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Protocol

A Pilot Randomized Controlled Trial for Hand Osteoarthritis

Version 5.0
5/6/2022

Grace H. Lo, MD MSc
Baylor College of Medicine
Michael E. DeBakey VA Medical Center
Houston, TX

History of Protocol Versions:

Version	Date	Summary of Revisions Made	Rationale
V 1.0	10-30-18	N/A	Original version created prior to receiving funding from NIAMS.
V 2.0	07-10-19	Slightly changed the title to allow blinding of the hypothesis and implementation of changes required once funding was received.	First version submitted to KAI prior to our Safety Officer Introductory Meeting.
V 3.0	11-18-19	Revisions to address requests identified by NIAMS after reviewing materials submitted for the Safety Officer Introductory Meeting and to address concerns raised at the Safety Officer Introductory Meeting.	Updated after our Safety Officer Introductory Meeting.
V 3.1	12-20-19	Revisions to address the plan to re-define difficulty donning or removing orthosis as something to track. It will no longer be considered an adverse event.	Treating difficulty donning or removing the orthosis as an adverse event will likely lead to unblinding of our primary assessor. By re-defining this as just something to track and not and adverse event, this will improve the likelihood that our primary assessor can maintain blinding.
V 4.0	7-8-20	Revisions to address the comments that arose from the KAI Introductory Site Visit.	Updated after the KAI Introductory Site Visit Meeting.
V 4.1	9-2-20	UADE defined. Revision made regarding how we will determine our n for the study.	Revisions to address the requests made based on the large round of revisions based on the KAI Introductory site visit. Issues raised included defining UADE –

			unanticipated device effects and revising our target recruitment numbers.
V 5.0	5/6/2022	Reduction of target N. The addition of NYU as an additional clinical site. They will perform all the same clinical activities, but will not be performing any blood draws or imaging.	Changes made to address challenges in recruitment and a change in personnel.

Contents

Abbreviation Glossary

Adverse Event (AE) – Any unfavorable and unintended diagnosis, sign (including laboratory finding), symptom or disease temporarily associated with the study intervention.

Australian Canadian Hand OA Index (AUSCAN) scale[1,2] – validated symptom and function scale for hand osteoarthritis.

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to record information about study participants.

Center for Epidemiologic Studies Depression Scale (CES-D) [3] – a validated measure of depression

Code of Federal Regulations (CFR) – An annual compilation of rules and regulations published in the Federal Register by the executive departments and agencies of the Federal Government.

Computerized Patient Record System (CPRS) – a Veterans Health Information Systems and Technology Architecture (VistA) computer application. CPRS enables providers to enter, review, and continuously update all the information connected with any patient. With CPRS, providers can order lab tests, medications, diets, radiology tests and procedures, record a patient's allergies or adverse reactions to medications, request and track consults, enter progress notes, diagnoses, and treatments for each encounter, and enter discharge summaries. In addition, CPRS supports clinical decision-making and enables review and analysis of patient data.

Conflict of Interest (COI) – A conflict of interest occurs when individuals involved with the conduct, reporting, oversight, or review of research also have financial or other interests that may be affected by the results of the research.

Consolidated Standards of Reporting Trials (CONSORT) – This encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials.

The CONSORT Statement – This is the main product of CONSORT. It is an evidence-based, minimum set of recommendations for reporting randomized trials.[4] It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. It is comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted; the flow diagram displays the progress of all participants through the trial.

Disabilities of the Arm, Shoulder, and Hand (DASH)[5] – developed in the 1990's, it is a patient-reported outcome measure for musculoskeletal conditions and injuries affecting the upper limb – the arm, shoulder, or hand.

Food and Drug Administration (FDA) – An agency within the U.S. Department of Health and Human Services (DHHS), responsible for protecting public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

Good Clinical Practice (GCP) – Section 2 from the International Council for Harmonisation provides guidance for good design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials to ensure data and results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – Public Law 104-191 provides for the protection of personal health information. The Privacy Rule, Title II of the Act, regulates the way certain health care

groups, organizations, or businesses, called covered entities under the Rule, use and disclose individually identifiable health information known as protected health information (PHI). Title II also establishes that covered entities ensure the security and privacy of PHI.

Institutional Review Board (IRB)– An independent body consisting of medical, scientific, and non-scientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and materials to be used to obtain and document the informed consent of trial participants.

International Conference on Harmonization (ICH) – An international collaboration between the United States, the European Union and Japan to harmonize the testing requirements of pharmaceutical products intended for human use. ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Harmonization is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side.

International Physical Activity Questionnaire (iPAQ)[6] – a validated questionnaire that asks questions about physical activity

Investigational New Drug Application (IND)/Investigational Device Exemptions (IDE) – An IND is the means through which the Food and Drug Administration (FDA) grants the sponsor permission to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application (21 CFR 312).

An IDE allows the investigational device to be used in a clinical trial to collect safety and effectiveness data for human use (21 CFR 812).

Manual of Operating Procedures (MOOP)/Manual of Procedures (MOP) – A “cookbook” that translates the protocol into a set of operational procedures to guide study conduct. A MOOP/MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) – The main veterans’ medical center in Houston and the setting where this study will take place.

National Archives and Records Administration (NARA) – guidance for the VA on how to manage records.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) – the funding body for this study.

Not Applicable (NA) –When recording data on a study form, if the information is not applicable, then the acronym NA should be used to fill out the field.

Not Available (NAV) – When recording data on a study form, if the information is not available, then the acronym NAV should be used to fill out the field.

Not Done (ND) – When recording data on a study form, if the evaluation required for a field is not done, then the acronym ND should be used to fill out the field.

Occupational Therapist (OT) – This is our study staff who provides occupational therapy to our participants and fits the participants with either the hand-based traction orthosis or the resting orthosis.

Office for Human Research Protection (OHRP) – A federal government agency within the Department of Health and Human Services (DHHS) charged with the protection of human subjects participating in government-supported research. The OHRP issues assurances to institutions reviewing human subjects research and oversees compliance of regulatory guidelines by research institutions.

Osteoarthritis (OA) – a common form of joint disease that most often affects the hands, hips, knees and feet and is the subject of study in this clinical trial.

Posterior-Anterior (PA) – Describes the direction that a radiograph is acquired.

Principal Investigator (PI) – The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial rules and requirements, administrative policies, and regulations associated with a grant or award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the research project rests with the Principal Investigator.

Proof of Concept (POC) – Describes the radiographs that evaluate the change in joint space that occurs with application of the traction and the resting orthoses.

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.).

Research Coordinator (RC) – An individual that handles the administrative and day-to-day responsibilities of a clinical trial. This person may collect or review data before it is entered in the study database.

Safety Monitoring Plan (SMP) – A plan that outlines the oversight of a clinical trial.

Safety Officer (SO) - The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single-site clinical studies. The Safety Officer advises the NIAMS Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Serious Adverse Event (SAE) – Any untoward medical occurrence that results in:

- death
- is life threatening
- requires or prolongs hospitalization
- causes persistent or significant disability/incapacity

- results in congenital anomalies/birth defects
- represents other significant hazards or potentially serious harm to research participants or others

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Unknown (UNK)- When recording data on a study form, if the information is unknown, then the abbreviation UNK should be used to fill out the field.

Veterans Administration (VA) – Health care system that serves United States veterans.

Veterans Health Administration Records Control Schedule 10-1 (VHA RCS 10-1) – Document which provides guidance for VA research on how long to retain and how to properly dispose of data.

Visual Analog Scale (VAS) – a psychometric response scale which can be used in questionnaires. It is a continuous scale.

STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

DATA COLLECTION INFRASTRUCTURE / SIGNIFICANT STATEMENT OF ATTESTATION

Most study data will be collected and managed using the REDCap electronic data capture tools, designed to comply with HIPAA regulations.[7,8] This is a VA approved electronic data capture software. As this is an electronic data capture tool, all users of this platform must access this tool using a computer with a stable internet connection. It is designed to support data capture for research studies from anywhere in the world with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption.[7] It provides: 1) an intuitive *interface for validated data entry* 2) *audit trails* for tracking data manipulation and export procedures 3) *automated export procedures* for seamless data downloads to common statistical packages, an essential feature for data back-up and 4) user-friendly procedures for importing data from external sources.[7] We will store all participant questionnaires, and study information on REDCap with the exception of screenshots used for eligibility assessments, consent forms, HIPAA forms, the primary source data for one functional assessment, photos, radiographs, MRIs, and daily log that participants will submit as a hardcopy at the end of the study. Only study personnel, NIH personnel, or IRB personnel who require information regarding the study will be given access to data stored in REDCap regarding this study.

A strong and consistent high speed internet connection accessed through a password protected desktop or laptop computer with a sufficient power source (either with sufficient charge in the battery or connected to a wall outlet) will be used to access REDCap to assure proper data capture, particularly at each in person visit but also with every instance of data entry.

All study related electronic data will be stored on R02HOUFPC001.r02.med.va.gov , and will be accessible through ***"\\r02.med.va.gov\Research\HOU\Production\Data\Housrd\Research\Lo_G_Hand_Study_H-44508".*** This folder will be housed on a secured server within the MEDVAMC network, which is part of the VA nationwide network. Hence, our computers conform to VA security policies and standards. These policies and standards include but are not limited to strong passwords, locking screensavers, up-to-date anti-virus protection, and storage of sensitive patient information stored on VA servers on the VA network. The servers are protected by user login and passwords. All servers are backed up daily to ensure data protection. Only study personnel, NIH personnel, or IRB personnel who require information regarding the study will be given access to data on this folder.

Study staff will collect data for use in this study only as specified above. Information will only be accessed as needed to schedule appointments, collect study-relevant data, and run data related analyses.

All staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

1.0 Executive Summary

Hand osteoarthritis (OA) is a common problem occurring between 37-44% of the general population,[9] and is associated with substantial functional limitations, similar to those who have rheumatoid arthritis.[10,11] To date, few therapies are effective in reducing pain in hand OA; and most are only based on expert opinion.[12-14] Current standard of care includes oral analgesics, oral/topical NSAIDs (if not contra-indicated), a thermal modality, orthoses, activity modification / joint protection education, and range of motion exercises.[12-14] Although nodal hand OA has traditionally not been viewed as a biomechanically driven the disease, there is growing evidence that indeed it is, including that collateral ligaments

surrounding a joint are consistently damaged,[15,16] which may lead to altered joint biomechanics. Highlighting the importance of this finding, other pathology is observed near these damaged ligaments in regions where features of OA tend to be found.[15-18]

For OA in the knee, a disease long known to be biomechanically driven,[19-27] surgical distraction is a novel treatment where peri-articular external pins and monotubes are placed preventing joint motion, providing intra-articular negative pressure, and increasing the joint space.[28] Distraction has been used successfully to treat people awaiting knee total knee arthroplasty, reducing pain, allowing growth of new articular cartilage, and ultimately delaying and sometimes obviating the need for arthroplasty.[28-33] Although an impressive observation, it is important to note serious complications associated with this intervention, including a 10% rate of pulmonary emboli despite anticoagulation and an 85% rate of pin site infection [28] that limit widespread use of this treatment. Nevertheless, this treatment provides an important proof of concept that unloading an osteoarthritic joint may allow both structure and symptom improvement.

Traction using non-invasive finger traps in nodal hand OA, a disease that may be biomechanically driven, has the potential of providing the benefits of distraction without the attendant complications. Therefore, in our study, we propose a pilot randomized controlled trial of traction on 40 participants recruited from the Michael E. DeBakey VA Medical Center with at least 3 joints affected by distal interphalangeal (DIP) nodal hand OA, with at least one joint with frequent pain. The hand with the DIPs with the greatest severity level of pain will be eligible for randomization into (1) standard of care or (2) traction plus standard of care. If results from this study support feasibility of implementing traction using finger trap splints, proof of concept that finger traps provide traction, as well as symptomatic / functional and structural improvement with traction therapy, we will use findings from this study to inform a larger R01 study that can be adequately powered to address efficacy and clinical utility of this treatment.

1.1 Schedule of Activities (SoA)

The schedule below is what is planned for our participants.

Procedures	Screening Visit - Day -30 to -1	Enrollment/Baseline Visit 1, Day 1 +/-7 days	Reminder Visit 1, Day 7 +/-3 days	Study Visit 2, Day 14 +/- 7 days	Reminder Visit 2, Day 21 +/-3 days	Study Visit 3, Day 28 +/- 7 days	Reminder Visit 3, Day 35 +/-3 days	Reminder Visit 4, Day 42 +/-3 days	Reminder Visit 5, Day 49 +/-3 days	Reminder Visit 6, Day 56 +/-3 days	Reminder Visit 7, Day 63 +/-3 days	Reminder Visit 8, Day 70 +/-3 days	Reminder Visit 9, Day 77 +/-3 days	Study Visit 4, Day 84 +/- 14 days	Reminder Visit 10, Day 91 +/-3 days	Reminder Visit 11, Day 98 +/-3 days	Reminder Visit 12, Day 105 +/-3 days	Reminder Visit 13, Day 112 +/-3 days	Reminder Visit 14, Day 119 +/-3 days	Reminder Visit 15, Day 126 +/-3 days	Reminder Visit 16, Day 133 +/-3 days	Reminder Visit 17, Day 140 +/-3 days	Reminder Visit 18, Day 147 +/-3 days	Reminder Visit 19, Day 154 +/-3 days	Reminder Visit 29, Day 161 +/-3 days	Final Study Visit, Day 168 +/- 14 days
Week	-4	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Screening Questionnaire	X																									
Eligibility Assessment		X																								
Baseline Demographics		X																								
Randomization		X																								
Create either the traction v resting hand orthosis		X																								
Repeated measures evaluation		X				X								X												X
Hand photographs		X				X								X												X
PA Radiographs		X																								X
MRI Screener		X																								X
Serum creatinine [a]		X																								X
Urine Pregnancy test [b]		X																								X
Proof of Concept Radiographs [c]				X																						
MRI of the most symptomatic DIP joint [c]				X																						X
Weekly Reminders (telephone, text, or email)			X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Adverse Event and Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Final Visit Assessment Questions																										X

[a] Only for those being screened for MRI
[b] Only for those of childbearing age who are women
[c] Only for a selected group of 10 participants

Table 1. Schedule of Activities.

2.0 Background and Significance

2.1 Hand Osteoarthritis Is a Public Health Problem. Hand osteoarthritis (OA) is a common problem occurring between 37-44% of the general population,[9] and is associated with substantial functional limitations and decreased quality of life, similar to those who have rheumatoid arthritis.[10,11] With aging of the general population, the burden of this disease is likely to increase. Additionally, few therapies are considered effective in reducing pain in hand OA; and most are only based on expert opinion.[12-14] Such therapies include oral analgesics, oral/topical NSAIDs (if not contra-indicated), thermal modalities, orthoses, activity modification / joint protection education, and range of motion exercises.[12-14] A proven treatment with even a modest effect could have a tremendous impact given the high prevalence of this debilitating disease.

2.2 Nodal OA is a Phenotype of Hand Osteoarthritis. Within hand OA, there are multiple phenotypes, including thumb base OA, nodal (Heberden's and Bouchard's) OA involving the interphalangeal (IP) joints, and erosive OA. The etiopathogenesis of these phenotypes are likely different. In this study, our primary interest is in nodal OA. Studies have shown that hand OA is symmetric and in women, is more likely to cluster by row of joints (i.e. involving multiple DIPs in the same hand) than by a ray (i.e. involving a DIP and a PIP in the same digit), although they also do cluster by ray.[34,35] For years, the prevailing thought regarding the underlying etiology of this phenotype was driven by this pattern of disease, suggesting a genetic or systemic factor driving the disease and less likely a biomechanical factor.[35]

2.3 Evidence of a Biomechanical Component to Hand Osteoarthritis. In an effort to better understand nodal OA, in particular to identify the anatomic region where non-traumatic hand OA begins, Tan et al performed a cross-sectional study evaluating differences among joints with chronic nodal OA, early nodal OA, latent OA, and normal joints using magnetic resonance imaging (MRI).[15] Tan et al found that joints with early and chronic nodal OA universally had some irregularity of their collateral ligaments, whether it was thickening, increased signal, and/or disruption of the collateral ligaments.[15] In figure 1, panel A is an MRI image where the black arrows indicate thickening and enhancement of the collateral ligaments and panel B is the companion diagram outlining the MRI findings where the green structures represent the collateral ligaments and the red arrows

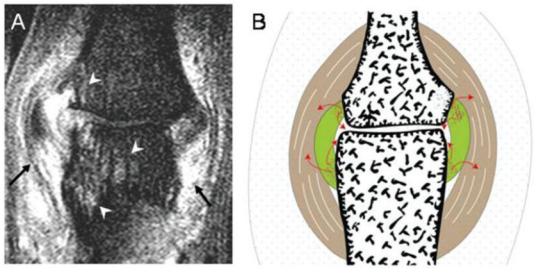

Figure 1. Panel A is an MRI image where the black arrows indicate thickening and enhancement of the collateral ligaments of a DIP. Panel B is a companion diagram outlining the findings from panel A MRI where the green structures are the collateral ligaments that have been subject to microdamage near the insertions, presumably resulting in inflammation (small red arrows) emanating from the ligament insertion sites. From McGonagle et al and Tan et al.

