ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** **x No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
x Yes ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☐ **Yes** **x No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** **x No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** **x No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
x Yes ☐ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;**
☐ **Yes** **x No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** **x No**	Include the use of recombinant or synthetic	*Complete the IBC application via eprotocol.umn.edu*	

	nucleic acids, toxins, or infectious agents?		**These groups each have their own application process.**
☐ Yes **x No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
X Yes **☐ No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
xYes **☐ No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ Yes **x No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham Pham0435@umn.edu*	
☐ Yes **x No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
x Yes **☐ No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
xYes **☐ No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Mechanisms of a Dynamic Stability Approach
Principal Investigator/Faculty Advisor	Name: Corey McGee
	Department: Occupational Therapy
	Telephone Number: 952-607-6387
	Email Address: mcge0062@umn.edu
Student Investigator	N/A
Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	Version 4; 05/25/2023

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/20/2022	Changing fluoroscopic methods to CAT scans and location of imaging to the Center for Clinical Imaging Research, U of MN	Yes
1.1	1/22/2023	Removed 12 week assessment and extended treatment period to 8 weeks and 1st follow up to 9 weeks. This addressed concerns of radiation exposure and recent issues with lower interventionist staffing.	Yes
2	4/11/2023	Added information exchange data to the ancillary review grid. The use of BPIC is already explicitly stated throughout the application. We just failed to acknowledge this in the ancillary review grid.	No
3.	5/25/23	Amended recruitment efforts to include the BPIC/FRA mailing service. Composed an invitation letter to use for recruitment.	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

- DS = dynamic stability exercises
- CMC=Carpometacarpal
- OA=Osteoarthritis
- PI=principal investigator
- Subluxation=incomplete joint dislocation
- SC = Standard Care
- DS = Dynamic Stability
- OP = Opponens Pollicis Muscle
- FDI = First Dorsal Interosseus Muscle
- MC = Metacarpal
- CTSI = Clinical Translational Science Institute
- EMR = Electronic Medical Record
- NERS = Non Employee Research Staff
- NIH = National Institute of Health
- CRF = Case Report Form

1.0 Objectives

1.1 Purpose:

Arthritis is our nation's most common cause of disability[1] and an estimated 25.6 million U.S. residents are affected by osteoarthritis (OA) of the hand.[2] Thumb carpometacarpal (CMC) joint OA is the most common and disabling form of symptomatic hand OA.[3] Symptoms and sequelae associated with thumb CMC OA include acute and chronic pain, grip and pinch strength weakness, reduced joint mobility, and difficulty carrying out common manual tasks.[4] Factors associated with the onset of thumb CMC OA include joint instability and concurrent misalignment and radiographic changes in these factors predict diminished hand function.[5] Non-operative approaches to reducing joint stress and symptomology are the first course of treatment for thumb CMC OA and standard care has taken the form of splint-wear and instruction on joint protection when completing manual tasks. Recently, the study of exercise as conservative treatment for hand OA has been recommended[6] and a novel exercise program designed by an occupational therapist, referred to as the "dynamic stability" (DS) program[7], has been adopted by some rehabilitation therapists and recommended by their surgeon counterparts. The DS program, at its core, aims to reduce thumb CMC instability through strengthening select muscles known to instantaneously reduce joint instability in the thumb.[8]

Preliminary retrospective evidence suggests patients who participated in the DS program have better pain and disability outcomes than those who received standard care alone.[9,10] However, major gaps in evidence for DS remain. Although evidence suggests that surgically stabilizing the thumb CMC improves hand function11, the hypothesized sustained stabilizing effects of the DS exercise program have not been tested in prospective research. It is important to know whether a six week course of a DS program can reduce thumb instability and whether these benefits are possible for patients with a range of CMC OA severity. Additionally, because the gold standard of evaluating thumb instability is not within the scope of practice of rehabilitation scientists and therapists, they are limited in their abilities to visualize thumb CMC joint mechanics when treating and when evaluating response of treatment. Rehabilitation therapists and scientists can, however, be certified in musculoskeletal sonography and sonographic methods can be used to quantify thumb CMC alignment.[12] However, the agreement between sonographic and fluoroscopic or computerized tomography (gold standard) measures for assessing thumb CMC instability is unknown and must first be established.

The *long term goal* of my research is to help *mitigate the pain and disability experienced by persons with upper limb musculoskeletal disorders through non-invasive and non-pharmacological approaches*. The proposed research aims to prospectively evaluate the impact of DS exercises on the thumb instability in persons with thumb CMC osteoarthritis. My training plan supports this long-range goal by providing me the background needed to measure and/or interpret the outcomes of interest and carry out a single-arm intervention study.

We expect, in part, to achieve our long term and training plan objectives by pursuit of these **two specific aims**:

1. **To describe changes in radiographic thumb CMC joint misalignment following a 6-week clinic-based dynamic stability exercise program.** Fifty patients will be enrolled in a prospective pre-post interventional study of a 8-week clinic-based dynamic stability program and will undergo computerized tomography (CT) measurements before treatment, and upon completion of the program (9 weeks). The primary outcome will be change in CMC subluxation in cm from pre-treatment to post-treatment at 9 weeks.

1a. **To describe the influence of arthritis staging on response to treatment.** Through the use of a stratified sampling strategy we will seek to enroll equal numbers of participants with Eaton Stages 1, 2, and 3 (16-17 participants per strata). Response to intervention will be adjusted based on baseline staging via regression.

1b. **To gather preliminary data on treatment adherence and self-reported disability for future use when planning a comparative effectiveness trial.**

2. **To evaluate the accuracy of ultrasound compared with CT (reference standard) for quantifying thumb CMC subluxation.** Up to 50 participants will undergo ultrasound (by Dr. McGee) during baseline and 9 week CT assessments.. Agreement of ultrasound and CT measurements (cm of subluxation) will be assessed by Bland-Altman method.

