Pulsed Electromagnetic Field (PEMF) Therapy in Thumb CMC Arthritis

Protocol Number: 64143

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Sponsor: Stanford University School of Medicine, Department of Orthopaedic Surgery

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation 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)

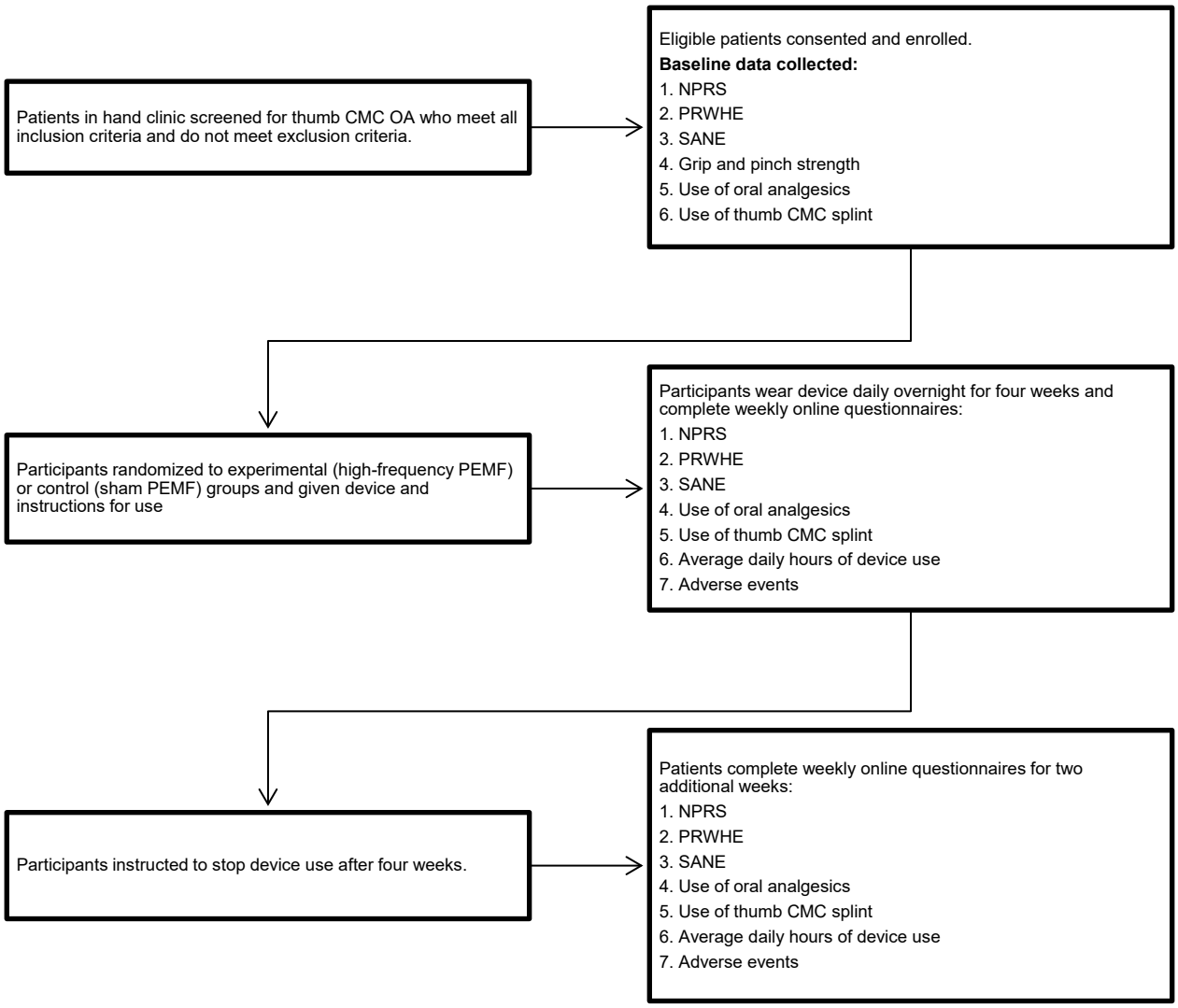
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the 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.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Pulsed Electromagnetic Field (PEMF) Therapy in Thumb CMC Arthritis
Study Description:	Thumb carpometacarpal (CMC) osteoarthritis (OA) is a common source of hand pain with limited non-operative treatment options. Pulsed electromagnetic field (PEMF) therapy has been recently shown in studies to be effective in providing sustained pain relief in knee osteoarthritis. This study aimed to assess the efficacy of PEMF therapy for treating thumb CMC OA pain.
Objectives:	To determine the effects of PEMF therapy on thumb CMC joint pain
Endpoints:	Numeric Pain Rating Scale (NPRS) at 4 weeks
Study Population:	60 participants over age 18 with diagnosis of thumb CMC OA
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Single outpatient orthopedic hand clinic
Description of Study Intervention:	PEMF device for 8 hours nightly for 4 weeks
Study Duration:	36 months
Participant Duration:	6 weeks