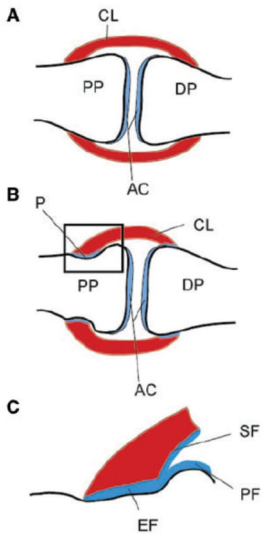

Figure 2. Schematic of collateral ligament attachments in the DIP joints. **Panel A** is a simplified diagram of the collateral ligaments, showing them attached to the bone just beyond articular cartilage. **Panel B** is a schematic providing greater detail of the true anatomic relationship of these structures where the position of the collateral ligaments on the proximal phalanx end is attached in a pit (P) further away from the joint, creating a unique spatial geometry in the way the ligament and bone interact. **Panel C** is an enlargement of the schematic in Panel B. This panel shows that there is enthesis fibrocartilage (EF), periosteal fibrocartilage (PF), and synovial fibrocartilage (SF) that[15] meet to form the Synovio-Entheseal Complex (SEC). From McGonagle et al.

represent resulting inflammation. [15,36]

Disease at the entheses was prominent in most joints with OA, most commonly at the collateral ligament entheses, though also present at the extensor tendon entheses.[16] Also there were 4 patterns of bone edema occurring in both early and chronic OA joints. The most common pattern was focal subchondral edema, mostly occurring on the proximal surface of the joints, just adjacent to where the collateral ligaments exert pressure on the proximal phalanx.[16] A second pattern of bone edema occurred at the site of collateral ligament attachment.[16] These two most common patterns of edema suggest that aberration in the collateral ligaments is potentially pathologic in developing bone edema.

Erosions, defined as cortical bone disruption in at least 2 planes, were observed in most patients with early and chronic OA, even when radiographs appeared normal and in many instances where articular cartilage was preserved.[16] There were 2 types of erosions. The less common type is the one that is well described in OA, the central erosions that are also called "seagull-wing erosions".[16] More interestingly, the more common type of erosions were peri-articular, often occurring adjacent to the collateral ligaments,[16] again suggesting that aberration of the collateral ligaments might be an instigating phenomenon in nodal hand OA. The observation of aberrant collateral ligaments with associated edema and proximate erosions has led to the concept of the synovio-entheseal complex (SEC) as seen in figure 2. If pathology in nodal OA indeed begins with derangement of the collateral ligament, this supports a biomechanical component to nodal hand OA.

2.4 Evidence that Biomechanics are Important in Knee Osteoarthritis. There is substantial data to support that biomechanics are important in the pathophysiology of knee OA, with research showing that static and dynamic alignment are potent predictors of compartment specific longitudinal progression,[20,21,25] including that varus and valgus (i.e. bow legged and knock-kneed) alignment are associated with longitudinal medial and lateral tibiofemoral joint space narrowing respectively. Also, bone marrow lesions, defined as increased signal within bone on intermediate weighted or T2 weighted fat suppressed images, have also been associated with longitudinal progression in a compartment specific manner where medial tibiofemoral bone marrow lesions are predictive of medial tibiofemoral joint space narrowing.[22,23] Furthermore, meniscal derangement is also associated with longitudinal compartment specific progression.[24] All taken together, the evidence for the central role of biomechanical factors in knee OA is strong.

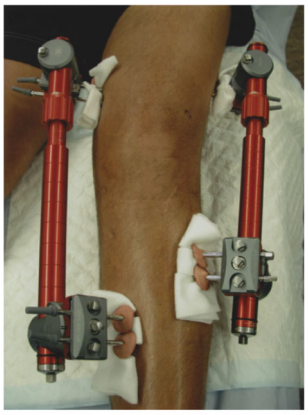

Figure 3. This is a knee that has been distracted, where peri-articular external pins and monotubes are placed to prevent joint motion, providing intra-articular negative pressure and increasing the joint space. Taken from Wiegant et al.

2.5 Distraction is a Treatment for Knee Osteoarthritis that Improves Structure and Symptoms. Distraction (figure 3) is a treatment where peri-articular external pins and monotubes are surgically placed preventing joint motion, providing intra-articular negative pressure, and increasing the joint space.[28] This treatment has successfully been used for people awaiting knee total knee arthroplasty, reducing pain, allowing growth of new articular cartilage, and ultimately delaying and sometimes obviating the need for arthroplasty.[28-33]

Although the distraction treatment was only applied for a total of 8 weeks, the benefits of the treatment extended to 12 and 24 months from a symptom and an articular cartilage perspective. There was an increase in the articular cartilage as

measured by MRI images with an improvement in cartilage thickness and in percent of bone that is denuded (figure 4). Furthermore, there was improvement in all domains of the WOMAC.[33]

Using a post-traumatic OA rat model where the anterior cruciate ligament (ACL) was transected and the medial meniscus was resected, the benefits of distraction, compared with fixation (where the joint was immobilized but negative pressure was not applied) compared to no treatment was studied.[31] Gross inspection of the articular cartilage showed that the rats receiving distraction had the smoothest articular cartilage and the fewest osteophytes.[31] (See figure 5.) Microscopically they also found less articular cartilage damage, lower levels of inflammatory markers in the serum and the less aberrant subchondral bone as measured by micro-CT and by immunohistochemistry with lower nestin and osterix levels in the distraction group.[31] These findings suggest that the benefits of distraction occur in multiple tissues in the joint and that those benefits exceed those of fixation alone. ***Distraction improves both structure and symptoms, unlike most other treatments for knee OA.***

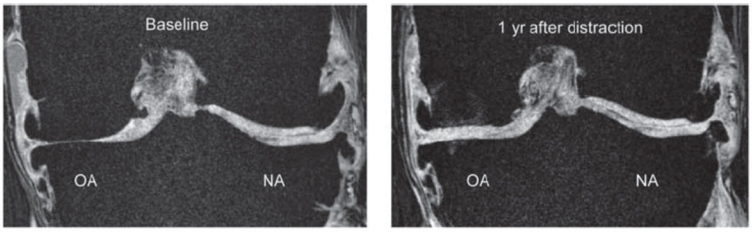

Figure 4. Over a one year follow up period, on the OA side of the knee, at baseline, the patient had almost complete denudation of the articular cartilage. One year after distraction, that part of the joint is resurfaced with articular cartilage. Taken from Intema et al.

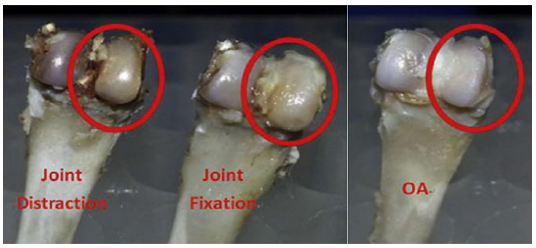

Figure 5. In an animal study of distraction versus joint fixation versus no treatment, those rats that received joint distraction had the least amount of articular cartilage damage on gross inspection after the animals were sacrificed. Taken from Chen et al.

2.6 Adverse Events Associated with Distraction. Although results from distraction are impressive, providing both symptom and structural benefits, serious associated complications, including a ***10% rate of pulmonary emboli despite anticoagulation*** and an ***85% rate of pin site infection*** [28] limit widespread use of this treatment. Nevertheless, this treatment provides an important proof of concept that unloading an osteoarthritic joint may allow structure and symptom improvement.

2.7 Finger Traps May Provide Traction to Finger Joints Similar to Distraction Without the Attendant Serious Adverse Events. Using knee OA as a model in which to think about hand OA, a joint where a biomechanical role has long been evident, (IA4.) we speculate that finger traps might be an effective non-invasive method of applying traction in hand OA. A finger trap is an medical device, already FDA-approved, that provides non-invasive traction to proximate joints, currently used as a treatment for distal radius fractures[37-40] and to assist in increasing the joint space for intra-operative procedures and for intra-articular small joint injections.[41] Unlike surgical distraction which is invasive, requiring placement of pins through bone, finger

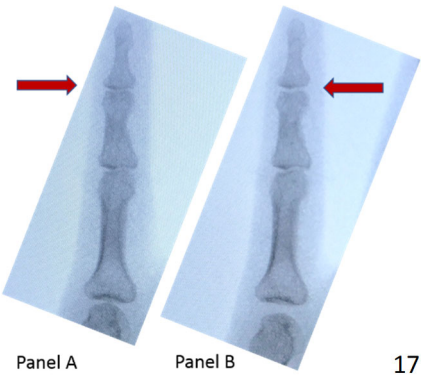

Figure 6. Fluoroscopic images of a 5th finger with nodal DIP OA. Panel A was obtained without a finger trap applied. Panel B was obtained with a finger trap applied. The red arrows highlight the increase in the DIP joint space with the finger trap applied.

traps are non-invasive and are not associated with an increased risk for infection. Also, since hands are not a common place for deep venous thrombosis, there is little risk for pulmonary emboli related to their use. Thus, finger traps may provide traction for hand OA without attendant serious adverse events associated with distraction.

We performed fluoroscopy on one volunteer with nodal hand OA, with and without a finger trap applied (Figure 6). With a finger trap there was an increase in the DIP joint space, indicated by the red arrows, as well as in all proximate joints. We also assessed tolerability of the traction orthoses on four volunteers. All were able to wear the orthoses for 30 minutes without any complaints. At 60 minutes, one volunteer complained of numbness that resolved within a few minutes after the finger trap was removed. There were no long-term sequelae related to application of the finger trap orthoses. These preliminary data support that finger trap orthoses provide traction as proposed and can be easily tolerated for a 30 - 60 minute wear time.

2.8 Expected Aims for the follow-up R01 to this R21. The findings from this study would provide essential feasibility and preliminary data for a follow up R01 that would fund a larger randomized controlled clinical trial of traction therapy to definitively assess its efficacy as a treatment for hand OA that would impact both structure and symptoms. In this R01, we would deploy comprehensive questionnaire, physical exams, radiographs, and MRIs on all participants for a longer duration of follow up. Information on participant compliance and comfort of the traction orthosis would be used to optimize traction delivery. Effect sizes of traction therapy for hand OA from this R21 would be instrumental in providing appropriate power calculations to design such a study. If we can show efficacy of this therapeutic intervention, this would be an impetus to widely disseminate this therapy for nodal OA.

*2.9 Innovation***.** There are three aspects of innovation in this study. The first is that the premise of this study is based on a novel idea that **nodal OA is a biomechanically driven disease** (2.3), supported by the widespread collateral ligament pathology in those with early and late OA and bone marrow edema and erosions occur in close proximity to the regions of collateral ligament derangement. This unique perspective inspired this pilot study. The second innovation is the use of knee OA as a model to consider hand OA which led us to consider the merits of **distraction, a unique treatment that has both symptom and structure benefits, in knee OA to hand OA**. The obstacles preventing wide-spread use of distraction in knee OA are potentially avoided by applying the proof of concept of this treatment to hand OA.(2.7) The final aspect of innovation is the **use of finger traps, a non-invasive medical device currently used for other purposes, to provide traction, as a possible combined symptom and structure treatment for nodal hand OA**.

3.0 Study Objectives

Specific aim 1. **Feasibility of a static hand based orthosis to apply finger traps**. The study OT will customize a static hand based orthosis that allows convenient application of finger traps for those receiving traction. We will record issues related to creating the traction orthoses, ease/difficulty of applying the intervention, comfort level while wearing the orthosis, hand pain, and compliance of wearing the orthosis. At the final study visit, we will also ask whether participants plan to use the orthosis after completion of the study.

Specific aim 2. **Proof of concept**. For 10 participants, 5 participants in each arm that are age and sex matched, at the two week follow up, we will obtain radiographs of the hand *with* and *without* orthoses applied to assess whether applying the traction orthosis results in an increase in joint space width.

Specific aim 3. **Symptomatic and functional outcomes**. At baseline, 1 month, 3 months, and 6 months follow up, we will assess outcomes including the visual analog scale (VAS) in the more symptomatic hand that includes the most symptomatic DIP joint (primary symptom outcome), the VAS pain scale of the most painful DIP, the AUSCAN function subscale,[1,2] the Functional Index for Hand Osteoarthritis (FIHOA),[42] the Disabilities of the Arm, Shoulder, and Hand (DASH)[5], the Functional Dexterity Test[43], grip and pinch strength, and tenderness on joint palpation on all participants.[44]

Specific aim 4. **Imaging outcomes**. On all participants, we will obtain bilateral hand radiographs at baseline and at 6 months to assess changes in Kellgren and Lawrence scores[45] (primary structure outcome), joint space narrowing, and osteophyte scores,[46] and Verbruggen-Veys [47] in the DIP joints. On 5 participants in each treatment arm (age and sex matched), we will obtain high resolution MRI imaging at week 2 and at 6 months to evaluate collateral ligament thickening, enthesial bone marrow edema, and erosions of the most symptomatic DIP.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary symptom objective is to assess whether traction therapy plus standard of care treatment for nodal OA reduces symptoms more than standard of care treatment that includes a resting hand splint.	The primary symptom endpoint will be pain as assessed on a visual analog scale (VAS) in the more symptomatic hand that includes the most symptomatic DIP joint by 24 weeks of use of traction therapy with standard of care treatment for hand OA to establish efficacy of traction therapy.	This outcome measure has been recommended by the OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis.[44] It has also been supported by the Update of OMERACT Hand OA Outcomes.[48]
The primary structure objective is to assess whether traction therapy plus standard of care treatment for nodal OA reduces structural progression compared with standard of care treatment that	The primary structure endpoint will be change in sum of the Kellgren and Lawrence score[45] of all DIPs in the hand that was braced over 24 weeks.	The use of radiographic imaging as a means of measuring structural outcome has been recommended by the OARSI Clinical Trials

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
includes a resting hand splint.		Recommendations: Design and conduct of clinical trials for hand osteoarthritis.[44] Although there are limitations to the use of Kellgren and Lawrence scoring which was first described in 1957, currently there are no agreed upon alternatives to this scoring strategy.
Secondary		
The secondary symptom objectives are to assess whether traction therapy plus standard of care treatment for nodal OA reduces symptoms more than standard of care treatment that includes a resting hand splint using alternative hand symptom and function outcomes.	The secondary symptom endpoint will be pain and function in the more symptomatic hand that includes the most symptomatic DIP joint by 24 weeks of use of traction therapy with standard of care treatment for hand OA to further support efficacy of traction therapy. These outcomes will include: • The Functional Index for Hand Osteoarthritis (FIHOA)[42] • The Disabilities of Arm Shoulder and Hand (DASH)[49-51] • The Functional Dexterity Test[43] • Grip strength • Pinch strength • Tenderness on joint palpation.	As this is a pilot study, we are making an attempt to include other measures that might also be of relevance and may perhaps be more useful in the follow up study to this pilot.
The secondary structure objectives are to assess whether traction therapy plus standard of care treatment for nodal OA reduces structural progression compared with standard of care treatment that includes a resting hand splint.	The secondary structure endpoints will be change in sum of the following scores all DIPs in the hand that was braced over 24 weeks: • joint space narrowing • osteophyte scores • Verbruggen-Veys scores	Although a 24 week follow up time period might be too short to see a difference in the treatment arms, it is worth a look at the different radiographic features of OA to see if

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		they are different between the two treatment arms.
Tertiary/Exploratory		
The tertiary / exploratory structure objective is to assess whether traction therapy plus standard of care treatment for nodal OA modifies features of OA seen on MRI more compared with standard of care treatment that includes a resting hand splint.	The exploratory endpoints include measurement in the most symptomatic DIP: • collateral ligament thickening • enthesial bone marrow edema • erosions Because this is a pilot study and we only had limited funds to obtain MRIs, we are only evaluating these changes on 5 people in each treatment arm.	Prior observational studies indicated that there is pathology in these structures visualized on MRI.[15,16,36] Perhaps these might change over a shorter period of time than radiographs. If there is a signal with these measures then we might include MRI for all participants for the follow up clinical trial.
The tertiary / exploratory clinical assessment objective is to evaluate whether traction therapy plus standard of care treatment for nodal OA modifies visual appearance of Heberden's nodes using photographs compared with standard of care treatment that includes a resting hand splint.	Visual inspection of the digital photographs for differences in erythema of the most symptomatic DIPs.	This is a low risk outcome measure. Although it is not currently viewed as a standard outcome measure, if we can show this is a useful outcome measure this might serve as preliminary evidence to use this in our follow up study.

