Trial of **U**ltrasound guided carpal tunnel release versus **T**raditional **O**pen **R**elease
(TUTOR)

CLINICAL STUDY PROTOCOL:

No. 90079-TP Revision 05
Dated November 18, 2022

SPONSOR:

Sonex Health, Inc.
950 Blue Gentian Road, Suite 200
Eagan, MN 55121

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

Trial of **U**ltrasound guided carpal tunnel release versus **T**raditional **O**pen **R**elease
(TUTOR)

Protocol Signature Page

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under me. I will discuss the material with them and ensure they are fully informed regarding the conduct of the study according to this protocol, applicable regulatory requirements, and IRB requirements.

I agree to and understand the material presented in this protocol and must not publicly disclose in any manner the design, results, or conclusions of this investigation without prior written consent of Sonex Health.

_____
Clinical Site Name

_____ _____
Site Principal Investigator Signature — Date

_____
Site Principal Investigator Printed Name

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1. PROTOCOL SYNOPSIS

Title	**T**rial of **U**ltrasound guided carpal tunnel release versus **T**raditional **O**pen **R**elease (TUTOR)
Purpose	To compare the safety and effectiveness of carpal tunnel release with ultrasound guidance (CTR-US) vs. mini-open carpal tunnel release (mOCTR) in patients with symptomatic carpal tunnel syndrome (CTS)
Study Design	Multicenter randomized controlled trial of subjects with symptomatic CTS who will be randomized in 2:1 fashion to treatment with CTR-US or mOCTR
Enrollment	120 subjects will be enrolled in the study and randomized (2:1) to CTR-US (n≈80) or mOCTR (n≈40)
Visit Schedule	Post procedure remote subject-reported outcomes visits: 1-14 days; 1, 3, 6, and 12 months
Clinical Sites	Up to 12 investigational sites located within the United States
Inclusion Criteria	1. ≥18 years of age 2. Clinical diagnosis of unilateral or bilateral idiopathic CTS 3. CTS-6 score ≥12 in target hand 4. Absence of carpal tunnel symptoms in the contralateral hand that interfere with normal daily activities or work at the time of consent and are not anticipated to interfere with return to activities or return to work within at least 3 months post-operatively 5. Median nerve cross-sectional area ≥10 mm^2 in the proximal carpal tunnel region of the target hand measured by diagnostic ultrasound 6. Prior failure of one or more nonsurgical treatment options for the target hand (e.g., physical activity modification, bracing, splinting, corticosteroid injection) 7. Subject agrees to complete follow-up questionnaires over a 12-month period 8. Subject has a valid mobile phone number and email address to receive and answer follow-up questionnaires
Exclusion Criteria	1. Prior surgery on the target wrist or hand with the exception of trigger finger that has clinically recovered 2. History of prior surgical CTR procedure in the target hand 3. History of prior surgical CTR in the contralateral hand within 3 months of enrollment or with persistent symptoms that interfere with normal daily activities or work at the time of consent 4. Corticosteroid injection in the target wrist or hand within 6 weeks of study procedure date 5. Presence of additional process in the target wrist or hand requiring additional intervention beyond carpal tunnel release (e.g. neurolysis, mass removal, tenosynovectomy) 6. Clinically significant degenerative arthritis of the upper limb (shoulder to hand) on the target side 7. Clinically significant inflammatory disease (including tenosynovitis) of the upper limb (shoulder to hand) on the target side

	8. Clinically significant trauma or deformity of the upper limb (shoulder to hand) on the target side 9. Clinically significant vascular disease (including Raynaud's phenomenon) of the upper limb (shoulder to hand) on the target side 10. Clinically significant neurological disorder (including complex regional pain syndrome) of the upper limb (shoulder to hand) on the target side 11. Planned surgical or interventional procedure on the contralateral wrist or hand 12. Systemic inflammatory disease (e.g., rheumatoid arthritis, lupus) 13. Amyloidosis 14. Chronic renal insufficiency requiring dialysis 15. Diabetes not controlled by a stable dose of medication over the past three months 16. Uncontrolled thyroid disease 17. Pregnant or planning pregnancy in the next 12 months 18. Workers' compensation subjects 19. Inability to provide a legally acceptable Informed Consent Form and/or comply with all follow-up requirements 20. Subject has other medical, social or psychological conditions that, in the opinion of the investigator, preclude them from receiving the pre-treatment, required treatment, and post-treatment procedures and evaluations
Main Outcomes	• Return to normal daily activities within 3 days postoperatively • Time to return to work among employed subjects • Boston Carpal Tunnel Questionnaire Symptom Severity Scale (BCTQ-SSS) change at 3 months • Boston Carpal Tunnel Questionnaire Functional Status Scale (BCTQ-FSS) change at 3 months • Numeric Pain Scale change at 3 months • EuroQol 5-Dimension 5-Level (EQ-5D-5L) change at 3 months • Device- or procedure-related adverse events at 3 months
Principal Investigator:	Kyle R. Eberlin, MD Division of Plastic Surgery Massachusetts General Hospital 55 Fruit Street, WAC 435 Boston, MA 02114
Study Sponsor and Data Management:	Sonex Health 950 Blue Gentian Road, Suite 200 Eagan, MN 55121 Tel: 888-518-8780 Email: tutor-study@sonexhealth.com