1.2 SCHEMA


Patients in hand clinic screened for thumb CMC OA who meet all inclusion criteria and do not meet exclusion criteria.
Eligible patients consented and enrolled.
Baseline data collected:
1. NPRS
2. PRWHE
3. SANE
4. Grip and pinch strength
5. Use of oral analgesics
6. Use of thumb CMC splint
Participants randomized to experimental (high-frequency PEMF) or control (sham PEMF) groups and given device and instructions for use
Participants wear device daily overnight for four weeks and complete weekly online questionnaires:
1. NPRS
2. PRWHE
3. SANE
4. Use of oral analgesics
5. Use of thumb CMC splint
6. Average daily hours of device use
7. Adverse events
Participants instructed to stop device use after four weeks.
Patients complete weekly online questionnaires for two additional weeks:
1. NPRS
2. PRWHE
3. SANE
4. Use of oral analgesics
5. Use of thumb CMC splint
6. Average daily hours of device use
7. Adverse events

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -7 to -1	Enrollment/Baseline Visit 1, Day 0	Questionnaire #1 Day 7	Questionnaire #2 Day 14	Questionnaire #3 Day 21	Questionnaire #4 Day 28	Questionnaire #5 Day 35	Questionnaire #6 End of Study, Day 42
Informed consent	X							
Demographics	X							
Medical history	X							
Randomization	X							
Physical Examination		X						
Administer study intervention		X	X	X	X	X		
Patient-reported outcome measures		X	X	X	X	X	X	X
Adverse event reporting			X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Recalcitrant pain from thumb carpometacarpal (CMC) osteoarthritis (OA) contributes significantly to failed non-operative management in 15-30% of patients.[1,2] High-frequency pulsed electromagnetic field (PEMF) therapy is a novel treatment option that has recently demonstrated pain reduction and improved function in knee OA after four weeks of daily, home-based, overnight treatment sessions.[3] This therapy is a safe, pain-free, non-pharmacologic solution that has the potential to solve the limitations of current conservative standard of care with CMC OA. No studies exist to date that have assessed whether PEMF therapy is effective for CMC OA, whether pain reduction effect persists beyond the treatment period, or if disease-modifying physiological changes occur as a result from treatment. To address this problem, we aim to provide high-quality evidence for the use of high-frequency PEMF therapy to treat CMC OA.

2.2 BACKGROUND

Thumb carpometacarpal (CMC) joint osteoarthritis (OA) is a common location of OA in the hand, with an estimated prevalence of 23.5% in patients over the age of 60.[4] According to 2019 American College of Rheumatology (ACR) guidelines for management of OA, current recommendations for standard of care for CMC OA include splinting, hand therapy exercises, oral non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroid injections. However, 15-30% of patients proceed to operative management within 1-2 years after starting non-operative management, most commonly due to continued pain rather than functional limitations.[1,2]

The current standard of non-operative care has substantial limitations. Splinting, although effective, limits daily hand function,[5] and has a known low therapy adherence. Hand therapy reimbursement in the United States is limited and home exercise adherence is poor. Long term use of oral NSAIDs can lead

to kidney and gastrointestinal damage. Corticosteroid injections provide only temporary relief in a subset of patients, and repeat injections may lead to greater cartilage volume loss.[6] In addition, there are limited options for patients who have pain recalcitrant to these non-operative management options.