Table 2. Study Objectives, Endpoints, and the Justification of those Endpoints.

4.0 Study Design

4.1 Overview of the Proposed Study. This is a pilot randomized controlled clinical trial (n=40) of finger traction therapy in the treatment of nodal hand OA where the control arm will receive the standard of care and the treatment arm will additionally use a finger traction orthosis.

4.2 Investigators/Co-Investigators/Collaborators/Consultants

Grace Hsiao-Wei Lo, MD MSc. Principal Investigator (PI) and Study Physician. She is an Assistant Professor at Baylor College of Medicine (BCM) in the Section of Immunology, Allergy, and Rheumatology, and an Affiliate Member of the Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) and BCM. She has a Master's of Science in Epidemiology and has been studying OA for the last 15 years, authoring more than 50 peer-reviewed manuscripts. Most of her research has focused on identifying and understanding risk factors, outcome measures, and treatments for knee OA. Her understanding of knee OA, in conjunction with the novel perspective regarding the biomechanical role in the etiopathogenesis of hand OA, has inspired this proposed study. Dr. Lo has recently been awarded an R03 (AR069323) where she has recruited offspring of the Osteoarthritis Initiative, a large observational cohort study of osteoarthritis to better understand risk factors of early OA. The experience she has and will accumulate from the R03 will inform the conduct of this proposed study. Additionally, this study will recruit from the MEDVAMC, where she has had her rheumatology clinical practice for the last 8 years. Her time at the MEDVAMC has fostered collaborative relationships with other health care providers, such as the occupational therapist on this study. She has an excellent understanding of the inner workings of the hospital where participants will be recruited and this study will be deployed. She will conduct all the eligibility assessments, provide physician visits should they be requested, and perform all adverse event assessments.

Jonathan Samuels, MD. Co-Investigator. He is an investigator in clinical and translational knee OA studies and is a board-certified rheumatologist. Since joining the New York University (NYU) faculty in 2006, he has initiated the largest registry and biorepository of North American patients with isolated hand OA, currently at N=160. Dr. Samuels has agreed to be the site PI for a second recruitment location at NYU/Langone as we have had difficulty recruiting for this clinical trial. He has agreed to aim to recruit 10 participants for our trial. Dr. Samuels a long-standing collegial relationship with Dr. Lo. Dr. Samuels has an excellent understanding of the inner workings of the hospital where participants will be recruited from the NYU clinical site. He will conduct all the eligibility assessments, provide physician visits should they be requested, and perform all adverse event assessments.

Kimberly Goldie-Staines, BS. Co-investigator. She is an occupational therapist and certified hand therapist who worked at the MEDVAMC for the last 10 years who is fellowship trained in hand therapy. She has always had a passion for academic medicine. She has collaborated on numerous research projects with hand surgeons related to surgical outcomes and has co-authored 5 peer-reviewed publications. She has been instrumental in creating orthosis that delivers the traction therapy and has trained our current Study Hand Occupational Therapists in how to fabricate this orthosis as well as a comparable control. She has recently moved abroad to the United Kingdom but maintains a Workers without Compensation (WOC) status to continue work on our study. She still meets with our team regularly via Zoom to assist with study related questions and will assist in interpretation and report of our findings once we close the data for analysis. She will liaise regularly with the OT team at NYU to address any questions or concerns regarding fabrication or application of the orthoses.

Gerald Virtanen, Masters of Occupational Therapy. Co-investigator and Study Hand Occupational Therapist (OT). He is an occupational therapist and certified hand therapist at the MEDVAMC for the last 5 years. To date, he spends most of her work hours as a clinician. From a clinical perspective, he treats people with hand OA daily. For this project, at the MEDVAMC clinical site, he will provide participants of this study with the standard of care for hand OA, including a thermal modality, joint protection strategies, and range of motion exercises. Additionally, he will customize either a resting hand orthosis or a traction hand orthosis, depending on the treatment group based on randomized.

Laura Welsh, MSc. Co-investigator and Study Hand Occupational Therapist (OT). She is an occupational therapist and certified hand therapist who joined NYU Langone Health in 2009 and is the Supervisor of the hand therapy department at NYU Langone Orthopedic Center. Laura earned her Master's of Science in Occupational Therapy from New York University and is a Certified Hand Therapist (CHT). She holds a number of advanced certifications in several therapeutic techniques. Her areas of interest include complex splinting, and conditions of the upper extremity. She has published in the journal of hand therapy in the area of wrist proprioception as well as in an orthopedic textbook on the topic of rehabilitation of the shoulder post arthroplasty. Laura has presented at a number of NYU academic conferences and is an active member of the Rusk Strategic Plan initiative. For this project, at the NYU clinical site, she will supervise the fabrication and application of orthoses to participants of this study, depending on the treatment group based on randomized. She will liaise regularly with the OT team at BCM/VA with any questions or concerns regarding fabrication or application of the orthoses.

Monica Seu, Co-investigator and Study Hand Occupational Therapist (OT). Monica is an occupational therapist who joined NYU Langone Health in 2000 and is the Hand Therapy Fellowship Coordinator at NYU Langone Orthopedic Center. Monica earned her Master's of Science in Occupational Therapy from Touro College and is a Certified Hand Therapist (CHT). She holds a number of advanced certifications in several therapeutic techniques. Her areas of interest include complex splinting, and conditions of the upper extremity. She has participated in a research project looking at instrument assisted mobilization in the treatment of de Quervain's and contributed to a chapter in Hand Clinics regarding the rehabilitation of patients with intrinsic muscle issues. Monica has presented at a number of NYU academic conferences and at AOTA. For this project, at the NYU clinical site, she will provide participants of this study with the standard of care for hand OA, including a thermal modality, joint protection strategies, and range of motion exercises. Additionally, she will customize either a resting hand orthosis or a traction hand orthosis, depending on the treatment group based on randomized.

Peter Richardson, PhD. Co-investigator. He is an Assistant Professor and senior biostatistician in the Department of Medicine, Section of Health Services Research at BCM. He also has an appointment at the IQuESt, at Baylor College of Medicine and the MEDVAMC and his office is housed in the same Center as Dr. Lo. Dr. Richardson will provide intellectual input on the overall design and execution of this study, statistical analyses, and interpretation of results for this project. Additionally, he will assist with issues related to quality control and quality assurance, generating randomization assignments for this study and assisting with subgroup selection for proof of concept x-rays and the group that will receive MRIs.

Timothy E. McAlindon, MD MPH. Co-investigator. He is Professor of Medicine and the Chief of the Division of Rheumatology at Tufts Medical Center. From 2004 – 2009, Dr. Lo was faculty in his division. She moved from Boston to Houston for personal reasons and was fortunate to find an academic position at BCM and MEDVAMC. Although Dr. Lo changed institutions, Drs. Lo and McAlindon have continued to collaborate on many projects, including two R01 funded

projects (AR054938 and AR060718) where he was PI and Dr. Lo was co-I. Dr. McAlindon has an exemplary track record of conducting clinical trials in OA, including two trials evaluating vitamin D and intra-articular corticosteroids in the treatment of knee OA. Further, he has an R01 (AR066378) studying hand OA within the Osteoarthritis Initiative. Dr. McAlindon will provide his expertise as a consultant in conducting OA clinical trials and general knowledge about hand OA to this project.

Ida K. Haugen, MD PhD, Consultant. Dr. Haugen is a rheumatologist at the Diakonhjemmet Hospital, Oslo, Norway and an accomplished hand OA researcher. She is co-chair of the Outcome Measures in Rheumatology (OMERACT) hand OA task force, co-chair of the development of EULAR classification criteria for hand OA, and principal investigator on the Oslo Hand Cohort and the Nor-Hand Study. She has extensive experience in evaluation of radiographic changes in hand osteoarthritis (OA), having undergone training in Kellgren-Lawrence,[45] OARSI atlas,[46] and Verbruggen-Veys[47]. The last 7 years, she has scored more than 5000 cases in various Norwegian (Oslo hand OA cohort, the MUST study) and North-American cohorts (Framingham and Osteoarthritis Initiative). For this study, Dr. Haugen will provide batched readings for bilateral hand x-rays at baseline and 6 month follow up x-rays on all participants after all participant follow up is completed. She will score paired Kellgren and Lawrence grades, OARSI osteophyte and joint space narrowing (JSN) scores, as well as the Verbruggen-Veys anatomic phase score for each hand joint on each film.

Andrew Grainger BMed Sci, BMBS, MRCP, FRCR, Collaborator. Dr. Grainger is a radiologist researcher and has been the consultant Musculoskeletal Radiologist to the Leeds Teaching Hospitals NHS Trust and Honorary Associate Professor to Leeds University. Within the subspecialty he has particular interests in arthritis and sports imaging. Drs. Grainger and Lo have a track record of collaboration, including two projects where they helped create semi-quantitative MRI based scoring systems for knee OA, the Boston Leeds Knee MRI Score (BLOKS)[52] and the MRI Osteoarthritis Knee Score (MOAKS)[53]. Dr. Grainger also collaborated with investigators Drs. Tan and McGonagle who first described the aberrant collateral ligaments in hand OA.[15,16,18,36] Using the same scoring system used in those prior studies with Drs. Tan and McGonagle, Dr. Grainger will score the MRIs for this study in a small subgroup of people in each treatment arm to evaluate for MRI benefits that might result from joint traction.

Michael Strayhorn, MPH, Research Coordinator. The research coordinator for this study will recruit for this study, assist Dr. Lo in assessing eligibility, consent participants, and administer all the baseline and 1 month, 3 month, and 6 month questionnaires and exams blinded to the treatment assignment. Additionally, he/she will schedule appropriate radiographs and MRIs for study participants. He/she will also be instrumental in creating and ultimately use the data management system for this study.

Apoorva Patil, MBBS, DNB, Research Coordinator. She joined NYU Langone Health in 2020 and works as a Research Coordinator in the department of Rheumatology. She completed her medical degree and surgical residency in India, and in recent years has pivoted to clinical research. She has been working with Dr. Jonathan Samuels on multiple hand and knee osteoarthritis studies. In addition to her core responsibilities, Apoorva has been involved in analyzing data and writing research papers for these studies. She will serve as the research coordinator for this study at the NYU clinical site. She will recruit for this study, assist Dr. Samuels in assessing eligibility, consent participants, and administer all the baseline and 1 month, 3 month, and 6 month questionnaires and exams blinded to the treatment assignment.

4.3 Subject Participation Duration

4.3.a Study Participation Duration:

- **Week -1**: Screening Visit (phone or email) (10 - 20 minutes) – Assess preliminary eligibility criteria
- **Week 0**: Eligibility/Baseline Visit (6 hours) – assess eligibility criteria, obtain informed consent, all clinical outcome assessments, hand x-rays, prescreening assessment for MRI, hand therapist will provide non-pharmacologic therapies for hand OA, randomization allocation, creation of hand orthosis based on randomization allocation.
- **Week 2**: Study Visit (0.5 – 3 hours) – All participants: hand therapist assess orthosis fit; for selected 10 people: proof of concept X-rays, with and without orthoses in place AND MRI of one finger DIP
- **Week 4**: Study Visit (1.5 hours) – all clinical outcome assessments, hand therapist assess orthosis fit.
- **Week 4 – 6**: Study Visit (0.5 hours) – MD visit if requested.
- **Week 12**: Study Visit (1 hour) – all clinical outcome assessments.
- **Week 24**: Study Visit (3-4 hours) – all clinical outcome assessments, bilateral hand X-rays, follow up MRI (if it was done at week 2.

4.3.b Study Duration: The estimated time between when study opens for enrollment and final data collection occurs is 18 months. The estimated time between when study opens for enrollment and final data analysis is completed is 30 months.

5.0 Study Population

5.1 Recruitment of Participants. We will recruit participants at the Michael E. DeBakey VA Medical Center in Houston, Texas. To maintain double blinding, during recruitment for this study, participants will not be explicitly told that the traction orthosis is the treatment intervention for this study.

We will recruit participants at the Michael E. DeBakey VA Medical Center in Houston, Texas. We will be recruiting people who are patients at the MEDVAMC in the outpatient setting through fliers posted in clinics as well as throughout the facility where outpatients spend time, including the cafeteria, the canteen, coffee stands, the phlebotomy lab and the information desk. Also, we will create a searchable informative study website with capability of administering a self-screening tool. A study phone number and e-mail address will also be provided which the participants can use to obtain more information about our study. To maintain double blinding, during recruitment for this study, participants will not be explicitly told that the traction orthosis is the treatment intervention for this study.

Additionally, we will send potentially eligible participants a letter notifying them of our intent to contact them via phone to enter our study. We will provide a phone number to call to opt out should they have no interest in participating in our study. Otherwise, we will contact these participants by phone and screen them for eligibility over the phone. Those who pass the phone screening will be invited for an in-person screen to assess for eligibility. For our study, the clinics that will be of interest will be the Women's Health Clinics, Geriatrics Clinics, and Primary Care Clinics.

The MEDVAMC serves nearly 130,000 veterans and hand OA prevalence is between 37 – 44%.[9] We are targeting people who have symptomatic nodal OA, so this prevalence will be lower with estimates from Framingham between 8-16% of participants.[9] Conservatively, this would mean that 10,000 veterans who attend the MEDVAMC likely have symptomatic hand OA from whom we can screen 800 so that we can randomize 40 participants, meaning that we would need to have a 1% recruitment rate.

To address possible sex differences in the use and efficacy of the intervention, we will make a concerted effort to ensure the study sample is similar to the larger hand OA population in terms of gender. To operationalize this recommendation, we base our target recruitment on Framingham data where age-standardized prevalence of symptomatic hand OA in women and men respectively were 15.9% and 8.2%[9]. Thus, we will oversample women in our VA at a ratio of 2:1, women : men to replicate a similar gender distribution to increase the generalizability of our findings. Our primary strategy for oversampling women is that we will use patient lists from the Women's Health Clinics to identify women who have upcoming visits to at our VA who are more likely to have hand OA. This will include women who have had hand x-rays that show evidence of hand OA and all who are over 60 years old. We will intentionally exclude those who carry a diagnosis of an inflammatory arthritis on their problems list or have a prior history of a hand surgery. To recruit the remainder of our population, we will similarly screen the geriatrics clinic and regular primary care clinics to invite those participants into our study.

Telephone or E-mail Screen. We will perform the telephone or e-mail pre-screen for all people who initiate contact with our study using traditional recruitment strategies as well as all those people identified from clinic panels who did not opt out of a contact from our study.

For all potential participants for whom we have contact with, our Research Coordinator, Michael Strayhorn, will administer the "***Telephone Screening Survey***," on RedCap. However as these people will not yet have consented none of these responses will be saved on RedCap. If they pass the survey as possibly being eligible, Michael will maintain their names and contact information on a separate Excel Spreadsheet entitled "***PreEnrollment Tracker***" (**Appendix G**) and invite them to attend an in-person eligibility evaluation visit. At the beginning of the visit, our Research Coordinator will obtain informed consent to conduct study activities. Once that is completed, then the "Screening Survey" will be administered at which time the information can and will be saved and stored on RedCap.

The objective of performing the pre-screening process is to reduce the number of study applications who later are found to be ineligible. Pre-screening will occur in on the telephone where a set of questions will be administered to vet out

those who are clearly ineligible. Those who complete this process and are viewed as potentially eligible will then be asked if they would like to be scheduled for an in-person screening visit.

Eligibility Assessment. People who pass the screen process and wish to be, will be scheduled for an in-person visit at the MEDVAMC in the Research Commons space. At that visit, the Research Coordinator will meet with the participant candidate and Dr. Lo will assess eligibility for the trial by reviewing all components of the inclusion and exclusion criteria. These responses will be recorded on RedCap under "**Eligibility Survey**." Additionally, participants who are deemed eligible will be asked if they are interested in enrolling in the study.

We anticipate that we may need to screen upwards of 800 participants in person to recruit 40 who are eligible and willing to participate in our study. This is an estimate. After we screen our first 20 participants and discern how many we are actually able to randomize into the study, we will review these recruitment numbers and potentially propose a different estimate that might more realistically reflect of how many participants we will be able to screen and recruit.