The proposed study directly aligns with the Centers for Disease Control's National Public Health Agenda for Osteoarthritis[12] priorities, which promote evidence-based interventions that address self-management and physical activity. The proposed study is innovative because it will bring together an interprofessional team of health researchers to prospectively evaluate the effects of an exercise-based approach to self-management on change in the instability believed to contribute to the onset and progression thumb CMC OA. Additionally, should sonography be a suitable proxy for CT assessment of thumb CMC alignment, rehabilitation therapists will be better equipped to practice 'precision' rehabilitation in this population with improved outcomes to follow. Lastly, this project will serve as the foundation for my training plan, which will prepare me to design rigorous prospective trials to test the effectiveness of this program relative to traditional approaches

2.0 Background

2.1 Significance of Research Question/Purpose:

The thumb, accounting for 50% of hand function,[13] is estimated to be afflicted by OA in 68% of adults who are 70 or more years of age.[3] Thumb CMC joint OA is the single most common and symptomatic form of hand OA and is a substantial source of hand dysfunction.[14,15,16] The precision, power, and mobility demanded from the thumb to perform precision tasks and grasp makes thumb CMC OA particularly debilitating.[17] Joint hypermobility is thought to be a major etiological factor in the development of thumb OA. An incomplete dislocation of the joint (i.e., subluxation) follows this laxity and results in an incongruent joint and subsequently the development of OA.[18,19]

While surgical approximation of this subluxation results in grip/pinch strength which is commiserate with the patient's unaffected hand,[11] it involves invasive ligament reconstruction and there is emerging evidence to suggest that exercise may also have a stabilizing effect.[8,20,21]

Non-operative approaches to reducing joint stress and symptomology are the recommended first line of intervention for thumb CMC OA.[15] Yet, the recently published results from a survey study revealed that only 21% of clients with CMC OA reporting received non-pharmacological treatment (i.e., rehabilitation) before a referral to surgical consultation.[22] Additionally, recent findings suggest that hand surgeons are less likely than other providers to offer non-surgical options for treatment[23] yet, in a recent study of the outcomes of 701 rehabilitation patients with CMC OA, only 15% went on to require surgery at a 2 year follow-up.[24]

Historically, non-operative treatment has standardly taken the form of occupational or physical therapy and involves wearing a splint and being taught how to protect the joint during daily

activities.[11] More recently, the European League against Rheumatism's task force on the management of hand osteoarthritis recommended that studies be conducted to "determine the most appropriate form or combination of exercise for the different subsets of hand arthritis."[25] In response to this call, researchers have published exercises that are based on studies of joint biomechanics[26] and are intended to address joint instability but were not grounded in outcome studies. In a retrospective cohort study, Skye, McGee, Geneva, and O'Brien[27] reported clinically meaningful reductions in disability and pain in response to these "Dynamic Stability"[7] exercises when combined with standard care.

Wouters et al.[16] took these findings one step further and conducted a retrospective 'propensity score matching' study where the disability and symptomology of those receiving standard care were compared to those who received dynamic stability (DS) exercises in addition to standard care (SC). These authors reported that, at 6 weeks, pain outcomes were superior in the DS+SC group and at 3 months, both pain and disability outcomes were superior.

Although these retrospective studies describe significant and clinically meaningful reductions in osteoarthritic symptomology and self-reported disability, they do not evaluate for any changes in joint mechanics associated with the condition. Changes to the aforementioned subluxation must be quantified in order to test assumptions that these exercises alter joint mechanics. Moreover, these retrospective studies and their findings lack the rigor of a prospective trial. Prospective trials are needed to investigate the added benefit of dynamic stability exercises relative to standard rehabilitation and should include the study of joint mechanics in addition to measures of symptomology and disability.

We propose a set of targeted exercises for persons with osteoarthritic thumb CMC joints[15] that are grounded in theory, thumb biomechanics research,[17,18] and recent validation studies.[19-21] This "dynamic stability" program focuses on the neuromuscular/strength training of select thumb muscles believed to restore the joint mechanics of the CMC. In this thumb CMC dynamic stability (DS) program, the opponens pollicis (OP) and the first dorsal interosseous (FDI) thumb muscles are strengthened in order to theoretically center the thumb metacarpal (MC) on its fulcrum, the trapezium bone. The ability of these muscles to instantaneously reduce a subluxated thumb CMC joint has been validated in cadaveric[22,20] and fluoroscopic studies of non-arthritic thumbs.[19] To date, however, sustained in-vivo mechanical benefits have not yet been investigated among persons with thumb OA who have participated in this intervention program.

While fluoroscopic or computerized tomography (CT) measures of joint subluxation are the gold standard and should be used as a measure of the thumb CMC's mechanical response to the DS program, due to licensure issues, rehabilitation therapists cannot use such methods to evaluate summative or 'real-time' changes in joint mechanics that occur in response to treatment. Sonography, unlike fluoroscopy or CT, does not omit ionizing radiation, can be used to quantify thumb subluxation,[12] and rehabilitation therapists can be certified to use musculoskeletal sonography. However, the agreement between it and the gold standard must first be established before it can be used by rehabilitation therapists and scientists as a safe alternative for measurement of thumb instability.

2.2 Preliminary Data:

The proposed study builds on my recent work.[8] In this study, we used a non-invasive manipulation of the thumb CMC joint and evaluated the instantaneous effect of the maximum

voluntary contraction of the FDI muscle on thumb CMC joint subluxation in 32 non-arthritic hands. The findings illustrated a significantly large effect of FDI loading on subluxation [t(31)=10.6(p<.001), d= 2.70] with maximum FDI strength significantly explaining 39% of the variance in the subluxation response. Prior to this investigation, none had investigated the radiographic in-vivo mechanics of the thumb CMC joint during periods of targeted muscle activity as a means of testing the stabilizing effects of exercise on a subluxated thumb joint. This study offers data from which we can draw conclusions on the sustained effects of the intervention.

2.3 Existing Literature: See section 2.1

3.0 Study Endpoints/Events/Outcomes

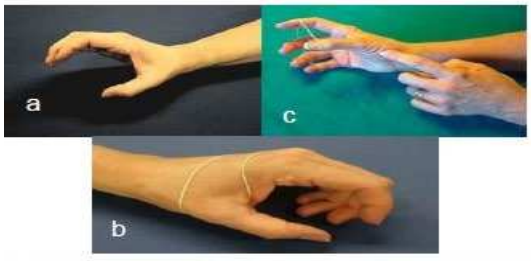
3.1 Primary Endpoint/Event/Outcome: CT assessments before treatment, and upon completion of the program (9 weeks). The primary outcome will be change in CMC subluxation in cm from pre-treatment to post-treatment at 6 and 12 weeks.

