has the right to make site visits to review project accomplishments and to provide such technical assistance as may be required. If any site visit is made by the Government representative on the premises of the recipient or subrecipient, the recipient shall provide, and shall require its subrecipients to provide, all reasonable facilities and assistance for the safety and convenience of the Government representatives in the performance of their duties. All site visits and evaluations will be performed in such a manner as will not unduly interfere with or delay the work.

REQUEST FOR ADVANCE PAYMENTS WITH FULL FUNDING

a. Payments. Advance payments will be made to the recipient 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. It is anticipated that the Defense Finance and Accounting Service (DFAS) will disburse funds within 30 days of receipt of a proper grant voucher.

b. **A copy of the most recently submitted Federal Financial Report (SF 425) shall be attached in the WAWF e-Business Suite and submitted with each grant voucher for all grant voucher submissions subsequent to the initial grant voucher submission.**

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

d. If the recipient fails to perform or if the WAWF grant voucher submission does not have the most recent SF425 attached, the grant voucher will be rejected.

e. Interest Bearing Account. Unless exempted by applicable Treasury-State agreements in accordance with the Cash Management Improvement Act (CMIA) (31 USC 3335), the recipient shall deposit all advance payments into an interest bearing account. Interest over the amount of $500 per year shall 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 shall be sent electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

f. Request Schedule for Advances

Year One $216,280

Amount	Grant Voucher Submission Periods	CLIN/Subclin
$54,070	2015/09/30 – 2015/12/29	(CLIN #0001)

$54,070	2015/12/30 – 2016/03/29	(CLIN #0001)
$54,070	2016/03/30 – 2016/06/29	(CLIN #0001)
$54,070	2016/06/30 – 2016/09/29	(CLIN #0001)

Year Two $22,140

Amount	Grant Voucher Submission Periods	CLIN/Subclin
$11,070	2016/09/30 – 2016/12/29	(CLIN #0001)
$11,070	2016/12/30 – 2017/03/29	(CLIN #0001)

ELECTRONIC PAYMENT INSTRUCTIONS

The Wide Area Work Flow (WAWF) e-Business Suite is the required method to electronically process recipient 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). Recipients shall (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.

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.

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 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:
GRANTS OFFICER:
ADDITIONAL CONTACT: **usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**

Additional Instructions for Advance Payments Only:

For successful processing of the grant voucher, requests for advances must be submitted **in advance of the start date** of the quarter being billed. Requests can be submitted up to 30 days in advance of the start date of the quarter, but cannot be submitted in excess of 30 days of the start date of the quarter.

In the fields entitled "Period From Date" and "Period To Date," enter the complete quarterly period being billed (e.g., 2013/04/01 through 2013/06/30). Quarterly dates entered must be identical to the quarterly "Grant Voucher Submission Periods" shown in the "Request for Advance Payments" term in this award.

AWARD CLOSE OUT

a. The following documents shall be submitted within 90 calendar days of the end of the term of the award:

(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.

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

(4) Cumulative listing of only the nonexpendable personal property acquired with award funds for which title has not been vested to the recipient, if applicable. This may be submitted on institution letterhead. Submit to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

(5) Statement that there is or is not a residual inventory of unused supplies exceeding $5,000 in total aggregate value. This may be submitted on institution letterhead. Submit the statement to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

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

c. The recipient shall promptly refund any unspent balances of funds the DoD Component has paid that is not authorized to be retained by the recipient. **Make check payable to the U.S. Treasury and mail to:**

USAMRAA
Attn: MCMR-AAP-C
Award No. W81XWH-15-1-0605
820 Chandler Street
Fort Detrick, Maryland 21702-5014

RETENTION AND ACCESS REQUIREMENTS FOR RECORDS

With the exception of types of records described in 2 CFR 200.333(a) through (f), the recipient must retain financial and programmatic records, supporting documents, statistical records, and all other records of a recipient that are required by the terms of an award, or may reasonably be considered pertinent to an award, for a period of 3 years from the date of submission of the final Federal Financial Report (SF 425).

If the information described in this section is maintained on a computer, recipients shall retain the computer data on a reliable medium for the time periods prescribed. Recipients may transfer computer data in machine readable form from one reliable computer medium to another. Recipients' computer data retention and transfer procedures shall maintain the integrity, reliability, and security of the original computer data. Recipients shall also maintain an audit trail describing the data transfer. For the record retention time periods prescribed in this section, recipients shall not destroy, discard, delete, or write over such computer data.

