ENDOSCOPIC TRIGGER FINGER RELEASE

Protocol Number: 00054088

National Clinical Trial (NCT) Identified Number: NCT03883477

Principal Investigator: Dr. David Kulber

Sponsor: Cedars-Sinai Medical Center

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. 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 of the Study: Endoscopic Trigger Finger Release

Number of Subjects: 24

Objective: The objective of this study is to compare recovery, scar and patient satisfaction after retrograde endoscopic trigger finger release versus standard open surgical treatment.

Methodology: Consecutive patients presenting with trigger finger interested in surgical release of the A1 pulley will be prospectively treated with endoscopic versus open surgical release of the A1 pulley. Study measures will include scar assessment based on the Patient and Observer Scar Assessment Scale (POSAS) administered at 1 week, 1 month, and 6 months post-operatively, overall satisfaction (scale of 1 to 10), days before return to work, duration of post-operative occupational therapy, pain medication use, operative time, and complication and recurrence rates..

Visit Schedule: Pre-operative visit, post-operative visits at 1 week, 1 month, and 6 months post-operatively.

Diagnosis and Main Inclusion Criteria for Inclusion/Exclusion: Subjects with diagnosis of trigger finger.

Inclusion Criteria:

- Male or Female >18 years of age
- Trigger finger, recommended for surgical release
- Be in good health other than the trigger finger
- Have realistic expectations of surgical results
- Understand and be willing to follow all aspects of the study protocol and have signed and dated the IRB-approved Informed Consent Form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed

Exclusion Criteria: To be eligible for enrollment, the subject must not:

- Have collagen-vascular, connective tissue, or bleeding disorders
- Be a smoker or have smoked in last 2 months
- Have any disease, including uncontrolled diabetes, which is clinically known to impact wound healing ability
- Have regional sympathetic dystrophy
- Be pregnant, lactating or expecting to be within the next 24 months
- Currently have an alcohol/substance abuse problem or have had a relapse within one year to screening visit
- Have an abscess or infection at the time of surgery
- Have a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

Duration of the Study: Subjects will be followed for 6 months post release of the A1 pulley.

Criteria for Evaluation: Primary outcome measures include scarring based on Patient and Observer Scar Assessment Scale (POSAS) scores administered 1 week, 1 month, and 6 months post-operatively between patients treated with endoscopic versus open surgical release of the A1 pulley. Secondary outcome measures include overall satisfaction (scale of 1 to 10), days to return to work, duration of post-operative occupational therapy, pain medication use as well as complication and recurrence rates between the two treatment groups.

Statistical Methods:

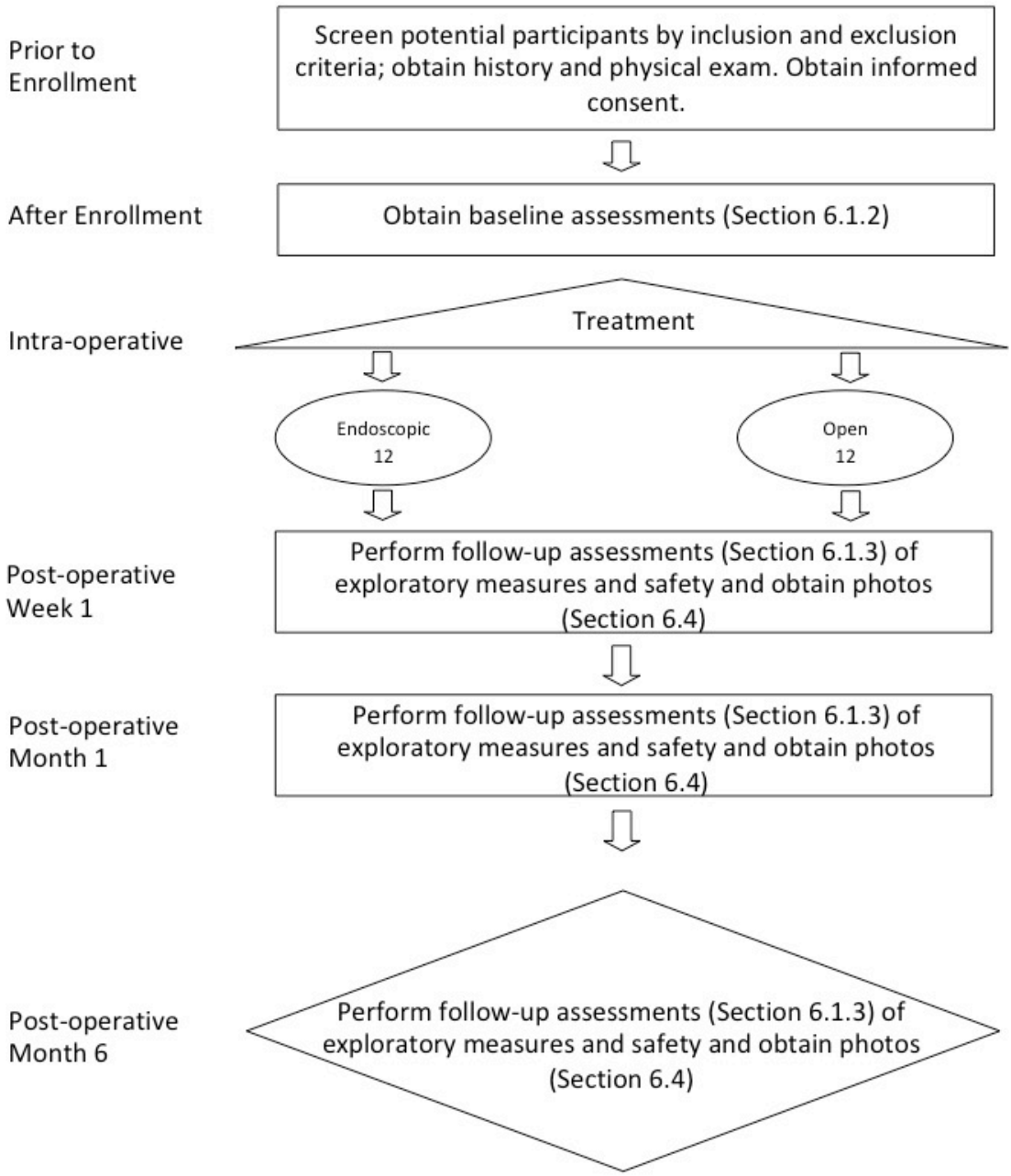
Sample size calculation: Total POSAS scores range from 12 to 120. Though the POSAS has not been used to assess scarring after trigger finger release, the tool is validated with high internal consistency and reliability.[1]

A total of 24 patients (12 in the endoscopic arm and 12 in the standard open arm) will provide sufficient information to produce descriptive summaries of study outcome endpoints and to perform exploratory analyses.

The purpose of this study is to compare scar and recovery after retrograde endoscopic trigger finger release versus standard open surgical treatment. We hypothesize that patients treated with the retrograde endoscopic approach will have improved scarring compared to patients treated with the open approach, based on POSAS scores. We also hypothesize that the patients in the endoscopic treatment arm will have a faster recovery (return to work sooner with fewer days of occupational therapy), have higher overall satisfaction (scale 1 to 10) and use less pain medication. We anticipate that the two treatments will not differ significantly in complication or recurrence rate.

Schedule of Visits and Procedures: As depicted in Section 1.2.

1.2 SCHEMA


Prior to Enrollment
Screen potential participants by inclusion and exclusion criteria; obtain history and physical exam. Obtain informed consent.
After Enrollment
Obtain baseline assessments (Section 6.1.2)
Intra-operative
Treatment
Endoscopic 12
Open 12
Post-operative Week 1
Perform follow-up assessments (Section 6.1.3) of exploratory measures and safety and obtain photos (Section 6.4)
Post-operative Month 1
Perform follow-up assessments (Section 6.1.3) of exploratory measures and safety and obtain photos (Section 6.4)
Post-operative Month 6
Perform follow-up assessments (Section 6.1.3) of exploratory measures and safety and obtain photos (Section 6.4)

2 INTRODUCTION

2.1 ABBREVIATIONS AND TERMS:

OT Occupational therapy
POSAS Patient and Observer Scar Assessment Scale

2.2 BACKGROUND AND CLINICAL RATIONALE FOR DATA REVIEW

Trigger finger is an entrapment tendinopathy in which the flexor tendon catches within a thickened or narrowed A1 pulley with flexion and extension of the digit.[2,3] Patients present with complaints of pain, snapping, or locking of the finger at the MCP joint[4]. With an incidence between 2 and 3% in the general population, trigger finger is one of the most common causes of disability and pain in the hand.[3,5,6]