Secondary Endpoint(s)/Event(s)/Outcome(s): one-time assessment via use of musculoskeletal ultrasound during baseline and 9-week CT assessment session. Secondary analysis will also include records of treatment adherence and self-reported disability before treatment, and upon completion of the 8 week program (week 9).

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

As per O'Brien and Giveans[10], the thumb CMC DS intervention involves four 45-minute occupational therapy visits as well as a daily home program across a 6-week period. Clinic visits focus primarily on home program coaching, and progression of the exercise regimen (Figure 6). Home programs involve daily exercises which follow the intensity and duration recommended for older adults.[31] The home program should require about 15-20 minutes of the client's time per day. This intervention program is standard care, protocolized and manualized and is summarized by Valdes, Algar, and McGee (2020)[32] summarize. The objective of the DS program is offer patients self-management strategies to restore thumb mechanics, delay further joint damage, reduce pain, and enable participation in daily activities. This is accomplished through a 3-phased approach that includes (1) stretching of a muscle which is often shortened in thumb CMC OA, the adductor pollicis,[4] (2) joint mobilization to relocate the thumb metacarpal and realign the CMC joint[33], and (3) neuromuscular reeducation and strengthening.[26] The latter phase focuses heavily on relearning patterns of muscle activity that best maintain the "stable C" positioning during prehension. The "stable C"



Figures 6a-c.Selected Dynamic Stability exercises.

Table 1. Summary of Dynamic Stability Program.

Phase	Components	Intervention Parameters
1	Manual release of the adductor and any over-active muscle	30 sec holds; 3x daily
2	Joint mobilization to reduce the subluxated metacarpal and realign the CMC joint	1-3 minutes; 3x daily
3	Early Phase: Neuromuscular re-education Late Phase: strengthening	Early: Retraining without resistance progressing to isometric exercise; three times daily for 10 to 15 repetitions. Late: Maximum isokinetic resistance, frequency and intensity reduce to once a day for 8 to 10 repetitions.

position is one where the ligaments of the CMC are taut and the joint most congruent. This position is accomplished through opposing the thumb to the second and third digits while keeping the distal joints of the thumb slightly bent (see figure 6a). Once a patient can maintain this position during lightly resistive activities, isometric exercise is added (Figure 6b) and clients are later progressed into maximally resistive isokinetic exercise as pain dictates (Figure 6c). Muscles targeted in the late phase are the first dorsal interosseous, opponens pollicis, flexor pollicis brevis, and extensor pollicis brevis; all responsible for stabilizing the thumb and maintaining the "C" posture during prehension. A summary of this program and intervention parameters is found in Table 1.

4.2 Drug/Device Handling: N/A

4.3 Biosafety: N/A

4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design: aim #1 will be accomplished via a pre-post interventional design to evaluate changes in CT measurements of thumb radial subluxation (cm) from pre-intervention to intervention completion (9 weeks). The 9-week assessment will be the primary follow-up.

Aim #2 will be accomplished with a cross-sectional concurrent validity study design. Patients enrolled in the DS exercise intervention study will undergo additional assessment of metacarpal subluxation with ultrasound during baseline and week 9 evaluations.

5.2 Study Procedures:

Aim #1.

Screening and consenting: Dr. McGee has provided the CTSI's BPIC service with the diagnostic inclusion criteria for the study and will be informed within 3-5 days if a patient who meets these criteria is scheduled at the MHealth Clinics and Surgery Center. Dr. McGee will be present during the Study Orthopedist's clinic when these potentially eligible patients are scheduled for appointments. The study orthopedist will screen patients for pregnancy/risk of pregnancy via interview and present the study to the eligible patient and, if interested, the informed consent process will follow. Dr. McGee or other IRB-approved personnel will be responsible for informed consent. After consenting, baseline assessments will be conducted.

Assessment: CT will be used at prior to beginning aforementioned rehabilitation intervention, and after completing intervention (9 weeks) as per the European guidelines on quality criteria for computed tomography.[34] A validated positioning jig reproduced by our lab[35] will be used to maintain standardized joint positioning as the volunteer participates in dynamic pinch activities during CT examination. "Radial subluxation" (i.e., the displacement of thumb metacarpal base from the lateral border of the trapezium)[36] is a measure of thumb CMC instability and will be measured in centimeters. Subluxation measurements will not be made until after participants complete the 8-week protocol. After which, de-identified CT images will be presented to study orthopedic surgeon by the PI in a randomized sequence of baseline, and 9 week films so as to not introduce bias. Four images will be taken for each affected hand:

unloaded lateral pinch, loaded lateral pinch, unloaded 3-point pinch, and loaded 3-point pinch. When unilateral thumb OA is present, eight 3-second CT assessments (unloaded lateral pinch x2, loaded lateral pinch x 2, unloaded 3 point pinch x 2, and loaded 3-point pinch x2) will occur by the time of the 9 week follow-up. In the instance that the participant has bilateral CMC OA, 16 three-second assessments will occur. If participants have not yet had an x-ray confirmation of arthritis, through fluoroscopy will be billed to participant's insurance but CT assessments will all be billed to research.

Computerize tomography data will be recorded though use of the Siemens Biograph MCT 64 slice PET/CTat U of MN's Center for Clinical Imaging Research (CCIR). CT images will be used to capture 'kinematic' data and and a wireless biometrics digital pinch meter will be used to capture the pinch 'kinetic' data.