TERMINATION

The Grants Officer may terminate or suspend, in whole or in part, this award by written notice to the recipient upon a finding that the recipient has failed to comply with the material provisions of this award, if the recipient materially changes the objective of the award, or if appropriated funds are not available to support the program. However, the Grants Officer may immediately suspend or terminate the award without prior notice when such action is necessary to protect the interests of the Government. No costs incurred during a suspension period or after the effective date of a termination will be allowable, except those costs which, in the opinion of the Grants Officer, the recipient could not reasonably avoid or eliminate, or which were otherwise authorized by the suspension or termination notice, provided such costs would otherwise be allowable under the terms of the award and the applicable Federal cost principles. In no event will the total of payments under a terminated award exceed the amount obligated in the award.

ENFORCEMENT

The procedures of 32 CFR 22.815 govern for processing recipient claims and disputes and for deciding appeals of Grants Officers' decisions. Appeals of a Grants Officer's decision will be resolved by the Head of the Contracting Activity (HCA). The decision by the HCA will be final and not subject to further administrative appeal. However, the recipient does not waive any legal remedy, such as formal claims, under Title 28 United States Code 1491, by agreeing to such provision. The enforcement remedies identified in this section, including suspension and termination, do not preclude a recipient from being subject to debarment and suspension under 2 CFR Part 1125.

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 the applicable protocol(s) proposed for this award will be issued in the form of an approval letter from the USAMRMC ACURO to the recipient. Furthermore, modifications to already approved protocols require approval by ACURO prior to implementation. For each fiscal year, the recipient shall maintain, and upon request from ACURO, submit animal usage information.

Non-compliance 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.

PROHIBITION OF USE OF HUMAN SUBJECTS

Research under this award involving the use of human subjects, to include the use of human anatomical substances or identifiable private information, shall not begin until the USAMRMC's Office of Research Protections (ORP) provides authorization that the research may proceed. Written approval to begin research will be issued from the USAMRMC ORP, under separate notification to the recipient. Written approval from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct research involving human subjects.

Research involving human subjects shall be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP. Complete study records shall be maintained for each human research study and shall be made available for review by representatives of the USAMRMC. Research records shall 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 major modifications to the protocol, continuing review documentation, and the final report are required 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, shall be promptly reported to the USAMRMC ORP.

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 including legal or medical actions, and any instances of serious or continuing noncompliance with regulatory requirements that relate to this clinical investigation or research, shall 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 the USAMRMC ORP Human Research Protection Office requirements and instructions can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.hrpo.

PROHIBITION OF USE OF HUMAN CADAVERS

Research, development, testing and evaluation (RDT&E), education or training activities involving human cadavers 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. Written approvals to begin the activity will be issued under separate notification to the recipient. Noncompliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

The recipient assures that all work involving the use of recombinant DNA will be in compliance with guidance provided at http://www4.od.nih.gov/oba.

NATIONAL POLICY REQUIREMENTS:

NONDISCRIMINATION

By accepting funds under this award, the recipient assures that it will comply with applicable provisions of the following national policies prohibiting discrimination:

a. On the basis of race, color, or national origin, in Title VI of the Civil Rights Act of 1964 (42 U.S.C. 2000d, et seq.), as implemented by DOD regulations at 32 CFR Part 195.

b. On the basis of sex or blindness, in Title IX of the Education Amendments of 1972 (20 U.S.C. 1681, et seq.), as implemented by DOD regulations at 32 CFR Part 196.

c. On the basis of age, in the Age Discrimination Act of 1975 (42 U.S.C. 6101, et seq.) as implemented by Department of Health and Human Services regulations at 45 CFR Part 90.

d. On the basis of handicap, in Section 504 of the Rehabilitation Act of 1973 (29 U.S.C. 794), as implemented by Department of Justice regulations at 28 CFR Part 41 and DOD regulations at 32 CFR Part 56, and the Architectural Barriers Act of 1968 (42 U.S.C. 4151, et seq.).