Initial treatment is conservative and nonsurgical management includes: non-steroidal anti-inflammatory drugs, activity modification, splinting, and corticosteroid injections.[7,8] Though some relief may be noted initially, the reported recurrence rate after corticosteroid treatment is up to 48%.[9] Definitive treatment often requires release of the A1 pulley through an open, percutaneous, or endoscopic surgical technique. In the open approach, an incision is made in the palm - most commonly at the distal palmar crease - which causes great discomfort to patients.[10,11] The endoscopic approach reported by Pegoli and colleagues requires two incisions: one at the proximal interphalangeal crease and one in the mid palm.[11] The percutaneous approach avoids use of these painful palmar incisions, but concerns exist over the safety of this blind technique.[12] As such, techniques currently available for the surgical treatment of trigger finger fall short in one of two ways: 1) they require an incision of the palm, which can be painful and unsightly to patients or 2) the release is performed blindly.

3 STUDY OBJECTIVES

The objective of this study is to compare scar and recovery after retrograde endoscopic trigger finger release versus standard open surgical treatment.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Consecutive patients (until 12 patients are enrolled in each treatment arm) presenting with trigger finger interested in surgical release of the A1 pulley will be offered participation in the study. Additional subjects may be enrolled, as needed to achieve 12 patients in each treatment arm, in the event of patient death or withdrawal from the study. Once enrolled, they will be treated with one of two techniques: endoscopic versus open surgical release. Study measures will include scar assessment based on the Patient and Observer Scar Assessment Scale (POSAS) administered at 1 week, 1 month, and 6 months post-operatively, overall satisfaction (scale of 1 to 10), days before return to work, duration of post-operative occupational therapy, pain medication use, operative time, and complication and recurrence rates.

4.2 STUDY STRUCTURE

This is a prospective clinical trial, as the participants will be treated, after enrollment, with endoscopic versus open release.

4.3 DURATION

Subjects will be followed for 6 months post-operatively. POSAS scores will be obtained at 1 week, 1 month, and 6 months post-operatively. These scores along with measures of pain medication use, days before return to work, and duration of OT will be obtained from each subject during their post-operative visit. Complication and recurrence rates will also be noted at each post-operative visit. Study visits will coincide with standard clinical course visits.

4.4 STUDY QUESTIONNAIRES/ASSESSMENT

The patients of Dr. David Kulber, Dr. Eugene Tsai, Dr. Ryan DellaMaggiora, and Dr. Stuart Kuschner eligible to participate in the study will proceed with baseline assessments once study consents have been signed and the patient has been enrolled in the study.

4.5 VISITS & PROCEDURES

Patients will undergo endoscopic or open treatment. Follow-up assessments will be performed at 1 week, 1 month, and 6 months post-operatively.

5 STUDY POPULATION CHARACTERISTICS

5.1 NUMBER OF SUBJECTS

Consecutive patients presenting with trigger finger interested in surgical release of the A1 pulley will undergo endoscopic versus open surgical release of the A1 pulley. A total of 12 subjects are to be enrolled for each treatment arm. Additional subjects may be enrolled, as needed to achieve 12 patients in each treatment arm, in the event of patient death or withdrawal from the study.

5.2 STUDY POPULATION CHARACTERISTICS

Subjects who meet the inclusion/exclusion criteria detailed below will be enrolled into the study.

5.3 INCLUSION CRITERIA

- Male or Female >18 years of age
- Trigger finger, recommended for surgical release
- Be in good health other than the trigger finger
- Have realistic expectations of surgical results
- Be willing to undergo treatment based on the treatment arm to which they are randomized
- Understand and be willing to follow all aspects of the study protocol and have signed and dated the IRB-approved Informed Consent Form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed

5.4 EXCLUSION CRITERIA PROCEDURES

- Have collagen-vascular, connective tissue, or bleeding disorders
- Be a smoker or have smoked in last 2 months
- Have any disease, including uncontrolled diabetes, which is clinically known to impact wound healing ability
- Have regional sympathetic dystrophy
- Be pregnant, lactating or expecting to be within the next 24 months
- Currently have an alcohol/substance abuse problem or have had a relapse within one year to screening visit
- Have an abscess or infection at the time of surgery
- Have a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

6 VISITS & PROCEDURES

6.1 PRE-SCREENING & VISITS

The physician's appointment calendar will be pre-screened of potential study candidates who would be eligible for surgical treatment. No study related data will be collected/administered until patient has signed consent and HIPAA.