Intervention: As previously mentioned, the thumb CMC DS intervention will involve four 45-minute occupational therapy visits as well as a daily home program across an 8-week period. Clinic visits will focus primarily on home program coaching, and progression of the exercise regimen. Home programs involve daily exercises which follow the intensity and duration recommended for older adults.[31] The home program should require about 15-20 minutes of the client's time per day. This intervention program is standard care, protocolized and manualized and is summarized by Valdes, Algar, and McGee (2020)[32] summarize. The objective of the DS program is to offer patients self-management strategies to restore thumb mechanics, delay further joint damage, reduce pain, and enable participation in daily activities. This is accomplished through a 3-phased approach that includes (1) stretching of a muscle which is often shortened in thumb CMC OA, the adductor pollicis,[4] (2) joint mobilization to relocate the thumb metacarpal and realign the CMC joint[33], and (3) neuromuscular reeducation and strengthening.[26] The latter phase focuses heavily on relearning patterns of muscle activity that best maintain the "stable C" positioning during prehension. The "stable C" position is one where the ligaments of the CMC are taut and the joint most congruent. This position is accomplished through opposing the thumb to the second and third digits while keeping the distal joints of the thumb slightly bent (see figure 6a). Once a patient can maintain this position during lightly resistive activities, isometric exercise is added (Figure 6b) and clients are later progressed into maximally resistive isokinetic exercise as pain dictates (Figure 6c). Muscles targeted in the late phase are the first dorsal interosseous, opponens pollicis, flexor pollicis brevis, and extensor pollicis brevis; all responsible for stabilizing the thumb and maintaining the "C" posture during prehension. A summary of this program and intervention parameters is found in Table 1. Table 2 illustrate the total time commitment expected during the treatment period.

Table 2. Intensity of the intervention.

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Clinic Visit	One 60 min session		One 60 min session		One 60 min session		One 60 min session	
Home program	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week	15-20 minutes Daily, 5 days a week
	Approximate duration of treatment per participant							840-1040 minutes

For **aim #2**, ultrasound measures will be obtained using a Sonocite X-Porte sonographic device. Sonographic assessment will occur at the time of participants'

baseline and 9-week CT assessments (aim #1). The PI will conduct sonographic measures of radial subluxation on all Aim #1 participants (n=49). The same stress view, positioning jig and standardized upper limb postures used for Aim #1 will again be employed. In addition to these standardized joint postures and forces, the thumb CMC joint sonographic procedures described by Oo et al.[12] and the general guidelines put forth by American Institute of Ultrasound in Medicine[37] will be followed. The device is the property of Dr. McGee and there will be no charges billed to the participant associated with the use of this instrument. Dr. McGee will work with Don McCarty from Fairview's biomedical engineering dept. to ensure the device is approved for use at the MHealth Clinics and Surgery Center.

The PI will quantify radial subluxation (cm) of the thumb metacarpal in the same manner as it was in Aim #1. The agreement between these values and those gathered through CT in Aim #1 will subsequently be assessed. The PI and the orthopedic surgeon evaluator will be blinded to each other's ultrasonography and CT findings.

The intervention and baseline diagnostic fluoroscopic assessment are standard care and would be conducted even if not for the purposes of this study. Sonography and the thee CT measurements would be considered above and beyond standard care.

Data to be pulled from patient records include age, sex at birth, arthritis staging, concomitant health conditions, pain, thumb mobility measurements, and disability ratings. Secondary data on treatment adherence via an exercise log and self-reported disability will also be captured (Michigan Hand Questionnaire) for secondary analyses.

Lastly, participants will be asked to report on adverse events during each encounter during weeks 1-6.

Assessment	Screening, Baseline: Visit 1 (Day 0, Week1)	Treatment Visit 1 (Week 1)	Treatment Visit 2 (Week 3)	Treatment Visit 3(Week 5)	Treatment Visit 4 (Week 7)	Follow-up #1 (Week 9)
Informed Consent Form	X					
Demographics	X					
Medical History/Arthritic staging	X					
Inclusion/Exclusion Criteria (Including radiographic confirmation of OA via fluoroscopy)	X					
Attestation of certainty of not being pregnant by women who are non-post menopausal	X					
Enrollment	X					
CT Measurements (Aim 1)	X					X

Ultrasound measurements (Aim 2)	x					x
Self-reported disability (Michigan Hand Questionnaire) – Aim 1b	x					x
Treatment Adherence (Exercise Log) – Aim 1b		x	x	x	x	x
Adverse Events		x	x	x	x	x

Note: "Week" = 7 days +/-3 days

5.3 Study Duration:

- Duration anticipated for an individual participant's participation in the study: 9 weeks
- The duration anticipated to enroll all study participants: 3 years
- The duration anticipated to complete all study procedures: 4 years

5.4 Use of radiation*:*

Note: the following calculations are based on static radiographic imagining.

Radiation exposures (Aim#1) will be minimized through, short exposure times, and wear of leaded aprons, thyroid shields, and protective eyewear for the participant.

Leaded aprons, thyroid shields, and leaded eye protection will worn by the evaluators and participants throughout each CT assessment. Without the attenuation expected from the above protective measures, a conservative estimate of maximal radiation exposure per session is $\mathbf{0.0078}\ \boldsymbol{mSv}$ (totaling $\mathbf{0.1248}\ \boldsymbol{mSv}$) when both thumbs are measured and 0.0624 $\boldsymbol{mSv}$ when only measuring one.

This exposure would respectively equate to 2.3% (unilateral) or 4.6% (bilateral) of the radiation one is naturally exposed to each year as a resident of Minnesota (3 $\boldsymbol{mSv}$).[42]Additionally, because investigators will not be working near but not within the beam of the CT device so there is no risk to the investigators.

5.5 Use of Center for Magnetic Resonance Research*:* n/a

6.0 Data and Specimen Banking

6.1 Storage and Access: De-identified data will be stored in Box, for future use by other researchers. Data will be available immediately following the first publication with no end date following article publication. Researchers (including those outside of the study) whose proposed use of the data has been approved by PI will have access to the data for individual participant data meta-analysis/to achieve aims in the approved proposal. The AHC-IE will be not used.

Publishing of these data may be required. Federal funders (e.g. National Institutes of Health), granting agencies (e.g. Bill & Melinda Gates Foundation), and journal publishers (e.g. PLoS) increasingly require datasets be made publicly available—often immediately upon associated article publication. If this is the case, all data published will be fully de-identified.

6.2 Data: The following deidentified data may be banked for future analyses and compilation into larger datasets: clinical and demographic information, clinical assessments, and imaging data.