DEBARMENT AND SUSPENSION

The recipient assures that it will comply with the requirements regarding debarment and suspension in Subpart C of the OMB guidance in 2 CFR Part 180, as implemented by the DOD in 2 CFR part 1125. The recipient shall communicate the requirement to comply with Subpart C to persons at the next lower tier with whom the recipient enters into transactions that are "covered transactions" under Subpart B of 2 CFR Part 180 and the DOD implementation in 2 CFR Part 1125.

ENVIRONMENTAL STANDARDS

By accepting funds under this award, the recipient assures that it will:

Comply with applicable provisions of the Clean Air Act (42 U.S.C. 7401, et seq.) and Clean Water Act (33 U.S.C. 1251, et.seq.), as implemented by Executive Order 11738 [3 CFR, 1971-1975 comp., p. 799] and Environmental Protection Agency (EPA) rules at 40 CFR Part 32. In accordance with the EPA rules, the recipient further agrees that it will:

Not use any facility on the EPA's List of Violating Facilities in performing any award that is nonexempt under 40 CFR 15.5 (awards of less than $100,000, and certain other awards, exempt from the EPA regulations), as long as the facility remains on the list.

Notify the awarding agency if it intends to use a facility in performing this award that is on the List of Violating Facilities or that the recipient knows has been recommended to be placed on the List of Violating Facilities.

Identify to the awarding agency any impact this award may have on:

The quality of the human environment, and provide help the agency may need to comply with the National Environmental Policy Act (NEPA, at 42 U.S.C. 4321, et seq.) and to prepare Environmental Impact Statements or other required environmental documentation. In such cases, the recipient agrees to take no action that will have an adverse environmental impact (e.g., physical disturbance of a site such as breaking of ground) until the agency provides written notification of compliance with the environmental impact analysis process.

Coastal barriers, and provide help the agency may need to comply with the Coastal Barriers Resource Act (16 U.S.C. 3501, et seq.), concerning preservation of barrier resources.

Any existing or proposed component of the National Wild and Scenic Rivers system, and provide help the agency may need to comply with the Wild and Scenic Rivers Act of 1968 (16 U.S.C. 1271, et seq.).

DRUG FREE WORKPLACE

By accepting funds under this award, the recipient assures that it will comply with the "Government –Wide Drug-Free Workplace (Grants)" requirements specified by DoDGAR Part 26, Subpart B (or Subpart C, if the recipient is an individual) of 32 CFR Part 26 (2004), which implements sec.5151-5160 of Drug-Free Workplace Act of 1988 (41 U.S.C. 701,et seq.).

OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this award, or to any benefit arising from it, in accordance with 41 U.S.C. 22.

PREFERENCE FOR U.S. FLAG AIR CARRIERS

Travel supported by U.S. Government funds under this award shall use U.S.-flag air carriers (air carriers holding certificates under 49 U.S.C. 41102) for international air transportation of people and property to the extent that such service is available, in accordance with the International Air Transportation Fair Competitive Practices Act of 1974 (49 U.S.C. 40118) and the interpretative guidelines issued by the Comptroller General of the United States in the March 31, 1981, amendment to Comptroller General Decision B138942.

CARGO PREFERENCE

The recipient assures that it will comply with the Cargo Preference Act of 1954 (46 U.S.C. 1241), as implemented by Department of Transportation regulations at 46 CFR 381.7, which require that at least 50 percent of equipment, materials or commodities procured or otherwise obtained with U.S. Government funds under this award, and which may be transported by ocean vessel, shall be transported on privately owned U.S.-flag commercial vessels, if available.

CAMPUS ACCESS FOR MILITARY RECRUITING AND RESERVE OFFICER TRAINING CORPS

The following requirement applies to institutions of higher education.

As a condition for receipt of funds available to the Department of Defense (DoD) under this award, the recipient agrees that it is not an institution of higher education (as defined in 32 CFR part 216) that has a policy or practice that either prohibits, or in effect prevents:

(A) The Secretary of a Military Department from maintaining, establishing, or operating a unit of the Senior Reserve Officers Training Corps (in accordance with 10 U.S.C. 654 and other applicable Federal laws) at that institution (or any subelement of that institution);

(B) Any student at that institution (or any subelement of that institution) from enrolling in a unit of the Senior ROTC at another institution of higher education;

(C) The Secretary of a Military Department or Secretary of Homeland Security from gaining access to campuses, or access to students (who are 17 years of age or older) on campuses, for purposes of military recruiting in a manner that is at least equal in quality and scope to the access to campuses and to students that is provided to any other employer; or

(D) Access by military recruiters for purposes of military recruiting to the names of students (who are 17 years of age or older and enrolled at that institution or any subelement of that institution); their addresses, telephone listings, dates and places of birth, levels of education, academic majors, and degrees received; and the most recent educational institutions in which they were enrolled.