2. LIST OF ABBREVIATIONS

AAOS	American Academy of Orthopedic Surgery
AE	Adverse event
BCTQ	Boston Carpal Tunnel Questionnaire
CFR	Code of Federal Regulations
CRF	Case report form
CTR	Carpal tunnel release
CTR-US	Carpal tunnel release with ultrasound guidance
CTS	Carpel tunnel syndrome
DSMB	Data Safety Monitoring Board
ECTR	Endoscopic carpal tunnel release
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IQR	Interquartile range
IRB	Institutional Review Board
MCID	Minimal Clinically Important Difference
mOCTR	Mini-open carpal tunnel release
OCTR	Open carpal tunnel release
PI	Principal Investigator
QDASH	Quick form of the Disabilities of the Arm Shoulder and Hand
SAE	Serious adverse event
SOP	Standard Operating Procedure
TCL	Transverse carpal ligament
UADE	Unanticipated Adverse Device Effect

3. BACKGROUND AND OBJECTIVE

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy, affecting approximately 5% of the population [1]. A multitude of treatments are available to treat CTS, including activity modification, bracing/splinting, hand therapy, modalities (e.g., therapeutic lasers or ultrasound, iontophoresis), acupuncture, corticosteroid injections, and carpal tunnel release (CTR) surgery performed using an open or an endoscopic approach [2-7]. Currently, there is no universally accepted algorithm to guide treatment for patients suffering with CTS. The American Academy of Orthopedic Surgery (AAOS) CTS Clinical Practice Guidelines reported that only three treatments are strongly supported in the literature: splinting, corticosteroid injections, and CTR [4]. Although some patients with mild-moderate symptoms are successfully treated with splinting and/or corticosteroid injections, those with progressive, refractory, or severe symptoms generally proceed to CTR for definitive management [2,3,5-9].

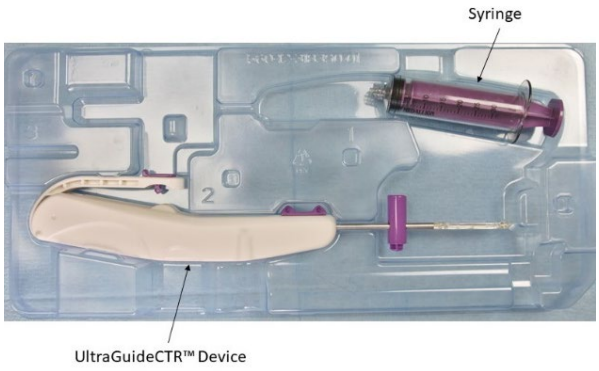
The goal of CTR is to reduce median nerve pressure by dividing the transverse carpal ligament (TCL) while avoiding iatrogenic injury to surrounding neurovascular structures. Among the ~600,000 CTR procedures performed in the United States annually [1,10], most (70-80%) use a traditional open technique (OCTR) during which a palmar incision is made to dissect down to the TCL and transect it using a scalpel, scissors, or a similar cutting device [11-13]. The OCTR technique requires a relatively large (3-5 cm) incision and may be associated with a prolonged recovery period due to palmar pain and the need to protect the wound [12,14-17].

Over time, there has been a trend to use smaller incisions (1-3 cm) to reduce surgical morbidity using mini-OCTR (mOCTR) or endoscopic CTR [11,16,17,19]. Because long-term outcomes and complication profiles are generally equivalent among these CTR procedures [18], factors related to patient recovery time such as time to return to normal activities and work absenteeism are important considerations that may assist in shared decision-making between physicians and patients.