6.3 Release/sharing: Should the investigators pursue data sharing, future studies seeking to compile data acquired from this protocol will obtain IRB approval before doing so. In the event that this occurs, only investigators or study personnel listed in an IRB-approved protocol pertaining to the data compilation will have access to this data. The requested will be released to the researchers in a de-identified manner.

6.4 Sharing of genetic testing: N/A

7.0 Sharing of Results with Participants.

7.1 Sharing of results with participants: We plan to share a brief summary of aggregated study results with participants either by email or USPS delivery depending on the participant's preference and will include a "thank you" note for participating. We plan to use the CTSI Dissemination Toolkit when framing the language.

8.0 Study Population

8.1 Inclusion Criteria: will include:

- Adults 18 years or older
- having radiographically-confirmed thumb CMC OA
- having been referred to occupational therapy.

A study orthopedist will use current radiographic evidence to screen and stage thumb CMC OA in all prospective candidates to ensure the diagnostic criteria required for inclusion are met. The same study orthopedist will screen recruits for pregnancy or risk of pregnancy via an interview. Both men and women will be included given the findings of Wilder et al.[29], who described the prevalence of radiographically confirmed thumb carpometacarpal osteoarthritis to be similar in men (20%) and women (21%).

In addition, should these recruitment efforts prove to be slow we will recruit through the existing health records of adults ages 18 and older who have a diagnosis of CMC OA and have received care within University of Minnesota Health/Fairview orthopedics/ Sports Medicine, or Rheumatology departments from December 2015 to April 30, 2023 Eligible participants will have any of the following ICD 10 codes: Primary OA CMC joint (M18.11, M18.12, M18.2), post-traumatic OA CMC joint (M18.31, M18.32, M18.4) and other secondary OA CMC joint (M18.51, M18.52) and will be identified via the I2B2 Data set and then run by BPIC and sent to Fairview for mailing. Alternatively, Fairview's Research Recruitment services may perform the same service.

Those recruited in this fashion will be required to be screened for pregnancy or risk of pregnancy via an interview by their preferred medical provider (i.e., women's health, family physician, internal medicine, orthopedic surgeon) prior to enrollment.

8.2 Exclusion Criteria will include:

- cortisone treatments to the affected thumb within the prior three months
- thumb CMC joint replacement
- a diagnosis of inflammatory arthritis
- a diagnosis of Ehlers Danlos Syndrome
- a diagnosis of Marfan's disease
- pregnancy or questionable pregnancy
- mothers who are breastfeeding

- cognitive disorders which would preclude a client from following the testing commands and home program participation
- a diagnosis of a concomitant condition affecting the arthritic thumb (i.e. Wartenberg's syndrome, deQuervain's, trigger thumb, intersection syndrome)
- grade 4 Eaton[29] OA staging
- ongoing hand rehabilitation (i.e., within prior 6 months)
- pain which precludes participants from completing testing
- an EMR flag for not wishing to participate in research

8.3 Screening: Dr. McGee has provided the CTSI's BPIC service with the diagnostic inclusion criteria for the study and will be informed within 3-5 days if a patient who meets these criteria is scheduled at the MHealth Clinics and Surgery Center. Dr. McGee will be present during the Study Orthopedist's clinic when these potentially eligible patients are scheduled for appointments. A study orthopedist will use current radiographic evidence to screen and stage thumb CMC OA in all prospective candidates to ensure the diagnostic criteria required for inclusion are met. The same study orthopedist will screen recruits for pregnancy or risk of pregnancy via an interview and present the study to the eligible patient. If the recruit is interested, the informed consent process will follow and will be conducted by Dr. McGee or other IRB-approved personnel.

9.0 Vulnerable Populations:

9.1 Vulnerable Populations

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Excluded from Participation
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation

Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	Included/Allowed to Participate
Active members of the military (service members), DoD personnel (including civilian employees)	Included/Allowed to Participate
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded from Participation
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

9.2 Additional Safeguards: All participants will be informed that their participation is voluntary, all of the information gathered throughout the course of the study will be kept confidential, and that choosing to not participate at any time in the study will not affect their relationship with the university or their health care providers. Furthermore, participants will be asked, at the time of seeking informed consent, to share their comfort with reading the consent form or any other study materials. If the prospective participant shares that they are uncomfortable with reading the materials, all materials will be read aloud and participants will be asked to do a teach-back to ascertain comprehension.

Undervalued or disadvantaged people may not be known, research staff will not be asking a direct question about socioeconomic status to potential participants. We do not anticipate vulnerability for this group to be increased by participating in this study.

Members of the military may not be known, research staff will not be asking a direct question about military status to potential participants. We do not anticipate vulnerability for this group to be increased by participating in this study.

Undervalued or disadvantaged people may not be known, research staff will not be asking a direct question about socioeconomic status to potential participants. However, we have taken special precaution to make sure participants are fairly and adequately compensated for their time in this study, yet not coerced by unreasonably high compensation amounts.

9.3 Rationale for exclusion (if potential for direct benefit): We plan to exclude expecting mothers/or women who are potentially expecting due to risk of exposure to ionizing radiation. This will impact very few potential recruits given that persons with thumb CMC OA are primarily post-menopausal women. We will exclude persons who are non-English speaking or illiterate because the Michigan Hand Questionnaire is only cross-validated in Brazilian Portuguese, Colombian Spanish and German and requires basic literacy to complete.

10.0 Local Number of Participants

10.1 Local Number of Participants to be consented: we plan to enroll as many as 50 and as few as 40 participants.

11.0 Local Recruitment Methods

11.1 Recruitment Process: Participants will be recruited from the MHealth Clinics and Surgery Center. The PI or research assistant (RA) will be notified by BPIC 3-5 days prior to a potential recruit's visit to orthopedics. The PI will confirm eligibility through reviewing the EMR. The PI/RA, as Nonemployee Research Staff (NERS), have approved access to such. The study orthopedist will be informed of the client's eligibility by the PI/RA and who will then briefly present the study and ask the patient for permission for the PI or study staff to present the study to them in more depth during their clinic visit. If interested, the informed consent process will follow.