If the recipient is determined, using the procedures in 32 CFR Part 216, to be such an institution of higher education during the period of performance of this agreement, the Government will cease all payments of DoD funds under this agreement and all other DoD grants and cooperative agreements to the recipient, and it may suspend or terminate such grants and agreements unilaterally for material failure to comply with the terms and conditions of award.

RADIOACTIVE MATERIALS

The recipient assures that it will comply with Title 10 CFR 21. This regulation established procedures and requirements for implementation of Section 206 of the Energy Reorganization Act of 1974.

TRAFFICKING VICTIMS PROTECTION ACT

Trafficking in persons.

a. Provisions applicable to a recipient that is a private entity.

1. You as the recipient, your employees, subrecipients under this award, and subrecipients' employees may not—

i. Engage in severe forms of trafficking in persons during the period of time that the award is in effect;

ii. Procure a commercial sex act during the period of time that award is in effect; or

iii. Use forced labor in the performance of the award or subawards under the award.

2. We as the Federal awarding agency may unilaterally terminate this award, without penalty, if you or a subrecipient that is a private entity—

i. Is determined to have violated a prohibition in paragraph a.1 of this award term; or

ii. Has an employee who is determined by the agency official authorized to terminate the award to have violated a prohibition in paragraph a.1 of this award term through conduct that is either—

A. Associated with performance under this award; or

B. Imputed to you or the subrecipient using the standards and due process for imputing the conduct of an individual to an organization that are provided in 2 CFR 180, "OMB Guidelines to Agencies on Governmentwide Debarment and Suspension (Nonprocurement)," as implemented by our agency at 2 CFR part 1125.

b. Provision applicable to a recipient other than a private entity. We as the Federal awarding agency may unilaterally terminate this award, without penalty, if a subrecipient that is a private entity--

1. Is determined to have violated an applicable prohibition in paragraph a.1 of this award term; or

2. Has an employee who is determined by the agency official authorized to terminate the award to have violated an applicable prohibition in paragraph a.1 of this award term through conduct that is either—

i. Associated with performance under this award;

ii. Imputed to the subrecipient using the standards and due process for imputing the conduct of an individual to an organization that are provided in 2 CFR part 180, "OMB Guidelines to Agencies on Governmentwide Debarment and Suspension (Nonprocurement)," as implemented by our agency at 2 CFR part 1125.

c. Provision applicable to any recipient.

1. You must inform us immediately of any information you receive from any source alleging a violation of a prohibition in paragraph a.1 of this award term.

2. Our right to terminate unilaterally that is described in paragraph a.2. or b. of this section:

i. Implements section 106(g) of the Trafficking Victims Protection Act of 2000 (TVPA), as amended (22 U.S.C. 7104(g)), and

ii. Is in addition to all other remedies for noncompliance that are available to us under this award.

3. You must include the requirements of paragraph a.1 of this award term in any subaward you make to a private entity.

d. Definitions. For the purpose of this award term:

1. "Employee" means either:

i. An individual employed by you or a subrecipient who is engaged in the performance of the project or program under this award; or

ii. Another person engaged in the performance of the project or program under this award and not compensated by you including, but not limited to, a volunteer or individual whose services are contributed by a third party as an in-kind contribution toward cost sharing or matching requirements.

2. "Forced labor" means labor obtained by any of the following methods: the recruitment, harboring, transportation, provision, or obtaining of a person for labor or services, through the use of force, fraud, or coercion for the purpose of subjection to involuntary servitude, peonage, debt bondage, or slavery.

3. "Private entity" means:

i. Any entity other than a State, local government, Indian tribe, or foreign public entity, as those terms are defined in 2 CFR 175.25.

ii. Includes:

A. A nonprofit organization, including any nonprofit institution of higher education, hospital, or tribal organization other than one included in the definition of Indian tribe at 2 CFR 175.25(b).

B. A for-profit organization.

4. "Severe forms of trafficking in persons," "commercial sex act," and "coercion" have the meanings given at section 103 of the TVPA, as amended (22 U.S.C. 7102).