In recent years, multiple studies have demonstrated the feasibility of using ultrasound to perform CTR through even smaller incisions while maintaining or even improving visualization of the carpal tunnel region, including its at-risk neurovascular structures. During CTR with ultrasound guidance (CTR-US), the carpal tunnel is typically accessed through a single small wrist or palmar incision <5 mm length and the TCL is transected using a small knife or similar cutting instrument while the carpal tunnel structures are continuously monitored using US. To date, a total of 13 clinical studies have been published reporting results on over 1300 hands in over 1000 patients at up to 2 years post-treatment comparing recovery time, effectiveness, and safety in subjects with CTS treated with CTR-US or mOCTR with US guidance [19-31]. Among these over 1300 hands, there were no major neurovascular complications, and the clinical success rate was >95%. Furthermore, two randomized controlled trials and one prospective non-randomized trial demonstrated superior early outcomes for CTR-US compared to mOCTR [21,24,28]. However, these trials were limited by small sample size, short follow-up duration, or both. No randomized controlled trial comparing CTR-US to mOCTR has been performed with a sample size over 100 patients and with at least 1 year of follow-up. Thus, the objective of this randomized controlled trial is to compare the safety and effectiveness of CTR-US vs. mOCTR in a large cohort of patients (n=120) with symptomatic CTS followed for 1-year post-treatment.

4. DEVICE DESCRIPTION

The UltraGuideCTR (Sonex Health, Inc., Eagan, MN) is a commercially available medical device specifically developed to facilitate CTR-US. The device is a single-use, hand-held device that is inserted into the carpal tunnel through a small (typically < 5 mm) wrist incision using continuous US guidance. The working tip of the UltraGuideCTR consists of two inflatable balloons that border a centrally located, retractable retrograde cutting knife. When inflated with sterile saline, the balloons increase the diameter of the tip from 4 mm to 8 mm. After the tip is positioned within the transverse safe zone, the balloons are inflated to create space in the carpal tunnel, the blade is activated, and the TCL is transected in a retrograde manner. Following TCL transection, the blade is recessed, the balloons deflated, and the device is removed. The TCL is probed to ensure a complete release. The entire procedure is performed using US guidance. The first commercial CTR-US procedure with the device was performed in February 2017. Since then, over 100 different physicians have been trained to use the UltraGuideCTR, who collectively have performed over 15,000 procedures. Labeled images of the device are provided below.



5. SUMMARY OF PRIOR CLINICAL EXPERIENCE

Representative prior experience with CTR-US using the UltraGuideCTR is derived from the APEX-CTR post market registry [31]. This multicenter, observational post-market registry enrolled patients treated with CTR-US in routine clinical practice in the United States. Data collection in this registry began after FDA clearance to collect post-market safety and effectiveness information on the device and patient outcomes. The research methods adhered to the guidelines set forth in the Declaration of Helsinki. This study was granted a waiver of consent exemption from WCG IRB (Puyallup, WA).

The eligibility criteria were purposely broad to reflect a heterogenous sample of CTS patients treated in routine clinical practice. Patient diagnosis was determined according to the practice patterns of each participating physician, all of whom were experienced in the diagnosis and management of CTS. CTS was diagnosed primarily on clinical grounds, with ancillary testing such as electrophysiological studies ordered at the discretion of the physician. Eligible patients were adults (age ≥18 years) who were treated with CTR-US and demonstrated a willingness to participate in the registry and participate in specified follow-up activities. No limitations were imposed on maximum patient age, medical or surgical history, or clinical presentation.

All patients were treated with CTR-US using the UltraGuideCTR device, which was inserted into the carpal tunnel through a small (typically <5 mm) wrist incision using real-time ultrasound guidance. The physicians in this study represented a variety of specialties and procedural experience and completed a formal cadaver-based training program prior to performing CTR-US in clinical practice. Factors such as patient selection, anesthesia, and postoperative care were determined by practice-specific preferences. Face-to-face follow-up visits varied according to the usual practice patterns of each participating physician and were not dictated by the study. There was no requirement for return follow-up visits as all data were collected via text message, e-mail, or chart review.

Patients completed a preoperative questionnaire, daily post-operative text message questions for up to 14 days post procedure, and emailed questionnaires at 2 weeks, 1 month, 3 months, and 6 months postoperatively. Pre-treatment patient assessments included demographic data, medical and surgical history, work status, and patient-reported outcomes including the Quick form of the Disabilities of the Arm, Shoulder, and Hand Questionnaire (QDASH), and the BCTQ-SSS and Functional Status Scale (BCTQ-FSS). Return to normal activities and return to work were collected via daily text messages for the first 14 days. Thereafter, postoperative outcomes were collected via e-mail or text message and included QDASH, BCTQ-SSS, BCTQ-FSS, return to normal activities, return to work, and patient satisfaction.