If recruitment efforts through these methods are slow, potential participants will also be identified in the i2b2 database then run by BPIC and sent to Fairview for mail-invitation. Alternatively, Fairview's Research Recruitment services may perform the same service. These letters or MyChart Messages will be sent to those who qualify via the Fairview Recruitment Mailing Service. Patients will then outreach to the PI for additional details and, in interested, will proceed with the informed consent process.

After which, the initial assessment and subsequent therapy sessions will be scheduled. We will use selective stratified sampling to enroll equal numbers of persons with baseline Eaton[30] thumb CMC OA stages 1, 2, and 3 respectively (i.e., 16-17 participants per strata). The study will be closed to recruitment for those of a strata which has achieved 16-17 participants.

Successful recruitment appears feasible given the findings of a recent analysis of Fairview/UHealth dataset through use of the University of Minnesota CTSI's "i2b2 Cohort Discovery tool." The survey of our participant pool revealed that 4,858 persons (3363 women and 1495 men) who met the inclusion criteria for participation were seen in Fairview/UHealth Sports and Orthopaedic Clinics from January 1st, 2018 to March 11th, 2021.

Although the prevalence of radiographically confirmed thumb CMC OA is similar in men and women[27], our survey of our participant pool appears to reveal a care-seeking gender discrepancy. This discrepancy is consistent with the findings of health service research[28] and thus, while evidence suggests that women and men are affected equally by this condition, we anticipate that the population from which we will recruit will be disproportionately female and, in a study of this nature, we will not attempt to selectively recruit men.

In being consistent with the demographics of Minneapolis we will aim to recruit the following racial distribution: White: 64%, Black or African American: 19%, Asian: 6%, other: 5%, multiracial 5%, and Native American: 1%. Thus we will work to selectively recruit approximately 30 white, 9 African American, 5 Latino American, and 5 Asian American participants. If this diversity is not met through recruitment on a rolling basis, we will work with BPIC to identify those who meet these criteria and selectively recruit these persons.

11.2 Identification of Potential Participants: The PI or research assistant (RA) will be notified by BPIC 3-5 days prior to a potential recruit's visit to orthopedics. The PI will confirm eligibility through reviewing the EMR. The PI/RA, as Nonemployee Research Staff (NERS), have approved access to such. The study orthopedist will be informed of the client's eligibility by the PI/RA and who will then briefly present the study and ask the patient for permission for the PI or study staff to present the study to them in more depth during their clinic visit.

If recruitment efforts through these methods are slow, potential participants will also be identified in the i2b2 database then run by BPIC and sent to Fairview for mail-invitation. Alternatively, Fairview's Research Recruitment services may perform the same service. These letters or MyChart Messages will be sent to those who qualify via the Fairview Recruitment Mailing Service

11.3 Recruitment Materials: Recruitment materials will include a brief description of the study. This will be provided at the time of the initial encounter with the surgeon. Please see the Participant handout provided in the ETHOS application.
If using health records to identify potential participants, an IRB and Fairview Research Administration approved letter will be mailed or sent via MyChart.

11.4 Payment: Greenphire ClinCards will be given to each participant to compensate for time and parking expenses. Cards will be loaded with a reimbursement of $25.00 after attending each study-associated therapy and evaluation session (6 sessions x 25.00 = 150.00). Additionally, $6.00 per visit will be provided for parking for 6 visits (6 x $6.00 = 36.00). In total, participants will receive compensation for attending 4 therapy-only visits, and 2 evaluation-only visits (i.e., baseline, and 9-week follow-ups). Should participants continue with therapy beyond the study period, the remaining therapy costs will be billed to participants' health insurance in the typical fashion. The maximum compensation amount for each participant would be $186.00.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- If they are lost to follow up
- If they behave inappropriately toward study staff
- Disease progression which requires discontinuation of the study intervention
- If they show signs of diminished capacity to consent
- Or it is in their best interest, as determined by the PI

Recruits will be informed that participation in this study is voluntary. They will be informed that their decision on whether or not to participate in this study will not affect their current or future relations with the University, University of Minnesota Medical Center, or Fairview. Recruits will be informed that, if they decide to participate, they are free to withdraw at any time without affecting those relationships.

12.2 Withdrawal Procedures: If participants choose to withdraw from the study, data collection will be discontinued with no further follow up. Participants who are withdrawing from the study will be asked to consider providing consent for subsequent data collection to follow up on their medical outcomes related to the project. Thus, participants will be presented with the option to sign a “Consent Collection after Withdrawal” to enable this future data collection. All data collected up to the point of participant withdrawal from the study will continue to be securely stored and analyzed. Primary and secondary outcomes will be handled through intent to treat analysis. Records will be kept on number of withdrawals as well as the reasoning for such.

12.3 Termination Procedures: 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 funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- 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

Records will be kept on number of withdrawals as well as the reasoning for such.

13.0 Risks to Participants

13.1 Foreseeable Risks: This proposed study involves human subjects. Human subjects are required for this study as we plan to test the effects of an intervention on human adults with thumb arthritis. This study cannot be carried out in an animal model nor does it pose any significant risks to the health and wellbeing of human subjects. 1) Participants might experience some mild hand fatigue or joint aches for 2-3 days following testing and at the onset of the intervention as a result of the repetitive nature of the tasks involved, 2) participants will be asked to give some information that you may be perceived to be of a personal nature 3) the primary outcome measure for this study is CT and this involves the aforementioned minimal amounts of ionizing radiation, and 4) at times, it may be necessary for the researchers to physically touch the participants' hands or sides to ensure that you are in the correct positions. This, to some, may be uncomfortable.

Radiation exposures will be minimized through short exposure times, and wear of leaded aprons, thyroid shields, and protective eyewear for the participant and rater alike, and leaded gloves for the rater.[39-41]

Participants will be allowed frequent rest breaks to limit any amount of fatigue and soreness participants may experience in their hands and arms following testing and when participating in exercise. If discomfort increases as a result of testing, participants will be instructed on self- managing symptoms through use of physical agents such as cryotherapy and rest. In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Participants who believe they have suffered a research related injury, will be asked to inform the researchers immediately. If participants are physically uncomfortable or uncomfortable with the nature of the questions or occasional touch, they will be instructed that they are free to withdraw from participation at any time without any impact to relationships with the university.