We will keep track of all individuals evaluated for study eligibility in the form of a **Screening Log**. This will include the following information:

- Potential participant initials
- Study ID number (Screening number)
- Age
- Sex
- Race
- Ethnicity
- Screening date
- Eligibility Status
    - Eligible for study participation (Y/N)
    - Date enrolled
    - If not eligible, provide reason
    - If refused consent, provide reason

5.2 End of Study Definition

This clinical trial will be considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

5.3 Inclusion/Exclusion Criteria.

Inclusion Criteria

- Enrolled to receive medical care at the Michael E. DeBakey VA Medical Center
- At least 3 joints affected by distal interphalangeal (DIP) nodal hand OA
    - DIP nodal hand OA will be defined as Heberden's nodes on physical exam.
- Sufficiently severe frequent pain of at least one DIP
    - Frequent pain: pain on most days of the month for at least one month in the last year.

- Minimum VAS pain severity of 40 on a 0 – 100 scale

Exclusion criteria

- History or current inflammatory arthritides
  (examples: gout, psoriatic arthritis, and rheumatoid arthritis)
- Prior surgery on the DIP joints
- Planned surgery for the DIP joints
- Pregnancy

Inclusion of Women and Minorities. Hand OA affects both men and women and all races and ethnicities. All will be welcomed into this study. It would be interesting to see if there seems to be a greater or lesser effect of the treatment in any of these groups. Therefore, women and minorities will be included in this study. We have projected the break-down of numbers based on the overall impression of the racial and ethnic make-up of patients at the Michael E. DeBakey VA Medical Center (MEDVAMC) and taking into account our plan to oversample women compared to women to replicate the gender distribution that occurs in the general community. Although in general, there are more men than women who are veterans, there are more women who have hand OA and women tend to participate more in clinical trials than men. Due to our plan to over-recruit women, we expect to recruit more women than men at a ratio of 2:1. Also at the MEDVAMC, African Americans and Latinos make up a substantial portion of this population. Thus we expect that each will likely represent about 15% of the enrolled participants. The pattern of enrollment into this study will help inform enrollment targets for the expected follow up R01.

Inclusion of Children. Because children are not part of our target population of interest because they don't tend to have hand OA and because they are not eligible to be veterans, children will be excluded from this study.

Eligibility Assessment. People who pass the pre-screen process will be scheduled for an in-person screening visit at the MEDVAMC in the Research Commons space. At that visit, the research coordinator will meet with the participant candidate. Dr. Lo will then assess for eligibility for the trial by reviewing all components of the inclusion and exclusion criteria. Additionally, participants who are deemed eligible will be asked if they are interested in enrolling in the study.

5.4 Screening Failures.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of insufficient pain, insufficient number of joints involved, pregnancy plans or status, or surgical plans may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Retention/Adherence Strategies. Although hand OA is common,[9] only a small portion of those with the problem seek medical attention for the problem.[54] Thus, irrespective of the group allocation a participant is assigned to, most

participants are likely get a greater level of attention to their hand OA than if they did not participate in this study. So, participation in the study itself is likely a benefit to the participants.

Additionally, our research coordinator will contact the participants to provide reminders via email, telephone, or text messaging, based on participant preference, one week and one day before our follow up visits.

To increase adherence to application of the orthoses, we will provide daily reminders by providing each participant with a portable alarm clock that will remind participants approximately an hour before their bedtime and at the time of awakening, that they should don their orthoses and write in their log books.

Our research coordinator will also provide weekly email or text messages, based on participant preference, to our participants to remind them to wear their orthoses on a daily basis.

Another important contribution to good adherence will be the positive relationship that study personnel will have with the participants.

6.0 Study Intervention

6.1 Consenting Process. All participants interested in enrolling in the study will be given a copy of the MEDVAMC/BCM approved consent form. Our research coordinator will review the contents of the consent form with the participant, allowing the participant to ask any questions or express any concerns that emanate from that discussion. Once all questions or concerns have been discussed and addressed, if the participant still wishes to participate in the study, he/she will sign the consent form. The original will be retained by the study coordinator and a copy will be given to the participant. There will be information in the consent form explicitly stating that participation in this research study is voluntary and that he/she may withdraw consent at any time without penalty.

6.2 Randomization.

Our Research Coordinator will contact our Statistician, Dr. Richardson, who will provide randomization allocation.

Dr. Richardson will use a macro in SAS that uses CALL RANUNI and PROC PLAN to generate permuted blocks of randomization stratified by sex.

- He will create a designation of group A v. group B, without knowing which group represents the intervention and the control.
- He will use block sizes of 4 for this process.

Dr. Richardson will then communicate to our Research Coordinator and our OT that the treatment allocation has been entered onto RedCap.

Our statistician, Dr. Lo, and our research coordinator will be blinded to treatment assignment. Only our OT will be unblinded to treatment allocation.

6.3 Masking and Unmasking.

Our Statistician, Dr. Lo, and our research coordinator will only be aware of group designations of A and B. They will be blinded to treatment assignment. Prior to receiving treatment allocation information for the first participant of the study, our OT, Kimberly Goldie Staines will flip a coin to assign whether treatment "A" represent traction orthosis or standard of care. She will keep this designation secret and will not share this designation with study staff or participants. Only our OT will be unblinded to treatment allocation. Opaque storage bags will be provided to the participants to store their orthoses. Our OT will make a specific point to tell the participants that they must store their orthoses in opaque bags when interacting with study staff. Masking will be maintained through the course of the study, during data collection, including when radiographs and MRIs are read and primary analyses are performed. Only when all primary data analyses are completed will our OT reveal which group is treatment "A" and unmask the treatment allocation.

Although we will make every effort to maintain blinding, it may be imperfect, where our research coordinator may accidentally have the treatment allocation revealed to him, by inadvertently seeing the orthosis or the participant might tell him which orthosis he/she received. Should this happen, , this will be viewed as a protocol deviation. Additionally,

we will make notation that our research coordinator may be unblinded to the treatment allocation. In those instances, we will have our alternate research coordinator who is still blinded, administer the treatment outcomes at the subsequent follow up visits.

Should the IRB, KAI, and/or our Safety Officer indicate a need to unblind the study prior to the end of data collection, Dr. Lo must confirm the need to unblind the study. Appropriate concerns that could be raised by any of these entities would include if there were unexpected or high numbers of SAEs that occurred in the study. Dr. Lo will instruct our OT to reveal which group is treatment "A" to our study statistician, Dr. Pete Richardson, breaking the study blind. All intentional and unintentional blinding will be reported to the IRB, KAI and our Safety Officer.

6.4 Standard of Care. Current standard of care includes oral analgesics, oral/topical NSAIDs (if not contra-indicated), a thermal modality, activity modification / joint protection education, and range of motion exercises.[12-14] Those not in the traction orthosis group will be offered a standard resting hand orthosis.

If participants are still symptomatic by the one month visit, he/she will be offered a clinic visit with the study physician, Dr. Grace Lo, who will assess whether medications are needed, including topical and/or oral analgesics.

Our OT will create a standard customized hand-based resting orthosis.

She will ask the participants to do the following:

- Please answer the relevant questions in your daily log book.
    - [At that time, a log book will be given to the participant and the entries they will be asked to complete will be reviewed.]
- Apply the orthosis every night for 30 - 60 minutes before going to bed.
- Remove the orthosis every morning 30 – 60 minutes after awakening.
- Please continue this schedule for the full 24 weeks of the study.

At the time that orthoses are created and customized for participants, our OT will provide instruction on how to don the orthosis and how to remove the orthosis.

Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities.

She will also provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to discuss issues related to these activities. A specific effort will be made to reinforce these points during the scheduled in clinic visits scheduled for weeks 2 and 4.

All participants will be given an opaque bag in which to carry their orthosis. They will be told that they should use this bag at all times and that the only study staff who should be allowed to open the bag will be our OT.

All non-pharmacologic modalities will be provided at the baseline visit by the OT.

6.5 Traction Therapy.

Our OT will create a customized hand-based orthosis that allows convenient application of finger traps. The most symptomatic DIP and any other digit that the participant requests will have a finger trap customized to that digit.

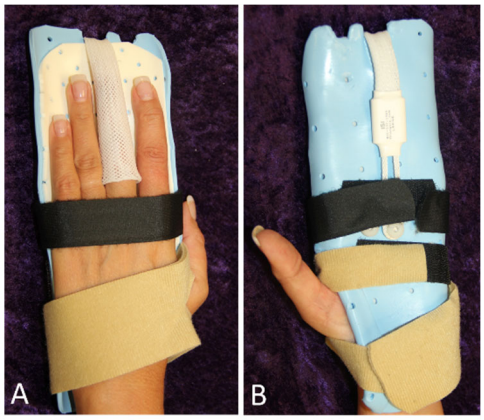

Figure 7. Mock-up of a hand based traction orthosis for a person who has 3rd DIP nodal OA. Panel A is a dorsal view and Panel B is a ventral view.

The resting hand orthosis will be fabricated using standard materials available in the Occupational Therapy Clinic. This will involve the use of a 1/8 inch low stretch and low memory material (e.g. Manosplint Wisconsin or Performance Health Polyflex). Our OT will draw a pattern for the orthosis at 1cm around the hand of interest, stopping just proximal to the wrist crease and extending radially to the thumb metacarpophalangeal joint. The center of the thumb flap will be cut out to form a thumb hole component for proximal stabilization of the orthosis. Our OT will then mold the orthosis to the volar hand with care to accommodate for palmar arches and to extend all fingers to a comfort position. Our OT will then flare the proximal edge of the orthosis to limit pressure on the volar forearm soft tissue. The strapping is then looped through the thumb hole component and attached at the palm obliquely over the phalanges. Soft padding will be added to the orthosis under the phalanges for comfort.

The traction orthosis is identical to the resting hand orthosis with the exception that there is an addition of finger traps that will be applied to the orthosis. The finger traps used in this study will be manufactured by Instrument Specialists, Inc (ISI). Finger traps have already received FDA approval under the Code of Federal Regulations, Title 21, Volume 8 (21CFR890.5925), Revised April 2016.

Title 21 – Food and Drugs
Chapter 1 – Food and Drug Administration, Department of Health and Human Services
Subchapter H – Medical Devices
Part 890 – Physical Medicine Devices
Subpart F – Physical Medicine Therapeutic Devices
Sec. 890.5925 Traction Accessory

(a) Identification. A traction accessory is a nonpowered accessory device intended for medical purposes to be used with powered traction equipment to aid in exerting therapeutic pulling forces on the patient's body. This generic type of device includes the pulley, strap, head halter, and pelvic belt.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter, subject to the limitations in 890.9. The device is also exempt from the current good manufacturing practice requirements of the quality system regulation in part 820 of this chapter, with the exception of 820.180, regarding general requirements concerning records and 820.198, regarding complaint files.

On the FDA website, there were no MedWatch complaints related to finger traps.

At the time that orthoses are created and customized for participants, our OT will provide instruction on how to don the orthosis and how to remove the orthosis. She will also provide instruction to the participant that if the finger trap is uncomfortable and difficult to remove, there is always the option of cutting the finger trap off the finger with a pair of scissors. She will provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to discuss issues related to these activities. A specific effort will be made to reinforce these points during the scheduled in clinic visits scheduled for weeks 2 and 4.

She will ask the participants to do the following:

- Please answer the relevant questions in your daily log book.
    - [At that time, a log book will be given to the participant and the entries they will be asked to complete will be reviewed.]
- Wear the full orthosis with finger traps in place every night for 30 - 60 minutes before going to bed.
- Wear the full orthosis with finger traps in place every morning after awakening for 30 - 60 minutes.
- At night, between the two wear periods, please remove the finger traps and just wear the remainder of the orthosis.
- Please continue this schedule for the full 24 weeks of the study.

Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities.

She will also review with the participant how to cut the finger trap off in the setting that the participant is unable to remove the finger trap.

At 2 weeks of follow up, we will have the participant return to the clinic setting with the OT to verify correct orthosis application and to provide any necessary adjustments to the orthosis. To provide comparable attention to the control group, we will also ask those participants to bring their resting hand orthoses to assess correct application of the orthoses and provision of any necessary adjustments.

The most symptomatic DIP will be fitted with a finger trap. Additionally, our OT will also ask the participant if there are other joints which he/she would like to also be fitted with a finger trap. We will have a variety of sizes of finger traps available at the time of fitting. Each finger that will be fitted with a trap will be sized for an appropriately sized finger trap that will be snug but easily removed by the participant.

Using a heat gun, our OT will heat and roll a slot at the distal edge of the orthosis to accommodate the center of each of the finger traps. Then, with each finger trap applied, the end of the traction device loop will be marked on the posterior surface of the orthosis. Our OT will perforate a hole in the orthosis at the end of the traction device length and insert a rubber band post upon which the loop of the finger trap will be applied. A Velcro attachment will be applied to maintain appropriate tension of the finger traps. Padding will be placed over the band after attachment on the volar orthosis surface.

The participants will be asked to put their orthoses in opaque traveling bags when transporting them. And at home, they are asked to store their orthoses in a clean, dry area, at room temperature when the orthoses are not being worn.

6.6 Definition of Enrollment Into the Study.

The participants who have consented into the study at the beginning of the screening visit are all considered to be enrolled. All participants who meet inclusion criteria, are randomized into a treatment allocation group, and receive their treatment will be included in the a-priori analyses for Aim 3 and for the radiographic findings for Aim 4.

6.7 Opportunity for a Doctor's Visit.

If a participant is still symptomatic by the week 4 visit, he/she will be offered a clinic visit with the study physician, Dr. Grace Lo, who will assess whether medications are needed, including topical and/or oral analgesics/NSAIDs (if not contra-indicated).

6.8 Feasibility of Implementing a Finger Traction Orthosis. Our OT will track ease/difficulty of creating customized traction orthoses. All participants wearing traction and traditional orthoses will be asked to keep a daily log of when they apply and remove the orthoses, comfort level of the orthoses, ease/difficulty of donning the orthoses, how well they like the orthoses, and overall hand pain using visual analog scales (VAS), providing scores from 0 -10. We will also give participants an opportunity to provide free text feedback in the daily log.

At the final clinic visit, we will ask participants if they plan to continue wearing their orthoses after completion of the study.

6.9 Potential for Bias. An expected bias is that our participants will be more symptomatic because we are requiring a minimum severity of symptoms to enroll in this study. Thus, our findings may not generalize to those with milder symptoms or earlier disease. This selection bias is intentional to improve our power to detect a difference to support feasibility and proof of concept in this pilot study. If we can prove efficacy of this treatment in those who are more symptomatic, then we can perform follow up studies that target those with milder disease. There will be a potential for confounding due to lack of blinding of all study personnel. We will attempt to minimize this risk of confounding using multiple strategies. We will limit the treatment allocation information to the OT only. Every effort will be made to maintain blinding of the PI, statistician and the research coordinator. When we notify participants of their clinic visits, we will remind them to refrain from telling anyone which orthoses they were given. We will provide opaque bags to carry the orthoses to help maintain blinding. The research coordinator will be the person performing the clinical assessments and will not be performing the statistical analyses for the study, decreasing the risk of confounding due to

lack of blinding. We will also ask the person performing clinical assessments to provide his/her best guess regarding treatment allocation at the final study to ascertain whether we were successful in maintaining a blinded assessor.

6.10. Assessment of Compliance

Participants will be given a daily log to complete through the course of the study to allow assessment of compliance in applying the traction hand orthosis or the resting hand orthosis on a daily basis. Participants will be reminded to complete this daily log on a weekly basis by our Research Coordinator. We will ask the participants turn in the daily log at their final in person 24 week clinic visit.

Additionally, we will have our research assistant contact participants on a weekly basis via participants' preferred method of contact: email, text or phone to ask participants the following questions:

1. Do you feel the orthosis is helpful? (0 – 100)
2. Did you wear your hand orthosis this week? Y/N
3. (If the person did not wear the orthosis) – Why didn't you wear your orthosis?
4. How many times did you MISS wearing the orthosis this week?
5. (If there were days that the participant didn't wear the orthosis) – Why didn't you wear the orthosis every time?
6. On average, how long have you been wearing the orthosis each night? (number of hours)
7. Have you been completing your daily log? Y/N
8. Have you had any problems with the orthosis? Y/N – if yes, fill out adverse event form.

To maintain blinding of our Research Coordinator, we will not make specific mention of what kind of orthosis was used for each participant. These responses will be recorded in our main database. At the end of each contact point, we will also use this as an opportunity to remind participants to wear their orthoses every morning and night to increase the likelihood of effectiveness of the orthoses.

6.11 Training of Research Coordinators and Occupational Therapists.

Dr. Lo will oversee training of the Research Coordinator and Occupational Therapists that are compulsory prior to the study staff initiating contact with participants as it relates to this study. Dr. Lo must sign off on their training and maintain documentation of training through the course of the study. Details of the training are provided in the MOOP (Section 6.2).