Co-primary endpoints of this study were QDASH, BCTQ-SSS, and BCTQ-FSS. The QDASH is an 11-item patient-reported questionnaire that has been validated for CTS where the total score ranges from 0 (indicating no disability) to 100 (indicating most severe disability) [32]. The BCTQ is a CTS specific questionnaire consisting of 11 symptom severity questions and 8 functional status questions. Scoring for the BCTQ- SSS and BCTQ-FSS ranges from 1 to 5, with higher scores indicating more severe symptoms [33]. Minimal clinically important differences (MCIDs) for the postoperative change in patient-reported outcomes were 15 points for QDASH [34], 1.14

points for BCTQ-SSS [35], and 0.74 points for BCTQ-FSS [35]. Return to normal activities was ascertained by asking patients when they had returned to normal daily activities outside of work. Return to work was ascertained by asking employed patients when they had returned to work in any capacity, a definition that is commonly used among CTS studies [36,37]. Patient satisfaction with the procedure was reported on a 5-point Likert scale ranging from 1 (very dissatisfied) to 5 (very satisfied); a score of 4 or 5 indicated that a patient was satisfied with the procedure. Postoperative complications were recorded via chart review performed by the treating physician.

Among 535 patients who enrolled in the registry and provided postoperative follow-up, data were available on 499 (93%) patients at 2 weeks, 475 (89%) at 1 month, 446 (83%) at 3 months, and 373 (70%) at 6 months. The cohort of 373 patients with 6-month follow-up form the basis for this report. Between November 2019 and July 2021, 373 patients (427 hands, mean age 55 years, 71% female, 62% employed) underwent CTR-US at 24 sites in the United States. A total of 329 (88.2%) procedures were performed using local anesthesia, 44 (11.8%) were performed using monitored anesthesia care, and no procedures were performed using general anesthesia. There were 217 unilateral CTR-US procedures, 51 bilateral staged CTR-US procedures, and 54 bilateral simultaneous CTR-US procedures. Bilateral simultaneous procedures consisted of 14.5% of cases and 25.3% of treated hands.

Patient-reported measures of symptom severity and physical function demonstrated rapid improvement following CTR-US. Mean QDASH scores were 41.7±20.1 at baseline, 21.4±15.9 at 2 weeks, 17.7±15.1 at 1 month, 13.3±15.0 at 3 months, and 11.0±15.2 at 6 months. QDASH scores decreased by 20.3 (95% CI: 17.5 to 23.0) points at 2 weeks and 30.8 (95% CI: 28.1 to 33.4) points at 6 months ($p<0.001$ at each follow-up interval).

Mean BCTQ-SSS scores were 3.0±0.7 at baseline, 1.7±0.6 at 2 weeks, 1.7±0.6 at 1 month, 1.5±0.6 at 3 months, and 1.4±0.6 at 6 months. BCTQ-SSS scores decreased by 1.3 (95% CI: 1.2-1.4) points at 2 weeks and 1.6 (95% CI: 1.5-1.7) points at 6 months ($p<0.001$ at each follow-up interval). Mean BCTQ-FSS scores were 2.4±0.8 at baseline, 1.7±0.6 at 2 weeks, 1.6±0.5 at 1 month, 1.4±0.5 at 3 months, and 1.3±0.5 at 6 months. BCTQ-FSS scores decreased by 0.7 (95% CI: 0.5-0.8) points and 1.0 (95% CI: 0.9-1.1) points at 2 weeks and 6 months, respectively ($p<0.001$ at each follow-up interval).

The median time to return to normal activities following CTR-US was 3 days (interquartile range [IQR]: 2-5 days), with 96.5% of patients reporting return to normal activities within 2 weeks of the procedure. Among employed patients, the median time to return to work following CTR-US was 5 days (IQR: 3-9 days), with 92.3% of patients reporting return to work within 2 weeks of the procedure. The median time to return to work based on employment type was 4 days (IQR: 3-6 days) for desk-based occupations, 6 days (IQR: 4-11 days) for light manual occupations, and 5 days (IQR: 3-14 days) for heavy manual occupations. The percentage of patients who were satisfied or very satisfied with the procedure was 91.6% at 2 weeks, 88.2% at 1 month, 88.0% at 3 months, and 89.8% at 6 months.

Among 346 (93%) patients with available complication data, no major neurovascular complications were reported. Specifically, there was 1 (0.3%) incomplete release confirmed during reoperation and no reports of superficial infection, deep infection, arterial laceration, or permanent nerve injury.

Overall, the results of the APEX-CTR post market registry confirmed that patients treated with CTR-US reported clinically meaningful improvements in symptoms and function, rapid return to normal activities, and minimal work absenteeism, with an excellent safety profile. Given the promising results with CTR-US in this registry, comparison of clinical outcomes with CTR-US vs. mOCTR in a randomized controlled trial is warranted.