High-frequency pulsed electromagnetic field (PEMF) therapy is an innovative treatment option that has the potential to address some of the limitations of current standard of care. Currently no studies exist that have assessed whether PEMF therapy is effective for CMC OA. PEMF wearable devices emit non-painful low-power pulsed shortwaves and have no reported adverse effects. Pain reduction with this therapy has been shown to persist beyond the treatment period for knee OA.[3] While pulsed shortwave therapy was previously performed in an outpatient setting, these devices allow for home use with more frequent treatment sessions. These proposed benefits will help address barriers to patient adherence with current treatment options for CMC OA and provide another nonpharmacologic modality for patients with recalcitrant CMC OA pain.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are no adverse effects reported in previously published studies.[3,7,8]

2.3.2 KNOWN POTENTIAL BENEFITS

Prior studies on PEMF therapy have largely focused on its application to knee OA. In a recent meta-analysis by Wu et al.,[9] there was significant pain reduction for patients with knee OA, though studies varied in the frequency and intensity of the pulsed electromagnetic field, as well as the frequency and duration of therapy. To date, there is only one pilot study on the effects of PEMF therapy on hand OA in 50 patients. Kanat et al. demonstrated that low-frequency (25 Hz) PEMF therapy when applied for 20 minutes per day for 10 days, combined with active range of motion and strengthening exercises, improved pain and Short Form-36 social function and general health outcome measures when compared to sham PEMF therapy with the same exercises.[8]

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

With no known potential adverse effects and a known potential benefit of pain reduction, more studies are needed that demonstrate efficacy of PEMF therapy in setting of an overall promising safety profile.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the effects of PEMF therapy on thumb CMC joint pain	Outcome measures at 4 weeks: • Numeric Pain Rating Scale (NPRS) • Patient Rated Wrist/Hand Evaluation (PRWHE) • Single Assessment Numeric Evaluation (SANE)	Previous studies have shown pain reduction after 4 weeks of PEMF therapy.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
Determine if sustained effects persist beyond the treatment period	Outcome measures at 6 weeks: • Numeric Pain Rating Scale (NPRS) • Patient Rated Wrist/Hand Evaluation (PRWHE) • Single Assessment Numeric Evaluation (SANE)	Several studies have reported pain reduction sustained for weeks to months past treatment cessation.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a single-center, double-blind, randomized, controlled trial. Participants will be randomly assigned to either the experimental group or control group in a block size of 10 with an allocation ratio of 1:1.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study design is based on the methodology of a published randomized controlled trial on PEMF therapy for knee OA.[3]

4.3 JUSTIFICATION FOR DOSE

The dosing is based on the methodology of a published randomized controlled trial on PEMF therapy for knee OA.[3]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form

2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Over the age of 18
4. Clinically and/or radiographically diagnosed thumb CMC OA
5. Reported average pain intensity during activities of daily living between “3” and “8” on the Numeric Pain Rating Scale (NPRS)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy
2. Inability to consent
3. Current infection of the upper extremity
4. Prior fracture, severe hand injury, tenosynovitis, complex regional pain syndrome and/or Dupuytren’s disease affecting the thumb
5. History of surgical or procedural intervention for CMC OA at the site of interest
6. Hand, wrist, heart, or brain implants

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN 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).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Members of the study team will review the clinic schedule through EPIC each week to identify eligible patients and recruitment will be through phone calls of patients with diagnosis of thumb CMC OA or at the time of their clinic visit. A member of the care team will introduce the study to the patient. If the patient is interested in learning more and/or participating, a member of the research team will provide study-related information and obtain informed consent via written or electronic consent. Recruitment flyers will be posted at the Stanford Orthopaedic Clinic with study information. Patients who may qualify will have the option to reach out to the study coordinator if they are interested in participating. A member of the research team will provide study-related information and obtain informed consent via written or electronic consent If a patient consents to participate, the patient will be randomized into either the study group or the control group. Recruitment will involve 60 participants total.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The experimental group will receive a PEMF device that has received 510(k) clearance by the United States Food and Drug Administration (FDA) (ActiPatch, BioElectronics Corporation, Frederick, MD), modified by the device manufacturer to have a shorter antenna size of 4.5 cm diameter while otherwise maintaining all other device parameters within its FDA clearance. The device emits pulsed electromagnetic waves in shortwave frequencies (27.12 MHz) at a rate of 1000 Hz with average spatial power density of 4.4 μWatts/cm^2.

The control group will receive a sham device that is identical in appearance but does not emit any electromagnetic wave.