6.1.1 PROCEDURES FOR FINAL STUDY ENTRY

A subject is considered "enrolled" when he/she has signed the IRB-approved consent form and HIPAA authorization in the presence of the Investigator, who will then collect and record the subject's demographic information and medical history.

6.1.2 PRE-OPERATIVE VISITS

The subject will be screened in accordance with the inclusion/exclusion criteria, medical history will be collected, a physical exam will be performed and medical photography will be obtained, as is the standard of care.

6.1.3 FOLLOW-UP VISITS

Subjects will be required to attend post-operative visits at 1 week, 1 month, and 6 months post-operatively, as is the standard of care. Review of medical history and physical examination will be conducted at all post-operative visits. At 1 week, 1 month, and 6 months post-operatively, pain medication use, days before return to work, duration of occupational therapy, as well as POSAS scores will be obtained and photos will be taken.

6.2 STANDARD AND RESEARCH PROCEDURES

All evaluations, procedures performed, and information obtained during pre-operative and post-operative visits will be within the standard of care with the exception of the POSAS questionnaire. The POSAS questionnaire contains a Patient Scale to be completed by the patient and an Observer Scale to be completed by the patient's surgeon-of-record. The Patient Scale is comprised of 6 questions regarding pain, itching, color, stiffness, thickness, and irregularity of their scar scored

numerically from 1 to 10. There is a 7th question, also on a scale of 1 to 10, that asks the patient for their overall opinion of the scar.

The POSAS questionnaire will be completed by patients at 1 week, 1 month, and 6 months post-operatively. In an effort to minimize inconvenience and avoid undue stress to the subjects, they will be given unlimited time to complete the questionnaire and will be allowed to skip questions as desired.

6.3 SURGICAL PROCEDURES

For subjects in open surgical treatment arm: A transverse incision is made at the distal palmar crease overlying the affected digit. Blunt dissection proceeds down to the level of the A1 pulley and the pulley is incised under direct visualization. The surgical site will then be irrigated and closed in usual fashion.

For subjects endoscopic treatment arm: The proximal interphalangeal crease is identified of the affected finger and incised transversely. Blunt dissection is then performed down to the level of the pulley. With the finger held in extension, the EndoSleeve is inserted from distal to proximal at a 15 degree angle. The A1 pulley is visualized via the endoscope. The tip of the EndoSleeve is then situated on the distal edge of the A1 pulley. As the tip is advanced proximally, the blade is seen incising the A1 pulley. The instrument is advanced to a point just before the distal palmar crease. The surrounding tissue is then inspected and the instrument removed. The surgical site is then irrigated and closed in usual fashion.

6.4 MEDICAL IMAGING

Photographs of the affected hand will be taken per medical photographic standards pre-operatively, on the day of surgery, and 1 week, 1 month, and 6 months post-op as is the standard of care.

A copy of any medical imaging results (e.g., hand radiology) collected during the study duration will be included in the study file. No radiographic imaging is required for the study.

6.5 INSTRUCTIONS FOR THE SUBJECTS

There are no special instructions for the subjects beyond those typically provided for hand surgery and in the informed consent. Subjects will be asked to complete the POSAS questionnaire at 1 week, 1 month, and 6 months post-operatively.

6.6 UNSCHEDULED VISITS

Each time the subject returns to the study site the Investigator will solicit and record information about any concurrent procedures or AEs as applicable though not anticipated.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 EARLY DISCONTINUATION OF SUBJECTS

Each subject reserves the right to withdraw from the study at any time without jeopardy to their future medical care. All follow-up assessments and procedures should be performed at the final study visit. For any subject who discontinues from the study, the date and reason for discontinuation will be recorded.

If a subject fails to return for one or more scheduled study visits, the Investigator will attempt to contact the subject to determine and document the reason the subject has failed to return and to encourage compliance with the study visit schedule.