6. STUDY PROCEDURES

6.1 INVESTIGATIONAL SITE SELECTION

Investigational sites will be selected based on the availability of the subject pool to be included in the study, the ability of the study site to perform the research in compliance with the investigational plan, and agreement to comply with the institutional review board (IRB) requirements. All investigators will be board certified orthopedic or plastic surgeons experienced in the diagnosis and treatment of CTS, including CTR-US and mOCTR. Each surgeon will complete a structured training program in musculoskeletal ultrasound including ultrasound machine controls, sonographic anatomy of the carpal tunnel region, identification and cross-sectional measurement of the median nerve, and CTR-US using the UltraGuideCTR device. In addition, all investigators must have treated a minimum of 10 procedures using CTR-US and 10 patients using mOCTR prior to treating subjects in the clinical trial.

6.2 SUBJECT SELECTION

Patients with suspected CTS will be consecutively evaluated for study eligibility at each site. Patients must meet all inclusion criteria and no exclusion criteria to be enrolled in the trial.

6.2.1 Inclusion Criteria

1. ≥18 years of age
2. Clinical diagnosis of unilateral or bilateral idiopathic CTS
3. CTS-6 score ≥12 in target hand
4. Absence of carpal tunnel symptoms in the contralateral hand that interfere with normal daily activities or work at the time of consent and are not anticipated to interfere with return to activities or return to work within at least 3 months post-operatively
5. Median nerve cross-sectional area ≥10 mm^2 in the proximal carpal tunnel region of the target hand measured by diagnostic ultrasound
6. Prior failure of one or more nonsurgical treatment options for the target hand (e.g., physical activity modification, bracing, splinting, corticosteroid injection)
7. Subject agrees to complete follow-up questionnaires over a 12-month period
8. Subject has a valid mobile phone number and email address to receive and answer follow-up questionnaires

6.2.2 Exclusion Criteria

1. Prior surgery on the target wrist or hand with the exception of trigger finger that has clinically recovered
2. History of prior surgical CTR in the target hand
3. History of prior surgical CTR in the contralateral hand within 3 months of enrollment or with persistent symptoms that interfere with normal daily activities or work at the time of consent
4. Corticosteroid injection in the target wrist or hand within 6 weeks of study procedure date
5. Presence of additional process in the target wrist or hand requiring additional intervention beyond carpal tunnel release (e.g. neurolysis, mass removal, tenosynovectomy)

6. Clinically significant degenerative arthritis of the upper limb (shoulder to hand) on the target side
7. Clinically significant inflammatory disease (including tenosynovitis) of the upper limb (shoulder to hand) on the target side
8. Clinically significant trauma or deformity of the upper limb (shoulder to hand) on the target side
9. Clinically significant vascular disease (including Raynaud's phenomenon) of the upper limb (shoulder to hand) on the target side
10. Clinically significant neurological disorder (including complex regional pain syndrome) of the upper limb (shoulder to hand) on the target side
11. Planned surgical or interventional procedure on the contralateral wrist or hand
12. Systemic inflammatory disease (e.g., rheumatoid arthritis, lupus)
13. Amyloidosis
14. Chronic renal insufficiency requiring dialysis
15. Diabetes not controlled by a stable dose of medication over the past three months
16. Uncontrolled thyroid disease
17. Pregnant or planning pregnancy in the next 12 months
18. Workers compensation subjects
19. Inability to provide a legally acceptable Informed Consent Form and/or comply with all follow-up requirements
20. Subject has other medical, social or psychological conditions that, in the opinion of the investigator, preclude them from receiving the pre-treatment, required treatment, and post-treatment procedures and evaluations

6.2.3 Screen Failures

Participants who are consented to participate in the clinical trial, but who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures. Screen failures will be immediately discontinued from the trial and will not be randomized to receive CTR-US or mOCTR. Participants who are discontinued from the study due to screen failure may not be reconsidered for study enrollment at a later date. Study sites will document screen failures by recording the date of screening, an anonymized patient identifier, and the primary inclusion and/or exclusion criterion failure that resulted in the decision to discontinue the patient from the study.

6.2.4 Timing of Patient Screening

All baseline testing and evaluations should be performed as close to the time of the procedure as possible. If the subject's procedure date is more than 30 days from the screening evaluation, subject screening validated questionnaires must be repeated to ensure accuracy of baseline condition at the time of procedure.