7.0 Study Intervention Discontinuation/ Participant Discontinuation / Withdrawal

7.1 Participant Withdrawal

Participants may withdraw voluntarily from the study. In addition, participants may discontinue the study intervention, but remain in the study for follow-up if he/she wishes. A dedicated Case Report Form (CRF) administered on RedCap entitled "Withdrawal Form" will be completed by our research coordinator to capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

7.2 Discontinuation of Study Intervention

The PI may discontinue a participant from the study for the following reasons:

- Inability to fit the hand orthosis after a good will effort by the participant and our OT.
- Pregnancy
- If any clinical adverse event (AE) occurs such that continued participation in the study would not be in the best interest of the participant
- If early termination of the study is deemed necessary

At the time that the orthosis is created and customized for the participant, our OT will provide instruction on how to don the orthosis and how to remove the orthosis. She will also provide instruction to the participant that if the finger trap is uncomfortable and difficult to remove, there is always the option of cutting the finger trap off the finger with a pair of scissors. Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities. She will also review with the participant how to cut the finger trap off in the setting that the participant is unable to remove the finger trap. She will also provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to schedule an as needed appointment to review how to perform these activities.

We will do our best to minimize any discomfort related to these orthoses as our OT will make every effort to address any discomfort the participants may complain of at the time that the orthoses are created by modifying or adjusting the orthoses. Also, we will schedule all participants to return for a 2 and 4 week follow up visit with our OT to assess for appropriate fit and to address any concerns the participants might have related to the orthoses. If these issues cannot be satisfactorily resolved, then the participants will be given an option to terminate use of the orthosis.

Discontinuation from the study intervention does not mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

A dedicated Case Report Form (CRF) administered on RedCap entitled “Early Termination Form” will be completed by our research coordinator to capture the date and the specific underlying reason for termination from study intervention.

Subjects who sign the informed consent form and are randomized but do not receive the study intervention will still be included in the baseline demographics description. Missing outcomes among participants who missed pain and function questions or lost to follow up will be addressed by multiple imputation using the Markov chain Monte Carlo method. Under the assumption of missing at random, we will include factors which may be related to missing of outcome in the imputation, such baseline demographic characteristics, disease severity, etc. We can use this method of imputation because all outcomes are continuous and they can be assumed to follow multivariate normality distribution. To use this method of multiple imputations, there is an assumption of missing at random. Though this assumption is not testable, multiple imputation method are viewed as less biased than a completers’ analysis, last observation carried forward, and single imputation method.[55] Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost-to-Follow-up

A participant will be considered **lost to follow-up** if he or she fails to return for the final 24 week follow up visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 14 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.0 Study Assessments

8.1 Justification of Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary symptom objective is to assess whether traction therapy plus standard of care treatment for nodal OA reduces symptoms more than standard of care treatment that includes a resting hand splint.	The primary symptom endpoint will be pain as assessed on a visual analog scale (VAS) in the more symptomatic hand that includes the most symptomatic DIP joint by 24 weeks of use of traction therapy with standard of care treatment for hand OA to establish efficacy of traction therapy.	This outcome measure has been recommended by the OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis.[44] It has also been supported by the Update of OMERACT Hand OA Outcomes.[48]
The primary structure objective is to assess whether traction therapy plus standard of care treatment for nodal OA reduces structural progression compared with standard of care treatment that includes a resting hand splint.	The primary structure endpoint will be change in sum of the Kellgren and Lawrence score[45] of all DIPs in the hand that was braced over 24 weeks.	The use of radiographic imaging as a means of measuring structural outcome has been recommended by the OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis.[44] Although there are

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		limitations to the use of Kellgren and Lawrence scoring which was first described in 1957, currently there are no agreed upon alternatives to this scoring strategy.
Secondary		
The secondary symptom objectives are to assess whether traction therapy plus standard of care treatment for nodal OA reduces symptoms more than standard of care treatment that includes a resting hand splint using alternative hand symptom and function outcomes.	The secondary symptom endpoint will be pain and function in the more symptomatic hand that includes the most symptomatic DIP joint by 24 weeks of use of traction therapy with standard of care treatment for hand OA to further support efficacy of traction therapy. These outcomes will include: • The Functional Index for Hand Osteoarthritis (FIHOA)[42] • The Disabilities of Arm Shoulder and Hand (DASH)[49-51] • The Functional Dexterity Test[43] • Grip strength • Pinch strength • Tenderness on joint palpation.	As this is a pilot study, we are making an attempt to include other measures that might also be of relevance and may perhaps be more useful in the follow up study to this pilot.
The secondary structure objectives are to assess whether traction therapy plus standard of care treatment for nodal OA reduces structural progression compared with standard of care treatment that includes a resting hand splint.	The secondary structure endpoints will be change in sum of the following scores all DIPs in the hand that was braced over 24 weeks: • joint space narrowing • osteophyte scores • Verbruggen-Veys scores	Although a 24 week follow up time period might be too short to see a difference in the treatment arms, it is worth a look at the different radiographic features of OA to see if they are different between the two treatment arms.
Tertiary/Exploratory		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
The tertiary / exploratory structure objective is to assess whether traction therapy plus standard of care treatment for nodal OA modifies features of OA seen on MRI more compared with standard of care treatment that includes a resting hand splint.	The exploratory endpoints include measurement in the most symptomatic DIP: • collateral ligament thickening • enthesial bone marrow edema • erosions Because this is a pilot study and we only had limited funds to obtain MRIs, we are only evaluating these changes on 5 people in each treatment arm.	Prior observational studies indicated that there is pathology in these structures visualized on MRI.[15,16,36] Perhaps these might change over a shorter period of time than radiographs. If there is a signal with these measures then we might include MRI for all participants for the follow up clinical trial.
The tertiary / exploratory clinical assessment objective is to evaluate whether traction therapy plus standard of care treatment for nodal OA modifies visual appearance of Heberden's nodes using photographs compared with standard of care treatment that includes a resting hand splint.	Visual inspection of the digital photographs for differences in erythema of the most symptomatic DIPs.	This is a low risk outcome measure. Although it is not currently viewed as a standard outcome measure, if we can show this is a useful outcome measure this might serve as preliminary evidence to use this in our follow up study.

Table 3. Study Objectives, Endpoints, and the Justification of those Endpoints.

8.2. Symptom Efficacy Assessments

All of the following assessments will be made by our Research Coordinator and itemization of the data will be collected in RedCap. These will include:

Outcomes: (Assessed at the baseline, week 4, week 12, and week 24 visits)

- the VAS pain scale, asking about pain in the hand that includes the most symptomatic DIP over the last 48 hours (primary outcome)
- Australian Canadian Hand OA Index (AUSCAN) pain scale,[1,2] (although we have requested copyright permission to use the scale, we have yet to receive permission to do so – we plan to administer the outcome, but if not given permission, we will not publish with this data).
- the VAS pain scale, asking about pain in the most symptomatic DIP in the last 48 hours,
- the AUSCAN function subscale,[1,2]
- the Functional Index for Hand Osteoarthritis (FIHOA)[42]
- the Disabilities of the Arm, Shoulder, and Hand (DASH)[51],
- the Michigan Hand Outcomes[56],
- the Functional Dexterity Test[43],
- grip and pinch strength, and
- tenderness on joint palpation on all hand joints.[44]
- photographs of the participant's hands
- We will also take a medication inventory (dichotomous assessments)
    i. Pain medications (e.g. acetaminophen, all non-steroidal anti-inflammatory medications, and opiod medications).
    ii. Glucosamine and chondroitin
    iii. Marijuana use

8.3. Additional co-variates of interest include:

- age, (Assessed at baseline visit only)
- sex, (Assessed at baseline visit only)
- race / ethnicity, (Assessed at baseline visit only)
- body mass index, (Assessed at baseline visit only)
- co-morbidities,[57] (Assessed at baseline visit only)
- a family history of hand OA, (Assessed at baseline visit only)
- occupations that they have performed in their life, (Assessed at baseline visit only)

- time spent on electronics (including smart phones, tablets, and computers) (Assessed at the baseline, week 4, week 12, and week 24 visits)

- International Physical Activity Questionnaire (iPAQ) questionnaire on physical activity,[6] (Assessed at the baseline, week 4, week 12, and week 24 visits)

- Center for Epidemiologic Studies Depression Scale (CES-D).[3] (Assessed at the baseline, week 4, week 12, and week 24 visits)

These data will help to assess whether randomization was successful and perhaps identify potential mediators to the effect of the traction orthosis.

8.4. Structural Modification Assessments

8.4.i. Posterior-Anterior Hand Radiographs (Obtained at the baseline and 24 week follow up visits)

Standardized bilateral posterior-anterior hand radiographs will be obtained on all participants using the same standardized operating procedure to minimize variability between studies. These images will be scored for Kellgren and Lawrence scores[45] (primary structure outcome), joint space narrowing, and osteophyte scores,[46] and Verbruggen-Veys [47] in the DIP joints by our collaborator, Dr. Ida Haugen, paired and as a batch once the study is completed.

8.4.ii Selecting Participants for Specialized Imaging to Assess Proof of Concept and MRIs. To select people who will get a single DIP high resolution MRI at week 2 and at 6 month follow-up, we will select 3 women and 2 men from each treatment group who are matched by age within 10 years. To assess the biologic effect of the traction orthosis, we plan to obtain x-rays before and after application of the orthoses during the one month follow up visit. We will select 5 men and 5 women to participate in this activity at this follow up visit to have the radiographs with and without the traction orthosis. We will make every attempt to include the 5 people who will have an MRI performed of one DIP to be included in this group.

8.4.iii. High Resolution MRI Imaging (Obtained at the week 2 and 24 week follow up visits)

On 5 participants in each treatment arm (for a total of 10 participants), we will obtain high resolution MRI imaging of the most symptomatic DIP joint.

The sequences that will be obtained will include the following:

- 3-Plane Localizer
- Coronal T1
- Coronal Proton Density
- Coronal T2 Fat Suppressed
- Axial T1
- Sagittal Merge 3D
- Coronal T1 Fat Suppressed with Gadolinium
- Axial T1 Fat Suppressed with Gadolinium

Our collaborator, Dr. Andrew Grainger, will score all these MRIs, paired and as a batch once the study is completed for collateral ligament thickening, enthesial bone marrow edema, and erosions.

8.5 Proof of Concept.

At the 2 week follow up visit, 10 participants, 5 men and 5 women, receiving traction will be asked to have radiographs of the hand with and without the traction orthosis applied to assess whether applying this treatment results in an increase in joint space width.

8.6 Monitoring Body Membership and Affiliation

This study is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). They have appointed a single Safety Officer who is impartial to this study, to oversee the risks and benefits as well as the adverse events associated with this study.

Safety Officer: Dr. Roy Davis Altman

Professor of Medicine, Division of Rheumatology and Immunology, University of California, Los Angeles

Conflict of Interests for Safety Officer:

The Safety Officer should have no direct involvement with the study investigators or intervention. He will sign a Conflict of Interest Statement which includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g. stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or non-commercial interests pertinent to study objectives.

8.7 Safety Reporting

8.7.a Adverse Event Definitions

Adverse Event (AE) – Any unfavorable and unintended diagnosis, sign (including laboratory finding), symptom or disease temporarily associated with the study intervention.

- AEs may or may not be related to the intervention.
- AEs include:
    - any new events not present during the pre-intervention period or
    - events that WERE present during the pre-intervention period which have INCREASED in severity.

Unexpected Adverse Event – Any adverse event that is not pre-defined as a potential adverse event.

Serious Adverse Event (SAE) – Any untoward medical occurrence that results in:

- death or is life threatening
- requires or prolongs hospitalization

- causes persistent or significant disability/incapacity
- represents other significant hazards or potentially serious harm to research participants or others

This also includes any unanticipated problem that is definitely related to the intervention.

Unanticipated Adverse Device Effects (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death the frequency, specificity, or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.)

8.7.b Adverse Event Reporting

Our Research Coordinator will assess for adverse events systematically at each in clinic visit. If an adverse event is detected, he will contact Dr. Lo to complete adverse event(s) form(s) at each of those visits where the details of such adverse events will be recorded in RedCap. Additionally, should any adverse events be reported to our Research Coordinator between in clinic visits, all those events will also be recorded in RedCap by Dr. Lo.

8.7.c Severity Assessment of Adverse Event.

All AEs will be assessed by the study clinician using a protocol defined grading system. The following guidelines will be used to **describe severity**.

- **Mild (Grade 1)** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate (Grade 2)**– Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe (Grade 3)** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- **Life-threatening consequences** (**Grade 4**); Urgent intervention indicated.
- **Death related to AE (Grade 5)**.

8.7.d Relatedness Assessment of Adverse Event.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or

chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.7.e Definition of Expected and Unexpected Adverse Events.

Expected *adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Based on preliminary data used to prepare our study where some volunteers wore the traction orthosis, we expect the following possible adverse events.*

- *Increased hand discomfort or pain*
- *Skin breakdown, erythema, and/or blistering*
- *Neurologic complaints such as numbness or tingling*
- *Vascular complaints such as poor circulation to the fingers*

The PI, Dr. Grace Lo, will be responsible for determining whether an adverse event (AE) is **unexpected**. We anticipate that the expected AEs might occur commonly but the severity will mostly be mild and rarely if ever will be severe. An AE will be considered **unexpected** if it is not included in the above list of expected events. Additionally, if the nature, severity, or frequency of the event is greater than what we have outlined, this will also be considered to be unexpected.

8.7.f Determination of whether or not an Adverse Event is Serious.

In the course of completing the adverse event forms, it will be determined whether or not it is a serious adverse event (see the definition in 8.7.a).

8.7.g Time period and frequency for event assessment and follow up.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF) in RedCap. Information to be collected includes event description, time of onset, Dr. Lo's assessment of severity, relationship to traction versus standard orthosis, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. For an expected AE, follow up for 30 days after the onset of the AE will be considered as an adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Our Research Coordinator, Michael Strayhorn, will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit (including in clinic visits and weekly telephone calls), the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.7.h Timing of reporting of AEs and SAEs to monitoring entities

Reporting of **Nonserious Adverse Events**

Cascade of communication of ***non-serious adverse events*** will be the following:

1. The Research Coordinator will inform Dr. Grace Lo, the PI, of non-serious adverse events as soon as they occur.
2. Dr. Lo will notify the NIAMS and Safety Officer of these events as part of the routine safety reports submitted biannually.
3. Dr. Lo will report on these events to the Baylor College of Medicine IRB during our annual renewal, according to local IRB requirement.

Cascade of communication of ***serious adverse events*** will be the following:

1. The Research Coordinator will inform Dr. Grace Lo, the PI, of serious adverse events as soon as they occur.
2. Dr. Lo will notify the NIAMS and Safety Officer **within 48 hours** of becoming aware of the event.
3. Dr. Lo will report the Serious Adverse Events to the Baylor College of Medicine IRB **within 5 business days** of becoming aware of the event, according to local IRB requirement.
4. Dr. Lo will also report the Serious Adverse Events to the MEDVAMC Research Office, the Privacy Officer, and the Facility Research Compliance Officer **within 5 business days** of becoming aware of the event, according to VA Research and Development requirement.
5. Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if there are unforeseen deaths or the threshold for SAE (of more than 10) has been met.

Additionally, ***all serious adverse events*** will need to be assessed to ascertain:

1. whether the adverse events are associated with one of the treatment allocation groups which may result in early study termination (performed by Dr. Richardson), and / or
2. if changes to the protocol are required and / or

3. if changes to the informed consent documents are required.

The ***on-line FDA MedWatch reporting system*** (Form FDA 3500 Voluntary Reporting) will be used to record adverse events for distribution.

- Serious adverse events will be reported using this schedule:
  - deaths: immediately, upon knowledge
  - all others: within 5 business days
- Non-serious adverse events will be cumulatively summarized every 6 months.
- This reporting schedule may be more frequent if requested by the IRB.

Dr. Lo will review all adverse events on a weekly basis ***until their conclusion*** OR ***consideration as chronic***. During each review, she will re-review whether there needs to be modification of the study intervention.

8.8 Unanticipated Problem Reporting

Unanticipated Problem – defined by OHRP as any incident, experience or outcome that meets **ALL** the following requirements:

1. ***Unexpected*** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the population being studied.
2. ***Related or possibly related to participation in the research***. Possibly related means there's a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.
3. Suggests that the ***research places participants or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) than was previously known or recognized.