A subject may be discontinued from the study for the following reasons:

- Subject did not undergo surgical treatment as it was deemed not warranted by the Investigator
- Since enrollment in the study, subject has had alternative treatment that would otherwise affect the study questionnaire/outcomes data
- Subject does not complete scheduled follow-up visits per protocol
- Subject has died

8 OUTCOME MEASURES AND SUMMARY OF METHODS OF DATA COLLECTION

8.1 OUTCOME MEASURES

8.1.1 PRIMARY OUTCOME MEASURE

Primary outcome measures include scarring based on Patient and Observer Scar Assessment Scale (POSAS) scores administered 1 week, 1 month, and 6 months post-operatively between patients treated with endoscopic versus open surgical release of the A1 pulley.

8.1.2 SECONDARY OUTCOME MEASURES

Secondary outcome measures include pain medication use, overall patient satisfaction (score 1 to 10), days to return to work, and duration of post-operative occupational therapy as well as complication and recurrence rates after endoscopic versus open surgical treatment. Complications will include injury to tendons, nerves, and digital vessels noted during or after surgical treatment, as well as surgical site dehiscence and surgical site infections requiring antibiotics. Recurrence will be defined as triggering, confirmed on physical exam by treating physician, at any time point post-operatively.

8.1.3 EXPLORATORY MEASURES

- Operative time

8.2 SAFETY MEASURES

The incidence and severity of AEs related to the study will be captured. Investigators will inquire about the occurrence of any AEs at all study visits and unscheduled visits. Subjects will also be asked to self- report AEs throughout the duration of the study. Adverse events will be recorded.

8.3 SUMMARY OF METHODS OF DATA COLLECTION

Paper documents will be used to collect standardized assessments for POSAS scores. Study-specific information, such as Investigator reviews and assessments will be recorded directly in the subject's medical record.

Pain medication use, days before return to work, duration of OT, complications, and recurrences will be recorded by the Investigator in the subjects' medical record.

Operative time will be obtained from the operative record within the patient's electronic medical chart, as recorded by operative staff.

9 STATISTICAL PROCEDURES

Every attempt will be made to collect complete data and limit the occurrence of missing data. Due to the descriptive nature of all analyses, no imputation of missing data will be performed. Descriptive summaries will be based on all observations available within each of the relevant analysis populations.

Descriptive statistics will be presented for key outcome measures.

9.1 POPULATIONS FOR ANALYSES

All subjects will be included in the full analysis population. The per protocol population is defined as subjects who have not had any major protocol deviations throughout the study (Section 9.8) and will be analyzed as the primary study group. Other subgroups may be analyzed as detailed in the subgroup analyses section. Subjects that have been discontinued will be excluded from data analysis.

9.2 COLLECTION AND DERIVATION OF PRIMARY AND SECONDARY OUTCOME MEASURES

All exploratory variables will be analyzed as reported, without further derivation, except for the calculation of change from baseline, or change from prior time-points.

9.2.1 PRIMARY OUTCOME MEASURES

Primary outcome measures include scarring based on Patient and Observer Scar Assessment Scale (POSAS) scores administered 1 week, 1 month, and 6 months post-operatively between patients treated with endoscopic versus open surgical release of the A1 pulley.

9.2.2 SECONDARY OUTCOME MEASURES

Secondary outcome measures include pain medication use, overall patient satisfaction (score 1 to 10), days to return to work, and duration of post-operative occupational therapy as well as complication and recurrence rates after endoscopic versus open surgical treatment. Complications will include injury to tendons, nerves, and digital vessels noted during or after surgical treatment, as well as surgical site dehiscence and surgical site infections requiring antibiotics. Recurrence will be defined as triggering, confirmed on physical exam by treating physician, at any time point post-operatively.

9.2.3 EXPLORATORY MEASURES

Operative time will be obtained from the operative record within the patient's electronic medical chart, as recorded by operative staff.

9.3 HYPOTHESIS AND METHODS OF ANALYSIS

We hypothesize that patients treated with the retrograde endoscopic approach will have improved scarring compared to patients treated with the open approach, based on POSAS scores obtained at 1 week, 1 month, and 6 months post-operatively. We also hypothesize that the patients in the endoscopic treatment arm will have a faster recovery (return to work sooner with fewer days of occupational therapy), have higher overall satisfaction (scale 1 to 10) and use less pain medication. We anticipate that the two treatments will not differ significantly in complication or recurrence rate.

9.3.1 PRIMARY OUTCOME MEASURE ANALYSIS

Primary outcome measures of POSAS scores at 1 week, 1 month, and 6months post-operatively will be analyzed using descriptive statistics, including n, mean, standard deviation, median, minimum, maximum, and skewness.