6.3 **RANDOMIZATION**

Subjects meeting all study inclusion/exclusion criteria after their screening evaluation will be randomized. This study will enroll 120 subjects who will be randomized in 2:1 fashion to receive CTR-US (n≈80) or mOCTR (n≈40). The randomization sequence for this trial will be computer-generated by the electronic data capture system (Viedoc). The randomization

sequence will be stratified by site with variable block sizes. Treatment assignment will be concealed until it is presented to authorized site personnel at the time of randomization. Only randomized and treated subjects will be considered enrolled in the study. Randomized patients who do not receive their assigned treatment will be discontinued from the trial.

6.4 BLINDING

Owing to obvious differences in surgical technique, it is not possible to blind the treating physicians. Owing to notable visual differences in the postoperative scar between surgical techniques (3-5 mm for CTR-US and approximately 3 cm for mOCTR), it is not possible to blind the subjects. Owing to the fact that all data collected in this trial will be self-reported, it is not possible to blind outcome assessors (i.e., subjects).

6.5 PROCEDURE

The key procedural steps involved in CTR-US are listed below.

1. Using direct US visualization, identify relevant anatomical structures within the carpal tunnel.
2. Dissect synovial tissue from the undersurface of the TCL via hydrodissection.
3. Insert the device through a small wrist incision and advance into the carpal tunnel.
4. Position the tip of the device distal to the distal TCL so that the TCL Blade will engage the distal TCL.
5. Confirm the position of the device under ultrasound.
6. Activate the Stealth MicroGuard balloons to create space within the carpal tunnel.
7. Deploy the TCL Blade by moving the slide button proximally to transect the TCL from distal to proximal until the TCL Blade passes into its proximal recessed position.
8. With the device or an elevator, probe the TCL to ensure a complete release.

Complete procedural details are provided in the Instructions for Use (https://sonexhealth.com/physicians/ultraguidectr/instructions-for-use).

6.6 POST-TREATMENT ASSESSMENTS

Postoperative patient care instructions will be standardized for each treatment group and among all participating sites to minimize bias. Investigators will instruct subjects to “participate in activities and return to work, as tolerated, based on pain, function, and wound healing status”.

6.7 FOLLOW-UP ASSESSMENTS

A list of the study assessments performed by the investigational site at each study interval is provided in the table below.

Assessment	Baseline Screening	Procedure	Post-Op	Day 7	Day 14	1 month	3 months	6 months	12 months
Demographics	√								
Ultrasound median nerve cross-sectional measurement	√								
CTS-6 (both hands)	√								
Randomization	√								
Procedure		√							
Image of incision		√							
Adverse events		√	√	√	√	√	√	√	√

A list of the patient reported outcomes provided by the patient at each study interval is provided in the table below.

Assessment	Baseline Screening	Procedure	Post-Op	Daily 1-14	1 month	3 months	6 months	12 months
Demographics	√							
Medical history	√							
BCTQ-SSS	√			√[1]	√	√	√	√
BCTQ-FSS	√			√[1]	√	√	√	√
EQ-5D-5L	√			√[1]	√	√	√	√
Numeric Pain Scale	√	√	√	√	√	√	√	√
Procedure		√						
Images of wound healing				√[2]	√	√	√	√
Return To Activities (RTA)				√	√	√	√	√
Return To Work (RTW)				√	√	√	√	√
Pain Medication	√	√	√	√	√	√	√	√

[1]Collected at 14-day evaluation
[2]Collected at Day 7 and Day 14

6.7.1 Unscheduled Follow-up Visits

If subjects are seen for unscheduled visits because of an AE or additional hand surgery, appropriate Case Report Form(s), will be completed, if applicable.

6.7.2 Loss to Follow-up

If a subject fails to comply with follow-up evaluations, the investigational site must make at least two repeated attempts to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records.

6.8 SUBJECT WITHDRAWAL FROM STUDY

6.8.1 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject had an AE, the subject should be followed until the resolution of the AE, if possible. Data from these subjects will be included in the analysis up to the point of each subject's withdrawal.

6.8.2 Involuntary Withdrawal

A subject also may be withdrawn by the investigator if the investigator determines that continued subject participation in the study will have a negative effect on the safety of the subject. Data obtained up to the date of subject withdrawal will be included in the study.

6.8.2.1 During First 3 months following Surgery

- Subjects who have <u>any</u> subsequent surgery on <u>either</u> hand during the first 3 months following their procedure will be withdrawn from the study.