Privacy/Confidentiality Risks: Risk of loss of confidentiality is unlikely, but could possibly occur as PHI is utilized as part of this study. This risk would be minimized by protections such as de-identification of participants via use of a study identifier, locked/secured/limited access to PHI, and electronic data securely stored and password-protected.

13.2 Reproduction Risks: Use of radiographic imaging is contraindicated for pregnant women. As such, women who are or could be pregnant will be excluded from this study.

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: The occupational therapy services received by all participants is known to aid in pain reduction, can assist participants in developing health management strategies, and is known to reduce the experience of disability

15.0 Statistical Considerations

15.1 Data Analysis Plan: For aim #1, the within-subjects outcomes will be compared primarily on the mean change in degree of subluxation from baseline to 9 week follow-up (the primary outcome). Additionally, given our recent retrospective findings[27] which support that advanced arthritic radiographic staging is also a negative predictor of response to the DS, mean change scores will be compared and adjusted for according to arthritic staging through use of linear regression for added precision of the treatment effect estimates. For aim #2, the agreement between baseline radial subluxation measurements via CT measurements and those via sonography will be assessed using the Bland-Altman method.[42]

15.2 Power Analysis:

Aim #1: Previous work[8] suggested that the mean immediate misalignment change in the treatment group will be 0.33 cm, with a standard deviation of 0.18.The proposed sample size was estimated a priori assuming a paired t-test of the change in misalignment, with two-tailed type I error of 0.05 and power of 90%. We conservatively estimate that the minimum clinically important change in misalignment will be between 0.05cm and 0.40cm, depending on how much the sustained effect is attenuated relative to the immediate effect (published value 0.42cm), and that the standard deviation (SD) of the misalignment measurement is 0.22cm. The correlation between the pre and post measurements is unknown, so we estimate the needed sample size for a range of correlation values between 0.20 and 0.80.

If we conservatively assume that the immediate misalignment change is 0.30cm, that the sustained change will be reduced by 50% to 0.15cm, and that the pre and post measurements will only be weakly correlated with a correlation coefficient of 0.2, then a sample size of 39 people (39 pre and post measurements) will be required. Assuming a potential loss-to-follow-up rate of 20%, we will enroll 49 participants.

Aim #2: A formal sample size estimate is not available for this aim given its novelty. However, because a sample of 30 participants is assumed to be adequate for bivariate correlational research[37], we anticipate that our sample of 49 participants will be adequately powered.

15.3 Statistical Analysis: See section 15.1.

15.4 Data Integrity: The PI is responsible for monitoring the integrity of the data. The PI will oversee regularly scheduled checks of both our outcome assessors and our interventionists. At each check, the PI will use a protocol checklist to document the number of evaluation and intervention protocol deviations and provide real-time feedback.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

X I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research: As mentioned in section 11.2, the PI or research assistant (RA) will be notified by BPIC 3-5 days prior to a potential recruit's visit to orthopedics. The PI will confirm eligibility through reviewing the EMR. The PI/RA, as Nonemployee Research Staff (NERS), have approved access to such. The study orthopedist will be informed of the client's eligibility by the PI/RA and who will then briefly present the study and ask the patient for permission for the PI or study staff to present the study to them in more depth during their clinic visit.

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

x I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

x I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed: As mentioned in section 11.2, the PI or research assistant will confirm eligibility through reviewing the medical record and will confirm that the patient has consented to sharing their health information for research purposes.

16.4 Approximate number of records required for review: 50-60 (to account for drop-outs).

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

X Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☐ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

16.6 Explain how the research team has legitimate access to patients/potential participants: The research team will be permitted to access sources of private information because all participants will be required to sign a HIPAA waiver at the time of informed consent. Additionally, the PI and research assistant are Non-Fairview Employed Research Staff (NERS) credentialed and thus, have legitimate access to the EMR.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

X In OnCore (oncore.umn.edu)

x Store ☐ Analyze ☐ Share

X In the University's Box Secure Storage (box.umn.edu)

X Store X Analyze X Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☐ Other. Describe:

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties. N/A

16.9 Links to identifiable data: Two data sets will be maintained until data collection is completed. One data set will contain identifiers linked to assigned participant numbers. The PHI dataset will link the PHI to participant numbers. Both datasets will be stored on university monitored, password protected, encrypted, and secured servers (Box data management system). Datasets will be password protected and stored in a secure and encrypted repository (Box). Access will only be granted to the PI and IRB approved study staff.

16.10 Sharing of Data with Research Team Members. Access to the datasets stored in Box will only be granted to the PI and associated personnel.

16.11 Storage of Documents: will be stored on university monitored, password protected, encrypted, and secured servers (Box data management system). Datasets will be password protected and stored in a secure and encrypted repository (Box). Access will only be granted to the PI and associated personnel.

16.12 Disposal of Documents: in compliance with NIH Policy 8.4.2 "Record Retention and Access", records will be retained for 3 years after study completion. At this time, all paper copies of research will be shredded and disposed of in PHI-compliant waste containers. Electronic records will be purged from the PI's laptop and Box. The recycling bin of the PI's laptop will also be purged.

17.0 Confidentiality

17.1 Data Security: Two electronic data sets will be maintained until data collection is completed. One data set will contain identifiers linked to assigned participant numbers. The PHI data set will link the PHI to participant numbers. Electronic datasets will be stored on university monitored, password protected, encrypted, and secured servers (Box data management system). Datasets will be password protected and stored in a secure and encrypted repository (Box). Access will only be granted to the PI and associated personnel. Hard copies of signed consent forms will be kept in a locked file cabinet in the PI's office. Additionally, because this study is occurring within the MHealth/Fairview system, a copy of the signed consent/HIPAA form will be sent to Health Information Management Services (HIMS) so that it can be entered into the participant's electronic medical record.

Because this is an NIH-funded project, the National Institutes of Health has granted a Certificate of Confidentiality. We will use this Certificate legally to refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. We will use the Certificate to resist any demands for information that would identify participants, except as explained below.