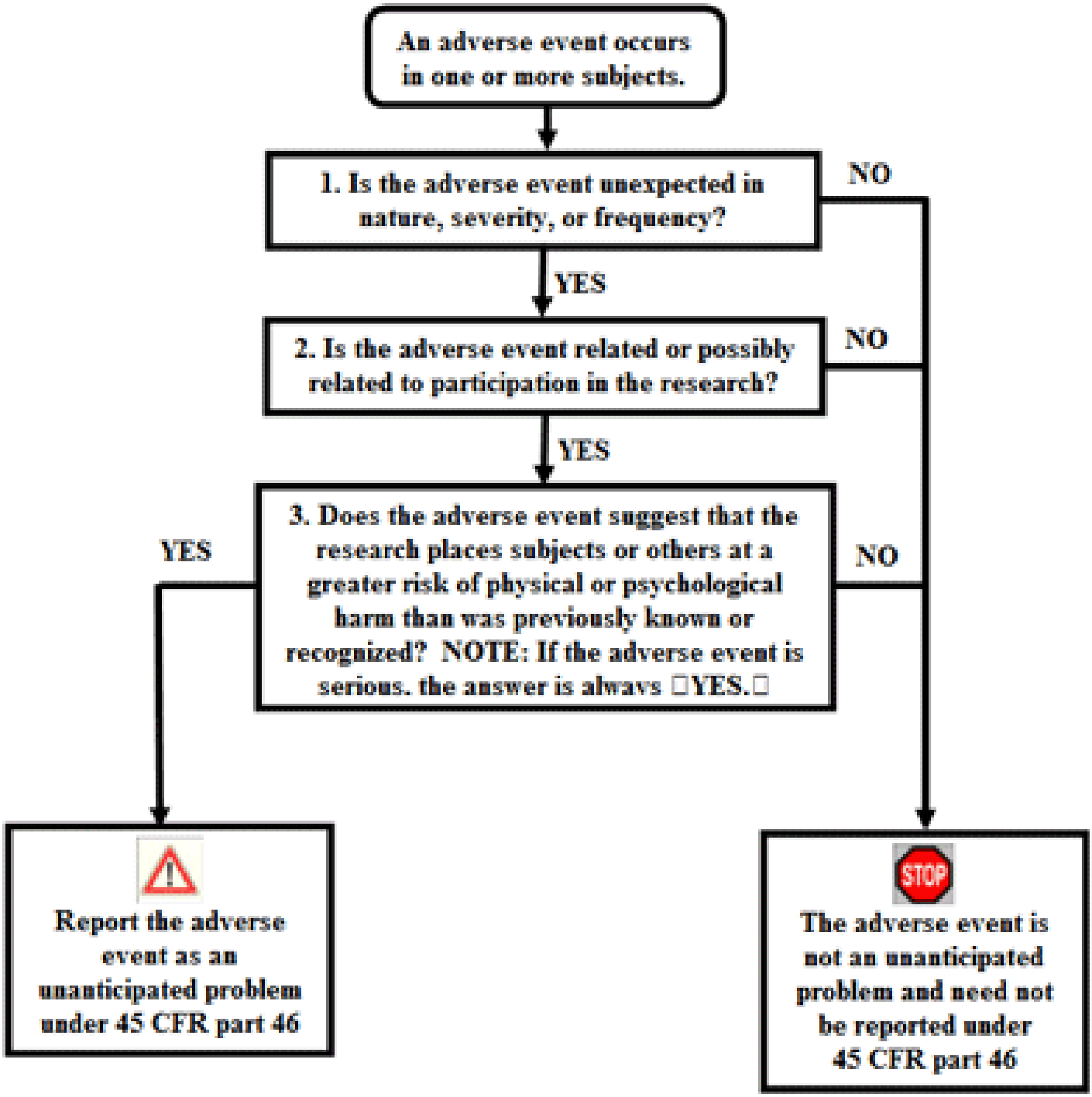

Figure 8. Flowchart indicating the determination of whether an adverse event is an unanticipated problem.

To be clear, only a SMALL number of serious adverse events will fit into this category. Additionally, there are situations not considered adverse events that can be considered an unanticipated problem.

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:

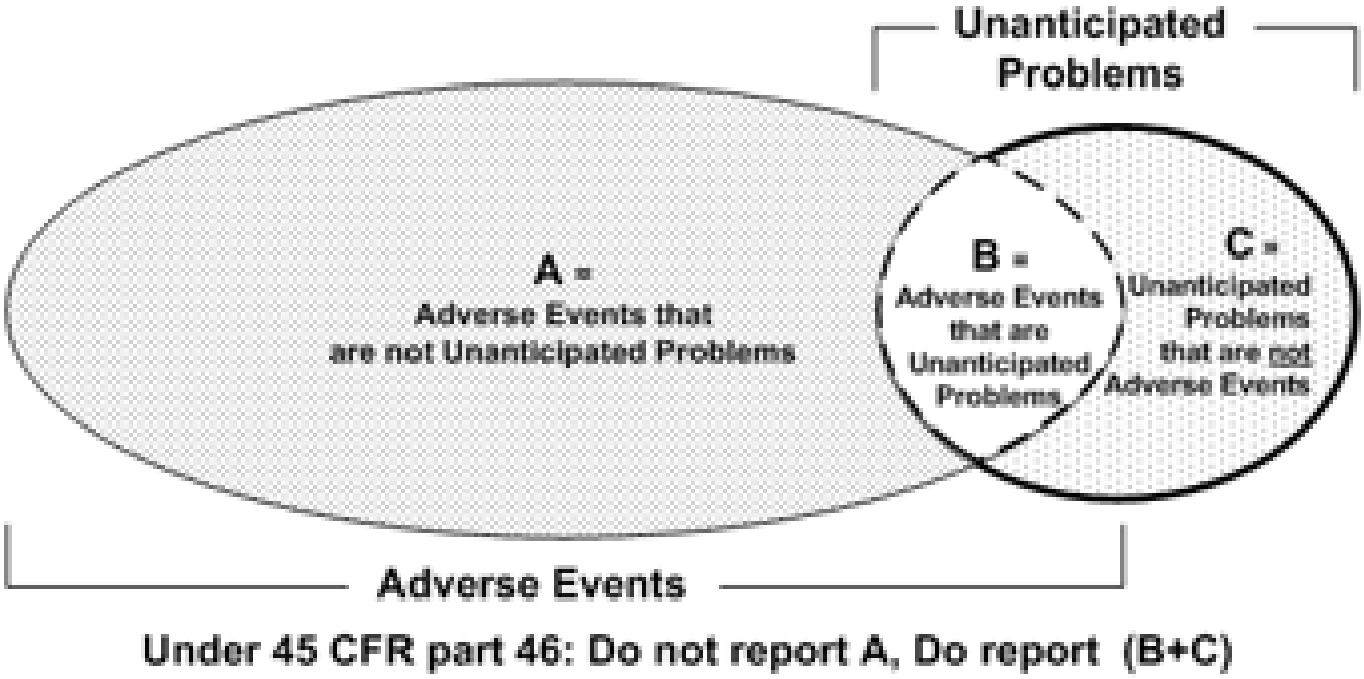

Figure 9. Venn diagram indicating the overlap of adverse events with unanticipated problems.

The diagram (figure 9) illustrates three key points:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

[Aside:

An example of an area C unanticipated problem would be:

An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

For additional examples: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AB]

Upon **notification of an Unanticipated Problem**, the **Research Coordinator** will notify all appropriate parties as outlined below:

1. The Research Coordinator will **immediately** notify the **PI, Dr. Grace Lo** via emergency contact information.
2. Dr. Lo will notify the NIAMS and Safety Officer (through the NIAMS Executive Secretary) **within 48 hours** of becoming aware of the event.
3. The Research Coordinator will **draft a notification email to the IRB** which will be **reviewed by Dr. Lo** and once modified and approved, will be **sent to the IRB**.

4. Dr. Lo will **immediately** advise the Study Team whether there will be any change in the protocol-outlined screening, enrollment, and ongoing participation.
5. **Upon advisement by the IRB**, Dr. Lo will determine the study's status and notify the Study Team.
6. Dr. Lo will also report the Unanticipated Problem to the MEDVAMC Research Office, the Privacy Officer, and the Facility Research Compliance Officer **within 5 business days** of becoming aware of the event, according to VA Research and Development requirement.
7. **Dr. Lo** will **review all unanticipated problems on a weekly basis** until there is **resolution of the event** or **completion of the study**. During each review, she will re-review whether there needs to be modification of the study intervention.

9.0 Statistical Considerations

Because this is a pilot study, we do not plan to adjust for multiple comparisons.

Specific aim 1. **Feasibility of a static hand based orthosis to apply finger traps.** We will calculate means and standard deviations for VAS scores for comfort level while wearing the orthosis ease/difficulty of donning the orthoses, how well they like the orthoses, and overall hand pain using visual analog scales (VAS), providing scores from 0 -10 at the 1 month, 3 month, and 6 month follow up visits.

Specific aim 2. **Proof of concept.** We will pair the radiographs of the hands with and without orthoses applied to subjectively assess whether the traction orthoses result in an improvement in joint space narrowing score. Because will only be performing these measures on 10 participants, we will not run formalized statistics on these comparisons.

Specific aim 3. **Symptomatic and functional outcomes**. Because this is a pilot study, we will be broad in our inclusion of outcome measures of interest with the understanding that these findings will help to inform our future outcome measure choices to select for follow up studies of traction therapy. Our primary outcome measures of interest will be overall hand VAS pain.[44] Other outcome measures will include AUSCAN pain,[1,2] VAS pain and tenderness in the most symptomatic joint and of all DIPs. For functional outcomes, we will evaluate the AUSCAN function subscale,[1,2] the Functional Index for Hand Osteoarthritis (FIHOA),[42] the Disabilities of the Arm, Shoulder, and Hand (DASH),[5] the Functional Dexterity Test,[43] grip and pinch strength.[44]

We will complete descriptive analyses of baseline characteristics of the treated and control groups to allow assessment of generalizability and success of randomization. We will use either Student t-tests or rank-based nonparametric tests where appropriate. Our primary analytic approach will be to use intention- to-treat (ITT) analyses to compare mean change of each symptom and function outcome during follow-up between traction therapy and the control groups with linear regression model for longitudinal repeated measures data. Missing outcomes among participants who missed pain and function questions or lost to follow up will be addressed by multiple imputation using the Markov chain Monte Carlo method. Under the assumption of missing at random, we will include factors which may be related to missing of outcome in the imputation, such baseline demographic characteristics, disease severity, etc. We can use this method of imputation because all outcomes are continuous and they can be assumed to follow multivariate normality distribution. To use this method of multiple imputations, there is an assumption of missing at random. Though this assumption is not testable, multiple imputation method are viewed as less biased than a completers' analysis, last observation carried forward, and single imputation method.[55]

Specific aim 4. **Imaging outcomes**. Given the exploratory nature of this study, we will be broad in our inclusion of outcome measures we will evaluate. The primary structural outcome measure will be change in sum of the Kellgren and Lawrence score of all DIPs in the hand that was braced.[44] We will also evaluate change in joint space narrowing, and osteophyte scores[46] and the Verbruggen-Veys [47] from baseline to 6 month follow up comparing the traction versus the control groups. For those randomized to traction, we will also compare the hand that received traction to the hand that did not. To address potential missing data, we will use a multiple imputation method, assuming the data are missing at

random. We will perform an ANOVA to compare mean change in the sum of radiographic scores over the 6 month follow up period between the traction therapy and the control groups. If there are unbalanced baseline covariates between the treatment groups, we will use an ANCOVA approach to include them as covariates in the analysis.

Power calculation: Assuming the SD of change in the summary score is 3, we can expect at least 80% power to detect a difference of 1.7 in the change of the summary score between the two arms with 100 participants (50 in each arm) for a two-sided type 1 error rate of 5%.

On 5 participants in each treatment arm (age and sex matched) for whom we will have high resolution MRI imaging at baseline and at 6 months, we will plot the measurements for collateral ligament thickening, enthesial bone marrow edema, and erosions of the most symptomatic DIP at baseline and then at 6 months to see if we can identify any differences by visual inspection.

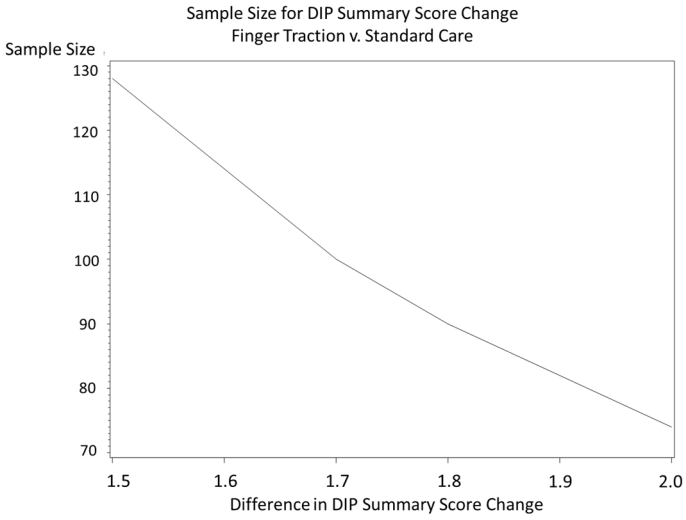

Figure 10. Power curve for change in the DIP summary score change in finger traction v. control groups.

10.0 Supporting Documentation and Operational Considerations

10.1 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 2 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the NIAMS Program Official and their executive secretary, KAI. Protocol deviations must be sent to the BCM Institutional Review Board (IRB) within 5 business days of becoming aware of the event only if there is a compliance concern. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOOP.

An example of a protocol deviation will include if the participant attends the in-person clinic visit outside of the visit window or a missed in person clinic visit.

10.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI. The PI will promptly inform study participants, the BCM IRB, the NIAMS and KAI of the

suspension or termination and provide the reason(s) for such action. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIAMS, BCM IRB and/or Food and Drug Administration (FDA).

*If the study is prematurely terminated, refer to Section **7.2, Study Intervention Discontinuation**, for handling of enrolled study participants.*

10.3 Data Archiving / Quality Control / Quality Assurance. All study data will be collected and managed using the REDCap electronic data capture tools, designed to comply with HIPAA regulations.[7,8] This is a VA approved electronic data capture software. It is designed to support data capture for research studies from anywhere in the world with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption.[7] It provides: 1) an intuitive *interface for validated data entry* 2) *audit trails* for tracking data manipulation and export procedures 3) *automated export procedures* for seamless data downloads to common statistical packages, an essential feature for data back-up and 4) user-friendly procedures for importing data from external sources.[7] We will store all consent forms, all participant questionnaires, and study information on REDCap. On a weekly basis, all acquired information will be uploaded to a VA server on the VA network, protected by user login and passwords and we will run simple logic checks to assure the data is downloading appropriately. All servers are backed up daily to ensure data protection. Weekly full backups are stored in a vault at a secure remote location. The heart of the server system is a Hewlett Packard Itanium System running under the UNIX operating system. This server is used for managing and analyzing the large datasets. The Itanium server has four 1.5-gigahertz (GHz) Itanium central processing units (CPUs) that have instruction set architecture of 64 bit Intel microprocessors (IA64), 28.0 gigabyte (GB) of random access memory (RAM), and approximately 8 terabytes (TB) of disk storage. In addition to the Hewlett-Packard Itanium, six Dell servers run the Windows operating system, used for network applications, Structured Query Language (SQL) database, file sharing, and print sharing with a total storage capacity of 4TB.

10.4 Publication and Data Sharing Policy.

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition,

every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting Dr. Grace Lo.

10.5 Manual of Operations

We will develop additional sections for the MOOP that describe in detail the procedures involved in this proposal. This will include a staff certification protocol and quality control activities.

10.6 Study Timeline

Activities	Year 1				Year 2				Year 3			
Write and finalize clinical protocol for the study												
Registration of clinical trial in ClinicalTrials.gov												
Creating Data Collection Platform												
Local IRB Application/Approval												
Completion of Regulatory Approvals												
Beta Testing of On-line Data Collection												
Training Clinical Staff												
Stocking Finger Traps in Preparation for the Trial												
Recruitment of Participants/ Baseline Assessments/Randomization/ Fabrication of Orthoses / Non-Pharm Standard of Care												
Enrollment of first participant												
First 25%												
Second 25%												
Third 25%												
Fourth 25%												
Follow up of Participants												
First 25%												
Second 25%												
Third 25%												
Fourth 25%												
Baseline Radiographs												
First 25%												
Second 25%												
Third 25%												
Fourth 25%												
6 Month Radiographs												
First 25%												
Second 25%												

Third 25%												
Fourth 25%												
Proof of Concept X-Rays (10 participants)												
Baseline MRIs (10 participants)												
6 Month MRIs (10 participants)												
Prepare Xrays and MRIs for Readings												
Xray and MRI readings												
Completion of Data Collection												
Statistical Analyses												
Completion of Primary and Secondary Endpoint Analyses												
Completion of Final Study Report												
R01 Application												
Manuscript Writing												
Reporting of Results to ClinicalTrials.gov												

Table 4. Estimated Timeline of Study Events

10.7 Participant Safety

10.7.a Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design

In our study, we propose a pilot randomized controlled trial of traction on 40 participants recruited from the Michael E. DeBakey VA Medical Center (MEDVAMC) with at least 3 joints affected by distal interphalangeal (DIP) nodal hand OA, with at least one joint with frequent pain. The hand with the DIPs with the greatest severity level of pain will be eligible for randomization into (1) standard of care or (2) traction plus standard of care. If results from this study support feasibility, proof of concept that finger traps provide traction, symptomatic/functional improvement with traction, we will use findings from this study to inform a larger R01 study that can be adequately powered to address efficacy and utility of this treatment in the general clinical setting.