6.8.2.2 After 3 month eVisit :

- <u>Treated Subjects</u>
    - Surgery in the Contralateral Hand - Subjects who have subsequent surgery on the <u>contralateral hand</u> (i.e., non-study hand), including CTR, will <u>not</u> be involuntarily withdrawn from the study. Note that a subsequent CTR in the contralateral hand is still not eligible for enrollment in TUTOR.
    - Surgery in the Study Target Hand –
        - Subjects who have subsequent surgery on the TUTOR hand that includes the wrist or carpal tunnel region, metacarpals, or thumb (with the exception of trigger thumb release) will be withdrawn from the study.
        - Subjects who have subsequent finger surgery (including trigger finger release) or trigger thumb release that does not affect the wrist or carpal tunnel region will <u>not</u> be withdrawn from the study.

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6.9 **END OF STUDY**

Subjects may exit the study at the end of the study (i.e., the study is discontinued by the Sponsor) or when the subject has completed the 12-month follow-up visit, whichever comes first, unless the subject opted to find an alternative treatment.

An End of Study CRF will be completed at the time the study is completed, discontinued, or lost to follow-up for each subject.

7. OUTCOMES

7.1 MAIN OUTCOMES

7.1.1 Time to Return to Normal Daily Activities within 3 Days

Time to return to normal daily activities will be collected through the ViedocMe ePRO module which asks whether the subject has returned to normal daily activities outside of work. Reminders will be sent to the subjects either by email or text messaging to minimize the risk of missing data. The time to return to normal daily activities will be defined as the number of days between treatment and the time the subject reports returning to normal daily activities, irrespective of work status.

7.1.2 Time to Return to Work Among Employed Subjects

Among study subjects who report full-time or part-time employment, time to return to work will be ascertained through the ViedocMe ePRO module by asking whether the subject has returned to work in full or limited capacity. Return to work within 3 days postoperatively will represent a secondary endpoint of the study. The time to return to work will be defined as the number of days between treatment and the time the subject reports returning to work in any capacity.

7.1.3 BCTQ-SSS Change at 3 Months

The BCTQ is a CTS specific questionnaire that has been shown to be highly reproducible, internally consistent, valid, and responsive to clinical change in CTS and subject status post-CTR. The BCTQ consists of 11 symptom severity questions (BCTQ-SSS). Scoring for the BCTQ- SSS ranges from 1 to 5, with higher scores indicating more severe symptoms, and is calculated as the mean of each response. The between-group mean difference in BCTQ-SSS change scores at the 3-month follow-up will represent a secondary endpoint of the study.

7.1.4 BCTQ-FSS Change at 3 Months

The BCTQ additionally consists of 8 functional status questions (BCTQ-FSS). Scoring for the BCTQ-FSS ranges from 1 to 5, with higher scores indicating more functional limitation, and is calculated as the mean of each response. The between-group mean difference in BCTQ-FSS change scores at the 3-month follow-up will represent a secondary endpoint of the study.

7.1.5 Numeric Pain Scale Change at 3 Months

Subjects will be asked to rate their wrist pain severity on a scale of 0 to 10, where 0 represents "no pain" and 10 represents "worst possible pain". The between-group mean difference in Numeric Pain Scale change scores at the 3-month follow-up will represent a secondary endpoint of the study.

7.1.6 EQ-5D-5L Change at 3 Months

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a generic preference-based questionnaire developed by the EuroQol Group to measure health-related quality of life. The EQ-5D-5L measures quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is scored on a 5-level severity ranking consisting of: no

problems, slight problems, moderate problems, severe problems, unable to/extreme problems. The between-group mean difference in EQ-5D-5L change score at the 3-month follow-up will represent a secondary endpoint of the study.

7.1.7 Device- or Procedure-related Adverse Events at 3 Months

Adverse events (AEs) occurring within 90 days of treatment and that are adjudicated as definitely related or probably related to the device, or definitely related or probably related to the procedure will be included in this endpoint. The incidence of device- or procedure-related AEs within 90 days of treatment in each study group will represent a secondary endpoint of the study.

7.2 **ADDITIONAL OUTCOMES**

Additional outcomes of the study will include:

- Median time to return to normal activities
- Median time to return to work
- BCTQ-SSS change at 2 weeks, 1 month, 6 months, and 12 months
- BCTQ-FSS change at 2 weeks, 1 month, 6 months, and 12 months
- Numeric Pain Scale change at 2 weeks, 1 month, 6 months, and 12 months
- EQ-5D-5L change at 2 weeks, 1 month, 6 months, and 12 months
- Device- or procedure-related AEs at 2 weeks, 1 month, 6 months, and 12 months
- Serious device- or procedure-related AEs at 2 weeks, 1 month, 3 months, 6 months, and 12 months

8. ADVERSE EVENTS

An AE is defined as any adverse change (i.e., *de novo* or preexisting condition) from the subject's baseline medical condition occurring after the initial procedural incision has been initiated. Any AE which resolved and then recurred will be reported as a separate AE. A pre-specified listing of AEs will be documented on the Adverse Event eCRF.