6.1.2 DOSING AND ADMINISTRATION

Both groups will be instructed to wear the device nightly for four weeks by fixing the loop of the device on their thenar eminence with medical-grade tape and place the center of the loop around the area of greatest pain.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The PEMF and sham devices will be provided to the investigator by the device manufacturer (BioElectronics Corporation, Frederick, MD), consecutively numbered by the device manufacturer based on a randomization schedule with a block size of 10 and allocation ratio of 1:1.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The PEMF and sham devices appear identical except for a label with the device number.

6.2.3 PRODUCT STORAGE AND STABILITY

Devices will be stored in a secure location.

6.2.4 PREPARATION

Devices will be tested prior to being provided to the study participant that it can be powered on/off.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To ensure the research study personnel and participants were blinded to the group allocation prior to study enrollment, the PEMF and sham devices will be provided, tested by, and consecutively numbered by the device manufacturer.

6.4 STUDY INTERVENTION COMPLIANCE

Participants will be provided a daily log to record number of hours of device use and will report this as an average in weekly questionnaires.

6.5 CONCOMITANT THERAPY

Participants will report average over-the-counter medication and thumb CMC splint use in weekly questionnaires.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of device use does not mean discontinuation from the study, and remaining study procedures should 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).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

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

- Pregnancy
- 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
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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 complete subsequent weekly questionnaires 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 counsel the participant on the importance of completing the assigned questionnaires weekly 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.
- 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 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Efficacy will be assessed with patient-reported outcome measures, including the Numeric Pain Rating Scale (NPRS), Patient Rated Wrist/Hand Evaluation (PRWHE), and Single Assessment Numeric Evaluation (SANE), on a weekly basis.

8.2 SAFETY AND OTHER ASSESSMENTS

Participants will additionally report any adverse events, oral analgesic use, or thumb CMC splint use on a weekly basis.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – 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".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 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 weekly questionnaires. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to 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.

The research coordinator will record all reportable events with start dates occurring any time after informed consent. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events will reported to the Principal Investigator who is responsible for data and safety monitoring.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention

caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.]

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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.

[This definition could include an unanticipated adverse device effect, 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 was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Numeric Pain Rating Scale (NPRS) at 4 weeks

- Secondary Efficacy Endpoint(s):

Numeric Pain Rating Scale (NPRS) at 6 weeks
Patient Rated Wrist/Hand Evaluation (PRWHE) at 4 and 6 weeks
Single Assessment Numeric Evaluation (SANE) at 4 and 6 weeks

9.2 SAMPLE SIZE DETERMINATION

A sample size of 54 participants (27 in each group, allowing for 10% withdrawals) was calculated to detect an estimated effect size of 1 in NPRS with a power of 0.80 and alpha of 0.05.

9.3 POPULATIONS FOR ANALYSES

The analysis dataset will be an intention-to-treat (ITT) analysis dataset including all randomized participants.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Baseline characteristics and all primary and secondary outcome measures will be analyzed using chi-square and Fisher's exact tests for categorical variables, Mann-Whitney U-tests for between-group comparisons of ordinal or continuous variables, and the Wilcoxon signed rank test for within-group comparisons of ordinal or continuous variables, using a 2-sided level of significance of 0.05. A minimally clinical importance difference (MCID) of 2 is established for changes in the NPRS.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

NPRS at 4 weeks will be analyzed with Mann-Whitney U-test for between-group comparison. Participants with missing data or lost to follow-up will be excluded from analysis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

NPRS at 6 weeks and PRWHE and SANE at 4 and 6 weeks will be analyzed with Mann-Whitney U-test for between-group comparison. Participants with missing data or lost to follow-up will be excluded from analysis.

9.4.4 SAFETY ANALYSES

Percentage of each adverse event reported will be calculated.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic information such as age and sex will be collected and analyzed using chi-square and Fisher's exact tests for categorical variables and Mann-Whitney U-tests for between-group comparisons of ordinal or continuous variables. Baseline NPRS, PRWHE, and SANE will be analyzed with Mann-Whitney U-tests.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES
Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA
Individual participant data will not be reported.

9.4.9 EXPLORATORY ANALYSES
Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 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 study participants and investigators. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the

termination or suspension. 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 sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in Stanford Medicine Box. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in Stanford Medicine Box.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in the Stanford Medicine Box. After the study is completed, the de-identified, archived data will be transmitted to and stored in the Stanford Medicine Box.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Raymond Chou, MD
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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined.

10.1.7 CLINICAL MONITORING

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).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) 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.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

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.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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6. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. *JAMA*. 2017;317(19):1967. doi:10.1001/jama.2017.5283

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