REQUIREMENTS FOR FEDERAL FUNDING ACCOUNTABILITY AND TRANSPARENCY ACT IMPLEMENTATION

Reference 2 CFR part 170, Appendix A to Part 170.

I. Reporting Subawards and Executive Compensation

A. Reporting of first-tier subawards.

1. Applicability. Unless you are exempt as provided in paragraph D. of this award term, you must report each action that obligates $25,000 or more in Federal funds that does not include Recovery funds (as defined in section 1512(a)(2) of the American Recovery and Reinvestment Act of 2009, Pub. L. 111-5) for a subaward to an entity (see definitions in paragraph e. of this award term).

2. Where and when to report.

i. You must report each obligating action described in paragraph a.1. of this award term to http://www.fsrs.gov.

ii. For subaward information, report no later than the end of the month following the month in which the obligation was made. (For example, if the obligation was made on November 7, 2010, the obligation must be reported by no later than December 31, 2010.)

3. What to report. You must report the information about each obligating action that the submission instructions posted at http://www.fsrs.gov specify.

B. Reporting Total Compensation of Recipient Executives.

1. Applicability and what to report. You must report total compensation for each of your five most highly compensated executives for the preceding completed fiscal year, if--

i. the total Federal funding authorized to date under this award is $25,000 or more;

ii. in the preceding fiscal year, you received—

(A) 80 percent or more of your annual gross revenues from Federal procurement contracts (and subcontracts) and Federal financial assistance subject to the Transparency Act, as defined at 2 CFR 170.320 (and subawards); and

(B) $25,000,000 or more in annual gross revenues from Federal procurement contracts (and subcontracts) and Federal financial assistance subject to the Transparency Act, as defined at 2 CFR 170.320 (and subawards); and

iii. The public does not have access to information about the compensation of the executives through periodic reports filed under section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m(a), 78o(d)) or section 6104 of the Internal Revenue Code of 1986. (To determine if the public has access to the compensation information, see the U.S. Security and Exchange Commission total compensation filings at http://www.sec.gov/answers/execomp.htm.)

2. Where and when to report. You must report executive total compensation described in paragraph b.1. of this award term:

i. As part of your registration profile at http://www.ccr.gov.

ii. By the end of the month following the month in which this award is made, and annually thereafter.

C. Reporting of Total Compensation of Subrecipient Executives.

1. Applicability and what to report. Unless you are exempt as provided in paragraph d. of this award term, for each first-tier subrecipient under this award, you shall report the names and total compensation of each of the subrecipient's five most highly compensated executives for the subrecipient's preceding completed fiscal year, if--

i. in the subrecipient's preceding fiscal year, the subrecipient received--

(A) 80 percent or more of its annual gross revenues from Federal procurement contracts (and subcontracts) and Federal financial assistance subject to the Transparency Act, as defined at 2 CFR 170.320 (and subawards); and

(B) $25,000,000 or more in annual gross revenues from Federal procurement contracts (and subcontracts), and Federal financial assistance subject to the Transparency Act (and subawards); and

ii. The public does not have access to information about the compensation of the executives through periodic reports filed under section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m(a), 78o(d)) or section 6104 of the Internal Revenue Code of 1986. (To determine if the public has access

to the compensation information, see the U.S. Security and Exchange Commission total compensation filings at http://www.sec.gov/answers/execomp.htm.)

2. Where and when to report. You must report subrecipient executive total compensation described in paragraph c.1. of this award term:

i. To the recipient.

ii. By the end of the month following the month during which you make the subaward. For example, if a subaward is obligated on any date during the month of October of a given year (i.e., between October 1 and 31), you must report any required compensation information of the subrecipient by November 30 of that year.

D. Exemptions. If, in the previous tax year, you had gross income, from all sources, under $300,000, you are exempt from the requirements to report:

i. Subawards, and

ii. The total compensation of the five most highly compensated executives of any subrecipient.

E. Definitions. For purposes of this award term:

1. Entity means all of the following, as defined in 2 CFR part 25:

i. A Governmental organization, which is a State, local government, or Indian tribe;

ii. A foreign public entity;

iii. A domestic or foreign nonprofit organization;

iv. A domestic or foreign for-profit organization;

v. A Federal agency, but only as a subrecipient under an award or subaward to a non-Federal entity.