We will be recruiting people who are patients at the MEDVAMC in the outpatient setting through fliers posted in clinics as well as throughout the facility where outpatients spend time, including the cafeteria, the canteen, coffee stands, the phlebotomy lab and the information desk. Additionally, we VA patients who are identified as likely to be eligible for our study through clinic patient lists who do not opt out of contact by our study staff will be approached for entry screening into our study. At enrollment, participants cannot be hospitalized. However, if participants become hospitalized during the course of follow-up, they will be allowed to continue in the study. We will make every effort to determine whether participation in the study is related to the participant's hospitalization.

As this is a pilot study, we have chosen a relatively small number of participants to enroll into this study. Information from this study will help to better inform an appropriate size for a study that could definitively assess efficacy of our proposed study treatment. To allow for comparability of our two groups, and to allow for all participants to receive the standard of care, we are recruiting people who are established at the MEDVAMC. Thus, participants will be at least 18 years of age.

Although hand OA is very common,[9,58,59] only a small percentage seek care from their providers for this condition. Therefore, engagement into medical care for hand OA will be useful as a retention strategy. Additionally, participants will all receive durable goods to provide the standard of care for hand OA including a thermal modality and the orthoses made for them by our OT. Also, they will be instructed on range of motion exercises and joint protective strategies that should help their hand symptoms.

Regarding special vulnerable populations, fetuses, neonates, and children will not be eligible for this study because we are targeting veterans who are patients at the MEDVAMC. Pregnant women will be excluded to mitigate any potential risks related to radiation exposure associated with obtaining radiographs and high powered magnetic fields related to obtaining MRIs. We do not expect that prisoners or institutionalized individuals will learn about this study and therefore will not be recruited into the study. Therefore, no vulnerable populations will be included in this study so none of these groups will be placed at increased risk relative to other participants included in our study.

Once a participant is deemed eligible for participation into the study and is consented for the study, he/she will have all his/her baseline assessments administered by the study research coordinator. After this is completed, the research coordinator will email Dr. Richardson, our statistician, who will generate a randomization assignment (designated as group A v. group B) stratified by gender. This allocation assignment will only be transmitted to our OT by email after the OT has also seen the participant at baseline and provided all other non-pharmacologic interventions for hand OA that are considered standard of care. Prior to the beginning of the study, the OT will use a coin flip to decide which group (A v. B) will be the treatment v. control group. The OT will be the only person in the investigative team to know this

designation until the study data set is closed and all analyses are finalized. At that point, the OT will customize the appropriate orthosis for the participant to take with him/her.

We will ask the participants wear the traction and the resting orthoses every night for 30-60 minutes before going to bed and upon awakening. At night, between these two wearing periods we ask that the participants wearing the traction orthoses wear the orthoses without the finger traps which are identical to the resting orthoses. The participants wearing the resting orthoses are also asked to keep their orthoses on overnight as well.

When radiographs and MRIs will be sent to Drs. Haugen and Grainger for to be read, all these studies will be de-identified with only a study ID being associated with these images. Therefore, performing those readings will not be considered as conducting human subjects research.

10.7.b Study Procedures, Materials, and Potential Risks

The research material obtained from living individuals will include electronically recorded questionnaires at baseline, 1 month, 3 month, and 6 month follow up visits including Australian Canadian Hand OA Index (AUSCAN) pain scale, the VAS pain scale, the AUSCAN function subscale, the Functional Index for Hand Osteoarthritis (FIHOA), and the Disabilities of the Arm, Shoulder, and Hand (DASH). We will also ask participants to report occupations that they have performed in their life. We will also ascertain data on time spent on electronics (including smart phones, tablets, and computers). We will also administer a validated physical activity questionnaire and a questionnaire on occupational activities. Additionally, we will perform a medication inventory including pain medications (e.g. acetaminophen, all non-steroidal anti-inflammatory medications, and opioid medications). We will also collect data on potentially important covariates such as age, sex, and body mass index and a family history of hand OA. We will also electronically record results from the physical exam including the Functional Dexterity Test, grip and pinch strength, and tenderness on joint palpation. Additionally, we will obtain radiographs and MRIs of the hands.

All study data will be collected and managed using the REDCap electronic data capture tools, designed to comply with HIPAA regulations.[7,8] This is a VA approved electronic data capture software. It is designed to support data capture for research studies from anywhere in the world with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption.[7] It provides: 1) an intuitive *interface for validated data entry* 2) *audit trails* for tracking data manipulation and export procedures 3) *automated export procedures* for seamless data downloads to common statistical packages, an essential feature for data back-up and 4) user-friendly procedures for importing data from external sources.[7] We will store all consent forms, all participant questionnaires, and study information on REDCap. On a weekly basis, all acquired information will be uploaded to a VA server on the VA network, protected by user login and passwords and we will run simple logic checks to assure the data is downloading appropriately. All servers are backed up daily to ensure data protection. Weekly full backups are stored in a vault at a secure remote location. The heart of the server system is a Hewlett Packard Itanium System running under the UNIX operating system. This server is used for managing and analyzing the large datasets. The Itanium server has four 1.5-gigahertz (GHz) Itanium central processing units (CPUs) that have instruction set architecture of 64 bit Intel microprocessors (IA64), 28.0 gigabyte (GB) of random access memory (RAM), and approximately 8 terabytes (TB) of disk storage. In addition to the Hewlett-Packard Itanium, six Dell servers run the Windows operating system, used for network applications, Structured Query Language (SQL) database, file sharing, and print sharing with a total storage capacity of 4TB.

All participants will be asked to turn in log books that are labeled with their study ID to our OT. In these log books, we will ask the participants to keep a daily log of when they apply and remove the orthoses, comfort level of the orthoses,

ease/difficulty of donning the orthoses, how well they like the orthoses, and overall hand pain using VAS scales. These data will be kept in a locked cabinet and the data will be transferred onto Red Cap to be managed in a similar manner that all the other clinic acquired data is managed.

All participants will have hand radiographs obtained at the baseline and 6 month follow up visits at the MEDVAMC. 10 participants, 5 (2 men, 3 women) in each treatment group, age matched within 10 years, will have MRIs of the most symptomatic DIP joint at week 2 and 24 follow up visits, performed at Baylor/St. Luke's Medical Center Radiology Department. At the 2-week visit, the same 10 participants will also have radiographs obtained with and without the orthoses donned. Radiographs when initially obtained will be stored on the MEDVAMC Picture Archiving and Communication System (PACS) prior to transfer to one of our secure, password protected research server at the MEDVAMC. The MEDVAMC's PACS system supports the clinical operations of the Hospital. Access to this platform is strictly limited to essential clinical and approved research staff through passwords and permission levels. MRIs obtained at Baylor/St. Luke's Medical Center will be burned onto a CD/DVD which will then be immediately uploaded and stored on our MEDVAMC research server secured through passwords, permission-levels and data encryption. Other digital data, including photographs of the hands that is collected through our electronic data collection system will be similarly stored on our the MEDVAMC research server labeled with a study ID but otherwise be de-identified and either stored on a secure server or in a locked cabinet. Copies of the de-identified radiographs and MRIs will be burned onto DVDs/CDs and shipped with confirmed receipt to Drs. Haugen and Grainger respectively so they can provide readings of those images for this study.

Potential Risks

The risks to the participants for this study are small. For all participants of this study, the time involved in the in-person visits will be a lost resource for the participants. Participants will also be asked to have both hands imaged by conventional radiography at multiple time points and one finger imaged by MRI at 2 time points. There is a small radiation exposure conventional imaging of the hands where each extremity radiograph exposes an individual to 0.06 microSeiverts of radiation exposure, equivalent to one third the exposure associated with a chest radiograph. MRI imaging is considered a safe procedure providing that people do have prohibited implants or objects on their person at the time of scanning. MRI scanners generate powerful magnetic fields which will attract metal objects with great force, including pulling on any metal-containing object in your body, such as medicine pumps and aneurysm clips. MRI scans can cause heart pacemakers, defibrillation devices and cochlear implants to malfunction. Therefore careful screening procedures will be conducted prior to placing any participant into an MRI scanner, making sure to screen out all people who have contra-indications for an MRI.

People who are randomized into the traction therapy group may have:

- *Increased hand discomfort or pain*
- *Skin breakdown, erythema, and/or blistering*
- *Neurologic complaints such as numbness or tingling*
- *Vascular complaints such as poor circulation to the fingers*

At the time that the orthosis is created and customized for the participant, our OT will provide instruction on how to don the orthosis and how to remove the orthosis. She will also provide instruction to the participant that if the finger trap is uncomfortable and difficult to remove, there is always the option of cutting the finger trap off the finger with a pair of scissors. Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities. She will also review with the participant how to cut the finger trap off in the setting that the participant is unable to remove the finger trap. She will also provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to schedule an as needed appointment to review how to perform these activities.

We will do our best to minimize any discomfort related to these orthoses as our OT will make every effort to address any discomfort the participants many complain of at the time that the orthoses are created by modifying or adjusting the orthoses. Also, we will schedule all participants to return for a 2 week follow up visit with our OT to assess for appropriate fit and to address any concerns the participants might have related to the orthoses. If these issues cannot be satisfactorily resolved, then the participants will be given an option to terminate use of the orthosis.

Additionally, if the participants voice any complaint about the orthoses at any of the follow up visits, we will arrange an as needed appointment with our OT to address those concerns. Again, if we are unable to adequately address a participant's concerns or complaints then the participant of course, has the option to terminate use of the orthosis.

If participants experience skin break down in areas in contact with the finger traps, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve fit if possible. The participants will be instructed to resume wearing the orthoses after all skin break down is healed.

If participants experience neurologic and/or vascular complaints (e.g. numbness/tingling or lack of blood supply) in the fingers that have finger traps applied, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve fit if possible. The participants will be instructed to resume wearing the orthoses after the participant can don the orthosis without the original complaint.

The alternative for people invited to be in this study is to decline participation in the study. In this case, those people will still receive routine care by their established care providers without knowledge of being offered to be entered into this study.

10.7.c Protections Against Risks

10.7.c.i Informed Consent

We will be recruiting people who are patients at the MEDVAMC through fliers posted in clinics as well as throughout the facility. People who are interested in knowing more about the study will contact the research coordinator either via phone or email. We will also screen patients from existing clinic schedules and send potentially eligible participants a letter notifying them of our intent to contact them via phone to enter our study. We will provide a phone number to call to opt out should they have no interest in participating in our study. For our study, the clinics that will be of interest will be the Women's Health Clinics, Geriatrics Clinics, and Primary Care Clinics.

A telephone screening process will occur to assess for possible eligibility to enter the study. During that screening process, our research coordinator will review a list of questions that will identify people who are more likely to be eligible to enter our study. No data will be collected on these people during this telephone call on RedCap. We will keep a telephone screening log that will include the person's name, contact information, date of the telephone call, and scheduled date to come in for in-clinic screening. This will be stored on a secure file on the M:drive in our study folder. This will not be maintained in RedCap.

At the in-person screening visit, our research coordinator will review the study consent form with the participant and have the participant sign the form if they agree to participate in this study. The consent form will include information allowing the participants to know that participation in the study is completely voluntary. The participant will not be penalized if he/she decides not to participate in the study. The participant can continue receiving usual care at the MEDVAMC just as he/she has in the past. The participant will be told that this is a study of hand OA treatments but will not be told which treatment is experimental to allow for double blinding in this study. Participants will be allowed to

terminate participation in the study at any time. If there is any concern that the participant may not have the capacity to give consent, then the study physician, Dr. Grace Lo, will be called upon to evaluate whether the potential participant is competent to provide consent into the study.

After informed consent is obtained, then our Research Coordinator will administer the screening survey. For those identified as likely to be eligible for the study, Dr. Grace Lo will then review full inclusion and exclusion criteria and determine whether participants meet criteria for inclusion into the study,

10.7.c.ii Protections Against Risk

People who are randomized into the traction therapy group may have:

- *Increased hand discomfort or pain*
- *Skin breakdown, erythema, and/or blistering*
- *Neurologic complaints such as numbness or tingling*
- *Vascular complaints such as poor circulation to the fingers*

Notably, finger traps are viewed by the FDA as Class 1 medical devices, the lowest risk devices, and are already available for use in the clinical setting. A search on the FDA website did not return any adverse events reported regarding finger traps.

At the time that the orthosis is created and customized for the participant, our OT will provide instruction on how to don the orthosis and how to remove the orthosis. She will also provide instruction to the participant that if the finger trap is uncomfortable and difficult to remove, there is always the option of cutting the finger trap off the finger with a pair of scissors. Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities. She will also review with the participant how to cut the finger trap off in the setting that the participant is unable to remove the finger trap. She will also provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to schedule an as needed appointment to review how to perform these activities.

We will do our best to minimize any discomfort related to these orthoses as our OT will make every effort to address any discomfort the participants many complain of at the time that the orthoses are created by modifying or adjusting the orthoses. Also, we will schedule all participants to return for a 2 week follow up visit with our OT to assess for appropriate fit and to address any concerns the participants might have related to the orthoses. If these issues cannot be satisfactorily resolved, then the participants will be given an option to terminate use of the orthosis.

Additionally, if the participants voice any complaint about the orthoses at any of the follow up visits, we will arrange an as needed appointment with our OT to address those concerns. Again, if we are unable to adequately address a participant's concerns or complaints then the participant of course, has the option to terminate use of the orthosis.

If participants experience skin break down in areas in contact with the finger traps, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve fit if possible. The participants will be instructed to resume wearing the orthoses after all skin break down is healed.

If participants experience neurologic and/or vascular complaints (e.g. numbness/tingling or lack of blood supply) in the fingers that have finger traps applied, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve

fit if possible. The participants will be instructed to resume wearing the orthoses after the participant can don the orthosis without the original complaint.

If there is detection of a high rate of unexpected adverse events grade 3 or higher, this may warrant termination or temporary suspension of the study (e.g., study closure based on PI decision or sponsor/funder decision). For any study that is prematurely terminated or temporarily suspended, Dr. Grace Lo will promptly inform the BCM/MEDVAMC IRB and NIAMS and provide the reason(s) for the termination or temporary suspension. An in-depth investigation will be performed to determine whether there are study activities or treatment related effects that are contributing to this signal. If the investigation does not support these possibilities, and this is agreed upon by NIAMS, the BCM/MEDVAMC IRB, and Dr. Grace Lo, the study PI, then the study can resume.

We will make every effort to assure the confidentiality of human subjects. Study identification codes that can link study data back to an individual's name are used for each participant will be created by Dr. Richardson. We will store all clinic obtained data using REDCap electronic data capture tools, designed to comply with HIPAA regulations.[7,8] This is a VA approved electronic data capture software. It is designed to support data capture for research studies from anywhere in the world with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption.[7] It provides: 1) an intuitive *interface for validated data entry* 2) *audit trails* for tracking data manipulation and export procedures 3) *automated export procedures* for seamless data downloads to common statistical packages, an essential feature for data back-up and 4) user-friendly procedures for importing data from external sources.[7] We will store all consent forms, all participant questionnaires, and study information on REDCap. On a weekly basis, we will download data from RedCap and archive the data on a password protected secure server at the Michael E. DeBakey VA Medical Center. PHI will be stored at the MEDVAMC on a secure server that is password protected, only accessible by key staff. Radiographs and MRIs will be labeled with a study ID but otherwise be de-identified and either stored on a secure server or in a locked cabinet.

To ensure confidentiality, all staff members are required to sign a confidentiality oath. Staff are informed about the importance of and the definitions of confidentiality. They are informed that any breach of confidentiality will result in disciplinary action up to and including termination of employment.

10.7.c.iii Vulnerable Subjects

Pregnant women, institutionalized individuals, and prisoners will be excluded from our study.