9.3.2 SECONDARY OUTCOME MEASURE ANALYSIS

Secondary outcome measures of pain medication use, overall satisfaction (scale 1 to 10), days to return to work, days of occupational therapy, complication rate, and recurrence rate will be analyzed using descriptive statistics, including n, mean, standard deviation, median, minimum, maximum, and skewness.

9.3.3 EXPLORATORY MEASURES ANALYSIS

All exploratory variables will be summarized with descriptive statistics appropriate to the scale of measurement for each variable.

9.3.4 SAFETY ANALYSIS

Safety analyses will include the incidence and severity of adverse events observed over the study assessment period. These will be tabulated and presented overall and by relatedness, severity, and preferred term.

9.4 SUBGROUP ANALYSIS

Subgroup analyses will be performed to explore their relationship to key study outcomes.

9.5 EXPLORATORY ANALYSES

POSAS scores at 1 week, 1 month, and 6 months post-operatively will be analyzed between patients treated with endoscopic versus open release using 2-sample t-tests. Differences in pain medication use, days before return to work, duration of OT, operative time, overall satisfaction, complication and recurrence rates between patients treated with endoscopic versus open surgical release of the A1 pulley will be tested for significance using 2-sample t-tests. Additional analyses of possible relationships between outcomes may also be performed using appropriate inferential tests.

9.6 SAMPLE SIZE CALCULATION

Total POSAS scores range from 12 to 120. Though the POSAS has not been used to assess scarring after trigger finger release, the tool is validated with high internal consistency and reliability.[1]

The trial will be powered to detect a difference in POSAS score of 10, deemed to be clinically significant by the investigators. The POSAS standard deviations in studies previously published on carpal tunnel release and carotid endarterectomies ranges from 1.0 to 11.0.[13,14] To detect a mean difference in POSAS score of 10 points (SD = 8) with a two-sided significance level of 5% and power of 80% with equal allocation to two arms would require 12 patients in each arm of the trial. Additional subjects may be enrolled, as needed to achieve 12 patients in each treatment arm, in the event of patient death or withdrawal from the study.

9.7 INTERIM ANALYSES

Not applicable.

9.8 PROTOCOL DEVIATIONS

Protocol deviations may include:

- Deviations from the protocol, contrary to protocol specifications (i.e., deviations from the protocol, eligibility, visit windows, etc.).
- Deviations affecting the endpoint outcome not previously specified in the protocol (i.e., deviation that had not been previously considered in the protocol or eligibility criteria, however having a clear impact on the primary outcome measure)

All protocol deviations will be reviewed and categorized as major (i.e., those that affect measurement or interpretation of the primary endpoint) or minor (those not affecting the primary endpoint).

10 STUDY ADMINISTRATION PROCEDURES

10.1 SUBJECT ENTRY PROCEDURES

10.1.1 OVERVIEW OF ENTRY PROCEDURES

Prospective subjects as defined by the criteria in Section 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into this study.

10.1.2 INFORMED CONSENT AND SUBJECT PRIVACY

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. Prior to any study-related procedures or change in treatment, subjects wishing to participate must give their written informed consent (IC). The subject must also give Authorization for Use and Release of Health and Research Study Information (HIPAA) and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related assessments/questionnaires. Subjects will be consented to provide a copy of all medical imaging (e.g. radiology) collected as standard-of-care or research during the study duration for inclusion in the study file. The Investigator will conduct the IC discussion and will document in the subject's medical records the process for acquiring IC and the subject's agreement or refusal to notify her primary care physician about the study. The subject should personally sign and date the IC form. The Investigator will retain the original copy of the signed IC form, and the subject will also receive a copy. Upon signing the IC form, the subject will receive a subject number that will be used on all documentation for the subject throughout the study. Subject numbers should be assigned in ascending order, and numbers should not be omitted or reused. The subject number is a unique identification for each subject.

10.2 COMPLIANCE WITH PROTOCOL

All eligible subjects to be treated by Dr. David Kulber, Dr. Eugene Tsai, Dr. Ryan DellaMaggiora, and Dr. Stuart Kuschner will be counseled on the techniques available for surgical release of the A1 pulley. Enrolled patients in both treatment

arms will be asked to complete POSAS questionnaires as indicated within the schedule outlined in section 6.