2. Executive means officers, managing partners, or any other employees in management positions.

3. Subaward:

i. This term means a legal instrument to provide support for the performance of any portion of the substantive project or program for which you received this award and that you as the recipient award to an eligible subrecipient.

ii. The term does not include your procurement of property and services needed to carry out the project or program (for further explanation, see Sec. ---- .210 of the attachment to OMB Circular A-133, ``Audits of States, Local Governments, and Non-Profit Organizations").

iii. A subaward may be provided through any legal agreement, including an agreement that you or a subrecipient considers a contract.

4. Subrecipient means an entity that:

i. Receives a subaward from you (the recipient) under this award; and

ii. Is accountable to you for the use of the Federal funds provided by the subaward.

5. Total compensation means the cash and noncash dollar value earned by the executive during the recipient's or subrecipient's preceding fiscal year and includes the following (for more information see 17 CFR 229.402(c)(2)):

i. Salary and bonus.

ii. Awards of stock, stock options, and stock appreciation rights. Use the dollar amount recognized for financial statement reporting purposes with respect to the fiscal year in accordance with the Statement of Financial Accounting Standards No. 123 (Revised 2004) (FAS 123R), Shared Based Payments.

iii. Earnings for services under non-equity incentive plans. This does not include group life, health, hospitalization or medical reimbursement plans that do not discriminate in favor of executives, and are available generally to all salaried employees.

iv. Change in pension value. This is the change in present value of defined benefit and actuarial pension plans.

v. Above-market earnings on deferred compensation which is not tax- qualified.

vi. Other compensation, if the aggregate value of all such other compensation (e.g., severance, termination payments, value of life insurance paid on behalf of the employee, perquisites or property) for the executive exceeds $10,000.

FINANCIAL ASSISTANCE USE OF UNIVERSAL IDENTIFIER AND CENTRAL CONTRACTOR REGISTRATION

Reference 2 CFR part 25, Appendix A to Part 25.

I. Central Contractor Registration and Universal Identifier Requirements

A. Requirement for Central Contractor Registration (CCR). Unless you are exempted from this requirement under 2 CFR 25.110, you as the recipient must maintain the currency of your information in the CCR until you submit the final financial report required under this award or receive the final payment, whichever is later. This requires that you review and update the information at least annually after the initial registration, and more frequently if required by changes in your information or another award term.

B. Requirement for Data Universal Numbering System (DUNS) Numbers. If you are authorized to make subawards under this award, you:

1. Must notify potential subrecipients that no entity (see definition in paragraph C of this award term) may receive a subaward from you unless the entity has provided its DUNS number to you.

2. May not make a subaward to an entity unless the entity has provided its DUNS number to you.

C. Definitions. For purposes of this award term:

1. Central Contractor Registration (CCR) means the Federal repository into which an entity must provide information required for the conduct of business as a recipient. Additional information about registration procedures may be found at the CCR Internet site (currently at http://www.ccr.gov).

2. Data Universal Numbering System (DUNS) number means the nine-digit number established and assigned by Dun and Bradstreet, Inc. (D&B) to uniquely identify business entities. A DUNS number may be obtained from D&B by telephone (currently 866-705-5711) or the Internet (currently at http://fedgov.dnb.com/webform).

3. Entity, as it is used in this award term, means all of the following, as defined at 2 CFR part 25, subpart C:

a. A Governmental organization, which is a State, local government, or Indian Tribe;

b. A foreign public entity;

c. A domestic or foreign nonprofit organization;

d. A domestic or foreign for-profit organization; and

e. A Federal agency, but only as a subrecipient under an award or subaward to a non-Federal entity.

4. Subaward:

a. This term means a legal instrument to provide support for the performance of any portion of the substantive project or program for which you received this award and that you as the recipient award to an eligible subrecipient.

b. The term does not include your procurement of property and services needed to carry out the project or program (for further explanation, see Sec. ----.210 of the attachment to OMB Circular A-133, ``Audits of States, Local Governments, and Non-Profit Organizations").

c. A subaward may be provided through any legal agreement, including an agreement that you consider a contract.

5. Subrecipient means an entity that:

a. Receives a subaward from you under this award; and

b. Is accountable to you for the use of the Federal funds provided by the subaward.

(End of Summary of Changes)