10.8 Potential Benefits of the Proposed Research to Research Participants and Others

The potential benefits of this study include the possibility of providing preliminary data needed to identify a new therapy for hand OA that could provide both symptom and structural benefits. This could information may help all those who have existing hand OA and could potentially alter the natural history of their disease. Additionally, it is known that people do not tend to address OA with their health care providers[54]. Therefore, participation in this study may lead to improved engagement into medical care for their hand OA.

Although the direct benefits related to this research are not enormous, the risks to subjects in this study are low; therefore risks to subjects are reasonable in relation to the anticipated benefits to the research participants and others.

10.9 Importance of Knowledge to be Gained

The potential benefits of this study include the possibility of providing preliminary data needed to identify a new therapy for hand OA that could provide both symptom and structural benefits. This could information may help all those who have existing hand OA and could potentially alter the natural history of their disease. If we are able to show feasibility, proof of concept, symptom and structure improvement over what is seen in the comparator arm, this would provide critical information that could inform the design of an R01 that could prove efficacy of the first treatment for hand OA with both a symptom and structure benefit.

10.10 Data and Safety Monitoring Plan

Clinical and Data Monitoring Program

10.10.a Part A: Clinical Monitoring Plan

The purpose of this plan is to assure that our clinical trial is being conducted and documented consistent with what is outlined in the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

As this is an exploratory double-blinded clinical trial that will be conducted at a single site of traction therapy using finger traps administered using a hand orthosis, a low risk intervention, compared to standard of care for nodal distal interphalangeal hand osteoarthritis. We are targeting enrollment of 40 participants. Dr. Grace Lo, the Principal Investigator and the Baylor College of Medicine / Michael E. DeBakey VA Medical Center Institutional Review Board (IRB) will be responsible for the DSM Plan.

Our plan is for continuous, close monitoring by Dr. Grace Lo, the study PI, with prompt reporting of toxicity to the IRB, FDA and/or NIH. We will monitor for toxicity through close monitoring of individual patients and through statistical comparisons of treatment groups if needed. Though we think the likelihood of these adverse events is low, potential side effects we will specifically report on the following possible adverse events:

- *Increased hand discomfort or pain*
- *Skin breakdown, erythema, and/or blistering*
- *Neurologic complaints such as numbness or tingling*
- *Vascular complaints such as poor circulation to the fingers*

We aim to enroll 40 patients over 15-18 months.

Inclusion Criteria

- Enrolled to receive medical care at the Michael E. DeBakey VA Medical Center
- At least 3 joints affected by distal interphalangeal (DIP) nodal hand OA
    - DIP nodal hand OA will be defined as Heberden's nodes on physical exam.
- Sufficiently severe frequent pain of at least one DIP
    - Frequent pain: pain on most days of the month for at least one month in the last year.
    - Minimum VAS pain severity of 40 on a 0 – 100 scale

Exclusion criteria

- History or current inflammatory arthritides
    (examples: gout, psoriatic arthritis, and rheumatoid arthritis)
- Prior surgery on the DIP joints
- Planned surgery for the DIP joints

- Pregnancy

This study will be monitored by a NIAMS-appointed safety officer (SO), Dr. Roy Altman. The SO will review reports electronically on a routine basis following the introductory meeting. Ad hoc meetings may be scheduled as needed, but are not the typical reporting method for SO-monitored studies.

Once enrollment begins, enrollment reports (template provided by KAI) will be sent monthly to KAI. Safety reports will be sent twice a year to KAI and the Safety Officer. These reports will include a detailed analysis of study progress, data and safety issues. These reports will continue until the completion of the last follow up visit of the last enrolled participant.

Because this is a small study of short duration of a low risk treatment, we do not plan to have an interim analysis unless requested by the BCM/MEDVAMC IRB or NIAMS.

During these reviews, our statistician (blinded to treatment allocation – though aware of group assignments as group A v. B), will systematically report:

- CONSORT diagram and actual versus expected enrollment figures that illustrate recruitment and participation status.[1]
- Rate of screening potential participants (number of participants screened over how many months)
- Rate of enrollment (number of participants enrolled over how many months)
- Rate of randomization (number of participants randomized over how many months)
- Proportion of study completion (number of participants who completed the 24 week follow up of the anticipated 40)
- Proportion of study withdrawal (number of participants who withdrew of the number successfully randomized)
- Proportion of early termination of participants (number of participants who had early termination of the number successfully randomized)
- Rate of treatment compliance
- Data tables that summarize demographic and baseline clinical characteristics.
- Data quality tables that capture missing visits and missing case report forms.
- Safety assessments of aggregate tables of adverse events and serious adverse events.
- Listings of adverse events, serious adverse events, deaths, unanticipated problems and protocol deviations/violations.
- Any problems or issues with the conduct of the study not listed above.

On a **weekly basis**, at our working meetings, Dr. Lo, the Research Coordinator, and our Statistician will review these same findings and evaluate whether there needs to be modification of the study intervention, modification of the protocol, modification of the consent form, or early termination of the study. If any of these concerns arise, Dr. Lo will contact the local IRB for further guidance on how to proceed.

10.10.b Part B: Data Monitoring Plan

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

[1] Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. Ann Int Med 2010; 152.

All study related electronic data will be stored on the M - HSRD on vhahouhsr10, and will be accessible through ***"\\r02.med.va.gov\Research\HOU\Production\Data\Housrd\Research\Lo_G_Hand_Study_H-44508".***

For all hard copies of data, a binder system with a binder per participant will be created and maintained. Our Research Coordinator will be responsible for creating and maintaining this system. These binders will be maintained in double-locked cabinets at MEDVAMC at 2450 Holcombe Blvd, Ste 01Y within the Health Services Research Center of Innovation at the McGovern Campus

Most study data will be collected and managed using the REDCap electronic data capture tools, designed to comply with HIPAA regulations.[7,8] This is a VA approved electronic data capture software. It is designed to support data capture for research studies from anywhere in the world with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption.[7] It provides: 1) an intuitive *interface for validated data entry* 2) *audit trails* for tracking data manipulation and export procedures 3) *automated export procedures* for seamless data downloads to common statistical packages, an essential feature for data back-up and 4) user-friendly procedures for importing data from external sources.[7] We will store all participant questionnaires, and study information on REDCap with the exception of the daily log that participants will submit as a hardcopy at the end of the study.

Data Download from RedCap

Our Research Coordinator will download data from RedCap on a weekly basis once we initiate participant screening and this will continue until the last participant enrolled is seen at his/her last in clinic visit.

- This data will be stored on our M-drive folder under the "Data Collection/Red_Cap" folder.
- Each download will be stored using the following naming convention: **RawDataHandRCT_<YYYYMMDD>**.
    - In this naming convention , <YYYYMMDD> = year, month, date that the data was downloaded.

Informed consent is required by the BCM/MEDVAMC IRB to be obtained by reviewing a hard copy of the consent form and having the participant sign that hard copy. Our Research Coordinator will have this informed consent scanned and uploaded to the MEDVAMC electronic medical record system. Additionally, he will scan and upload another copy of the consent form on

- Our M-drive folder under the "Data Collection/Consent" folder.
- Each form will be stored using the following naming convention: **Consent_<YYYYMMDD>_<studyID>**.
    - In this naming convention:
        - <YYYYMMDD> = year, month, date that the consent was obtained
        - <studyID> = the participant's study ID number.

HIPAA form is required by the BCM/MEDVAMC IRB to be obtained by reviewing a hard copy of the HIPAA form and having the participant sign that hard copy. Our Research Coordinator will have this HIPAA form scanned and uploaded to the MEDVAMC electronic medical record system. Additionally, he will scan and upload another copy of the form on

- Our M-drive folder under the "Data Collection/HIPAA" folder.
- Each form will be stored using the following naming convention: **HIPAA_<YYYYMMDD>_<studyID>**.
    - In this naming convention:
        - <YYYYMMDD> = year, month, date that the HIPAA form was signed
        - <studyID> = the participant's study ID number.

A hardcopy of the ***Daily Log*** will be turned in by each participant at the 24 month visit. Our Research Coordinator will manually data enter all information from each daily log returned electronically into an Excel spreadsheet file stored in the same M:drive file listed above. We will make extra effort to verify that data recorded electronically will accurately reflect information derived from source documents.

- This data will be stored on our M-drive folder under the "Data Collection/Daily_Log" folder.
- Each week after the first daily log is submitted and the forms are being data-entered, we will store a copy of the daily log stored using the following naming convention: Daily_Log_**<YYYYMMDD>_<studyID>**.
    - In this naming convention:
        - <YYYYMMDD> = year, month, date that the HIPAA form was signed
        - <studyID> = the participant's study ID number.

The original of the consent and HIPAA form and the daily log that the participants will return at the end of the study will be stored in the study binders.

Itemization of the data that will be collected in RedCap includes the following:

Outcomes:

- the VAS pain scale, asking about pain in the hand that includes the most symptomatic DIP over the last 48 hours (primary outcome)
- Australian Canadian Hand OA Index (AUSCAN) pain scale,[1,2] (although we have requested copyright permission to use the scale, we have yet to receive permission to do so – we plan to administer the outcome, but if not given permission, we will not publish with this data).
- the VAS pain scale, asking about pain in the most symptomatic DIP in the last 48 hours,
- the AUSCAN function subscale,[1,2]
- the Functional Index for Hand Osteoarthritis (FIHOA)[42]
- the Disabilities of the Arm, Shoulder, and Hand (DASH)[51],

- the Michigan Hand Outcomes[56],
- the Functional Dexterity Test[43],
- grip and pinch strength, and
- tenderness on joint palpation on all hand joints.[44]
- photographs of the participant's hands
- We will also take a medication inventory (dichotomous assessments)

    iv. Pain medications (e.g. acetaminophen, all non-steroidal anti-inflammatory medications, and opiod medications).

    v. Glucosamine and chondroitin

    vi. Marijuana use

Additional co-variates of interest include:

- age, (Assessed at baseline visit only)
- sex, (Assessed at baseline visit only)
- race / ethnicity, (Assessed at baseline visit only)
- body mass index, (Assessed at baseline visit only)
- co-morbidities,[57] (Assessed at baseline visit only)
- a family history of hand OA, (Assessed at baseline visit only)
- occupations that they have performed in their life, (Assessed at baseline visit only)
- time spent on electronics (including smart phones, tablets, and computers) (Assessed at the baseline, week 4, week 12, and week 24 visits)
- International Physical Activity Questionnaire (iPAQ) questionnaire on physical activity,[6] (Assessed at the baseline, week 4, week 12, and week 24 visits)
- Center for Epidemiologic Studies Depression Scale (CES-D).[3] (Assessed at the baseline, week 4, week 12, and week 24 visits)

These data will help to assess whether randomization was successful and perhaps identify potential mediators to the effect of the traction orthosis.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be directly entered by our Research Coordinator into RedCap, a 21 CFR Part 11-compliant data

capture system provided by BCM. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

For all participants who sign consent forms and HIPAA authorization forms for an interventional study, to maintain compliance with VA Research and Development regulations, our Research Coordinator will write a "Protocol Entry Note" in the VA electronic medical record system, CPRS. For all other participant encounters related to the study, a "Research Note" will be recorded in the VA electronic medical system, CPRS.

Procedures for Reporting Adverse Events are extensively outlined in section 8.7.

Treatment Modification or Discontinuation

People who are randomized into the traction therapy group may have:

- ***discomfort related to wearing the orthosis***
- ***skin break down in areas in contact with the finger traps***
- ***neurologic and/or vascular complaints in the fingers that have finger traps applied***

Notably, finger traps are viewed by the FDA as Class 1 medical devices, the lowest risk devices, and are already available for use in the clinical setting. A search on the FDA website did not return any adverse events reported regarding finger traps.

At the time that the orthosis is created and customized for the participant, our OT will provide instruction on how to don the orthosis and how to remove the orthosis. She will also provide instruction to the participant that if the finger trap is uncomfortable and difficult to remove, there is always the option of cutting the finger trap off the finger with a pair of scissors. Our OT will observe the participant donning and removing the orthosis in the clinical setting to verify that the participant has good understanding of how to perform these activities. She will also review with the participant how to cut the finger trap off in the setting that the participant is unable to remove the finger trap. She will also provide the participants with a handout describing these activities that participants can take with them. If the participants still have difficulty donning and/or removing the orthoses, the participants will be instructed to contact our OT to schedule an as needed appointment to review how to perform these activities.

We will do our best to minimize any discomfort related to these orthoses as our OT will make every effort to address any discomfort the participants many complain of at the time that the orthoses are created by modifying or adjusting the orthoses. Also, we will schedule all participants to return for a 2 week follow up visit with our OT to assess for appropriate fit and to address any concerns the participants might have related to the orthoses. If these issues cannot be satisfactorily resolved, then the participants will be given an option to terminate use of the orthosis.

Additionally, if the participants voice any complaint about the orthoses at any of the follow up visits, we will arrange an as needed appointment with our OT to address those concerns. Again, if we are unable to adequately address a participant's concerns or complaints then the participant of course, has the option to terminate use of the orthosis.

If participants experience skin break down in areas in contact with the finger traps, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve fit if possible. The participants will be instructed to resume wearing the orthoses after all skin break down is healed.

If participants experience neurologic and/or vascular complaints (e.g. numbness/tingling or lack of blood supply) in the fingers that have finger traps applied, they will be instructed to stop wearing the orthoses and to contact our OT to make an appointment with her to re-assess fit of the orthosis at which time she can also make adjustments to improve fit if possible. The participants will be instructed to resume wearing the orthoses after the participant can don the orthosis without the original complaint.

Study Termination

If there is detection of a high rate of unexpected adverse events grade 3 or higher, which may or may not be associated with one treatment allocation group, this may warrant termination or temporary suspension of the study (e.g., study closure based on PI decision or sponsor/funder decision). For any study that is prematurely terminated or temporarily suspended, Dr. Grace Lo will promptly inform the BCM/MEDVAMC IRB and NIAMS and provide the reason(s) for the termination or temporary suspension. In depth investigation will be performed to determine whether there are study activities or treatment related effects that are contributing to this signal. If the investigation does not support these possibilities, and this is agreed upon by NIAMS, the BCM/MEDVAMC IRB, and Dr. Grace Lo, the study PI, then the study can resume.

Describe methods and systems to ensure data confidentiality and subject privacy.

All study personnel will be trained in best practices in human subjects studies prior to embarking on any study related activities and no study related activities will commence until the study protocol is approved by Baylor College of Medicine/MEDVAMC's IRB. With the exception of a master list that links study ID to PHI, including first and last name, street address, email address, and phone number, all other study related materials will only be labeled with the study ID number to maximize the likelihood that data confidentiality will be maintained through the course of the study. This master list will only be stored on a secured server within the MEDVAMC network, which is part of the VA nationwide network. Hence, our computers conform to VA security policies and standards. These policies and standards include but are not limited to strong passwords, locking screensavers, up-to-date anti-virus protection, and storage of sensitive patient information stored on VA servers on the VA network. The servers are protected by user login and passwords. All servers are backed up daily to ensure data protection. Weekly full backups are stored in a vault at a secure remote location. The heart of the system is a Hewlett Packard Itanium System running under the Unix operating system. This server is used for managing and analyzing the large datasets. The Itanium server has four 1.5-GHz Itanium CPUs (IA64), 28.0 GB of RAM and approximately 28.0 GB of RAM, and approximately 8TB of disk storage. In addition to the HP Itanium, there are six Dell servers running the Windows operating system, used for network applications, the SQL database, file sharing, and print sharing, with a total storage capacity of 4TB. Only study personnel who require information from the master list to conduct activities related to the study will access the master list.

Describe process for locking the final trial datasets and the planned procedures on data access and sharing, as appropriate. Once the final study participant has been seen for his/her 6 month follow up visit and all radiographs and MRIs have been read for the planned features, procedures will commence to clean the data and invoke a high level of quality control of the dataset. The full dataset will be evaluated for logic errors and missing data. Dr. Lo (PI) will make a best effort to reconcile logic errors and complete missing data if possible. This should result in a complete and final trial dataset and Dr. Peter Richardson (statistician) will then be asked to lock the dataset. If data or resources from this project are requested by external qualified individuals within the scientific community, we will make every effort to share the data with those individuals using privacy respectful practices and following all the guidelines expected when handling data from human subjects research.

11.0 ClinicalTrials.gov Requirements

ClinicalTrials.gov facilitates registration of trials in accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical trials in a public registry as a condition for publication. Therefore, we will register this study with clinicaltrials.gov. Also, ClinicalTrials.gov allows the registration of trials that (1) are approved by a human subject review board (or equivalent) and (2) conform to the regulations of the appropriate national health authorities.

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