The Investigator is responsible for the overall conduct of the study and compliance with the protocol including subject recruitment, IC, screening evaluations, eligibility, assessment/procedure, study evaluations, and any study-related medical care. The Investigator may choose to delegate some of these tasks to suitably trained research staff personnel, but the Investigator is ultimately responsible for these activities.

10.3 STUDY TERMINATION

If conditions arise during the study that indicate that the study should be terminated, the Investigator, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- Failure of the Investigator to comply with pertinent national or state regulations, IRB imposed conditions, or protocol requirements
- Submission of knowingly false information from the Investigator to IRB, or any regulatory agency

11 ADVERSE EVENTS

Throughout the course of the study, AEs will be monitored and reported on an AE CRF, including seriousness, severity, relationship to device, and action taken. If AEs occur, the first concern will be the safety of the study participants. The Investigator and the research staff will monitor each subject closely, and record any complications that may arise, though not anticipated. Study clinicians will use his/her medical judgment to do whatever is necessary to help treat the problem. Potential risks and/or side effects include:

Foreseeable Risk

- Discomfort
- Pain
- Redness
- Swelling
- Scarring
- Local or systemic infection
- Dehiscence and/or necrosis due to poor revascularization

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or temporal disease, whether or not related to the study assessment(s)/questionnaire(s).

Pre-existing disease or symptoms thereof prior to study enrollment are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition, or the condition worsens in intensity or frequency during the study. Normal post-operative sequelae will not be recorded as adverse events. Specifically, normal post-operative pain, swelling, tenderness, loss of skin sensation and ecchymosis within the first two weeks postoperative, requiring normal levels of medication will not be recorded; all abnormal intensity or duration will be recorded and considered an adverse event as well as following the two-week post-operative period.

Adverse events will be monitored throughout the study. At each post-baseline visit, the Investigator will begin querying for adverse events by asking each subject a general, nondirected question such as “Have you had any changes to your condition since your last visit?” Previous adverse events and changes in therapy/concomitant medications should be updated. Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented.

11.1.2 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2 PROCEDURES FOR REPORTING ADVERSE EVENTS

Adverse events should be reported to governing IRB per governing IRB reporting requirements.

11.3 REPORTING AN SAE

Any SAE occurring during the study period and for at least 30 days after the last study visit should be immediately reported (within 24 hours) and recorded. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy report, pathology report, operative report, terminal medical report, etc.).

12 ADMINISTRATIVE ISSUES

This protocol is to be conducted in accordance with the applicable Good Clinical Practice regulations and guidelines, e.g., the International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (GCP).

12.1 PROTECTION OF HUMAN SUBJECTS

12.1.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

12.1.2 COMPLIANCE WITH IRB REGULATIONS

This study is to be conducted in accordance with applicable IRB regulations. The Investigator must obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually.

12.1.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

12.2 SUBJECT CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., HIPAA).

12.3 DOCUMENTATION

12.3.1 SOURCE DOCUMENTS

Source documents may include a subject's original (or certified copy) medical records, hospital charts, clinic charts, the Investigator's subject study files, as well as the results of diagnostic tests.

The following information should be entered into the subject's medical record:

- Subject's name
- Subject's contact information
- Date that the subject entered the study and subject number
- The study title and/or the protocol number
- A statement that informed consent was obtained and the process for obtaining consent, including the date. A statement that HIPAA Authorization or other country and local subject privacy required documentation for this study has been obtained, including the date.
- Dates of all subject visits
- All concomitant procedures
- Subject standardized radiology as specified in the outcome metrics
- Occurrence, treatment for, and status of any adverse events
- Date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.
- Protocol deviations, as applicable

12.3.2 DOCUMENT COMPLETION

Source documents must meet the criteria to be acceptable in assessing the quality and integrity of the data during inspection or review of that data: attributable, legible, contemporaneous, original, accurate and available upon request. The Investigator is responsible for ensuring that data is properly recorded on each subject's record.

12.3.3 RETENTION OF DOCUMENTATION

All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of device, and copies of documentation should be maintained on file. Documents should be retained and available for audit by regulatory authorities until at least 2 years after the latest among the following scenarios: completion or termination of the study, the last approval of a marketing application, no pending or contemplated marketing applications, or formal discontinuation of clinical development of the device. These documents should be retained for a longer period, however, if mandated by the applicable regulatory requirements, by conditions imposed by the IRB.

13 REFERENCES

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