It is unclear if the Certificate will work in foreign countries. The Certificate does not prevent a researcher from reporting information learned in research when required by other state or federal laws, such as mandatory reports to local health authorities for abuse or neglect of children/vulnerable adults, or information to the Food and Drug Administration (FDA) when required in an FDA audit. However, the Certificate limits the researcher from disclosing such information in follow up civil, criminal, legislative or administrative legal proceedings if the information was created or compiled for purposes of the research.

A Certificate of Confidentiality does not prevent participants or a member of their family from voluntarily releasing information about participants or their involvement in this research. If an insurer, medical care provider, or other person obtains participants' written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The PI will conduct the monitoring on-site at initial assessment and training and periodically throughout the study via a random review of safety data. Independent audits will not be conducted.

18.1 Data Integrity Monitoring: The PI is responsible for monitoring the integrity of the data. The PI will oversee regularly scheduled checks of both our outcome assessors and our interventionists. At each check, the PI will use a protocol checklist to document the number of evaluation and intervention protocol deviations and provide real-time feedback.

18.2 Data Safety Monitoring: It will be the responsibility of the Principal Investigator to oversee the safety of the study. The PI will review cumulative raw data, trends in AEs, SAEs and UPIRTSO on an ongoing basis. Safety data will be captured in the eCRFs for each visit. Any safety event meeting the IRB's urgent reporting criteria will be reported to the IRB within its published timelines.

At each contact with the participant, the PI will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder. A second copy will be sent to the sponsor.

The PI will be responsible for 1) collecting, reporting, and risk management of adverse events, 2) data collection, entry, transmission and analysis, 3) site coordination and enrollment, 4) regulatory issues such as IRB actions, and conflict of interest

disclosures, and 5) reporting the interim analysis to IRB. All collaborators will be immediately notified of any adverse events occur.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participants who are withdrawing from the study will be asked to consider providing consent for subsequent data collection to follow up on their medical outcomes related to the project. Thus, participants will be presented with the option to sign a "Consent Collection after Withdrawal" to enable this future data collection.

19.2 Access to Participants*:* Participants will be fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to initiating any study procedures.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to participant's insurance company. If participants believe they suffered a research related injury, they will be encouraged to inform the PI or staff immediately.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process: Dr. McGee has provided the CTSI's BPIC service with the diagnostic inclusion criteria for the study and will be informed within 3-5 days if a patient who meets these criteria is scheduled at the MHealth Clinics and Surgery Center. Dr. McGee will be present during the Study Orthopedist's clinic when these potentially eligible patients are scheduled for appointments. The study orthopedist will present the study to the eligible patient and, if interested, the informed consent process will follow. Dr. McGee or IRB-approved personnel will be responsible for garnering written consent. To ensure that the appropriate consent form is used, we will only print the most recently

approved version housed within Ethos. The consent form will be read to recruits. Further, recruits will:

- be asked to explain in their own words the details of the study,
- be invited to ask further questions and these questions will be addressed by study personnel,
- be invited to discuss with others if uncertain about participating and will be provided a written copy of form to facilitate this discussion
- receive a photocopy of the signed copy of their consent/HIPAA form after being consented, and
- have the informed consent process witnessed by another, likely a family member or interpreter, when non-English speaking

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

21.4 Non-English Speaking Participants: N/A

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.7 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites: Screening, consenting, and all interventions will be carried out at The University of Minnesota Health's Clinics and Surgery Center. All assessments will occur at the Center for Clinical Imaging Research.

22.2 International Research: N/A

23.0 Multi-Site Research

N/A

24.0 Coordinating Center Research

N/A

25.0 Resources Available

25.1 Resources Available:

Scientific Environment: The University of Minnesota (U of MN) Academic Health Center (AHC) is a major Midwestern academic health care center located directly on the University of Minnesota's Twin Cities Campus. The AHC provides comprehensive health care and education to a large population of patients and supports related research on such populations. The Program in Occupational Therapy and Department of Orthopaedics are all housed within the AHC.

Space: Dr. McGee has a 120 sq. ft. office space which is equipped to support data management, and secured storage of data. Equipment in this lab includes a secured file cabinets; a Dell Latitude E6440 Laptop with i5 processor, 500GB hard drive, 8GB DDR3 RAM; Dell V725w printer; MS Windows 7; MS Office 2007; and the statistical software package, SPSS ver.22. Peripherals include docking station, (2) Dell U2414H 24 Ultra HD Monitors for split-screen work and a Dell V725w color printer. The office is housed in the University of Minnesota - Twin Cities Campus, in the Children's Rehabilitation Center, 3 floors below the Program in Occupational Therapy's offices and two blocks from the CSC and CCIR.

Enrollment, interventions, and data collection will be carried out at the Hand Therapy and Surgery Suites at the UHealth Clinical and Surgery Center which possesses several designated hand therapy and orthopaedics assessment and treatment areas. The interventions and testing for this project will be carried out within this space.

Training: Research Assistants will complete HIPAA and CITI training.

Equipment: The program in occupational therapy and orthopedics therapy center will donate 2 calibrated Jamar™ Dynamometers for the quantification of maximum grip strength, 2 calibrated force gauges for torque-controlled circumferential edema measurements, and 2 Baseline™ 180 degree wrist goniometers for wrist and forearm range of motion measurements. Dr. McGee uses a Dell Latitude E6440 laptop with i5 processor, 500GB hard drive, and 8GB DDR3 RAM. Software includes MS Windows 7; MS Office 2007; and SAS 9.3 and SPSS ver.22 statistical software packages. Dr. McGee also possesses network access to a high capacity Cannon iR2535 black and white and color printer**.**

Recruitment: Successful recruitment appears feasible given the findings of a recent analysis of Fairview/UHealth dataset through use of the University of Minnesota CTSI's "i2b2 Cohort Discovery tool." The survey of our participant pool revealed that 4,858 persons (3363 women and 1495 men) who met the inclusion criteria for participation were seen in Fairview/UHealth Sports and Orthopaedic Clinics from January 1st, 2018 to March 11th, 2021.

26.0 References

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