8.1 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as one that suggests a significant hazard or side effect, regardless of the relationship to the device or procedure. This includes, but may not be limited to, any event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Important medical events may be considered serious by the investigator although they may not be immediately life threatening or result in death or prolong hospitalization. Such important medical events are those that may jeopardize the subject, require intervention to prevent one of the outcomes listed above, or result in urgent investigation.

SAEs should be reported to the study Sponsor as soon as possible (24 hours recommended), but no more than 10 working days after the date the site becomes aware of the event.

Sites are also required to adhere to the reviewing IRB requirements for reporting of SAEs.

8.2 UNANTICIPATED ADVERSE DEVICE EFFECT

An unanticipated adverse device effect (UADE) is any serious adverse effect on the health or safety of a subject, any life-threatening problem or death caused by, or associated with a device, if such effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (e.g., ICF, Study Protocol, Instructions for Use (IFU), publications, etc.), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse effect associated with the device occurs, the investigator shall notify the Sponsor and the IRB as soon as possible.

The Sponsor will investigate the event and notify the FDA and all other participating IRBs and investigators. Should the Sponsor determine that an unanticipated adverse effect presents an

unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs, country regulatory bodies and FDA.

8.3 RELATIONSHIP OF ADVERSE EVENTS TO THE DEVICE OR PROCEDURE

A description of how an AE relates to the study device or procedure will be reported on the Adverse Event CRF.

- A device-related AE is directly attributable to the device or to improper use of the device.
- A procedure-related AE is directly attributable to the procedure, irrespective of the device, including complications from anesthesia or other procedures incidental to the main procedure.

The relationship of the AE to the device or procedure will be determined by the Investigator using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.
- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

8.4 DEVICE FAILURES, MALFUNCTIONS AND NEAR INCIDENTS

Device failures or malfunctions will be reported to Sonex Health by the clinical sites. If the failure or malfunction results in an AE, the event shall be reported to the Sponsor within two (2) working days after the Investigator becomes aware of the event and reported to the IRB (if required) within the IRB required timeframe. The device involved in the incident should be returned to the Sponsor for evaluation.

8.5 REPORTING OF ADVERSE EVENTS

AEs will be recorded on the Adverse Event CRF and described by (a) duration (onset and resolution dates); (b) relationship to the study device or procedure; (c) action taken to resolve the event; (d) outcome of the event; and (e) whether or not such event is considered to have been

serious. Additional information, such as procedural notes, treatment notes, or a signed clinical summary may be required as supporting documentation for the reported AE.

During the study, all deaths must be reported to the Sponsor within 48 hours and should also be reported on the End of Study CRF. A copy of the subject's death records, medical records for the events that led to the subject's death, and a death certificate (if available) should be provided.

Determination of whether a subject experienced an AE can be made in three different ways. First, an AE can be documented by the site during the study procedure. Second, a subject may report an AE directly via phone call to the investigative site. Third, an AE can be identified by the site during the review of the subject-uploaded wound healing images. If the site identifies a potential AE based on image review or is notified of a potential AE by the subject, confirmation of the AE will occur by a phone call with the subject or, if necessary, by asking the subject to return for a follow-up clinical evaluation.

8.6 **INDEPENDENT MEDICAL REVIEWER**

Evaluation and adjudication of all AEs will be performed on an ongoing basis by an independent medical reviewer. The independent medical reviewer will review AEs for AE classification, seriousness, and relationship to the device or procedure. Discrepancies between the investigational site and the independent medical reviewer will be handled by discussion, with the determination by independent medical reviewer serving as the final classification.

8.7 **DATA SAFETY MONITORING BOARD**

A Data Safety Monitoring Board (DSMB) will oversee enrollment and safety of the subjects for the study. Members of DSMB will be independent of the sponsor and investigational sites. The DSMB for the study will consist of three (3) clinicians with expertise in orthopedic or plastic surgery, and with experience and expertise in clinical trials. The DSMB will convene at least once during the subject enrollment period and will review, at a minimum, subject enrollment status and incidence of AEs. Based on a review of these data, the DSMB will advise the Sponsor to continue the trial with no modification, or to modify the trial as appropriate if enrollment or safety concerns are identified.

9. RISK-BENEFIT ANALYSIS

9.1 RISK ANALYSIS

Complications and risks that exist for other CTR treatments may also exist for the UltraGuideCTR technique. The UltraGuideCTR technique has undergone extensive risk analysis testing and is designed with safeguards built into the device to mitigate the serious risks. The full list of anticipated adverse events is provided on the Adverse Event CRF. All complications that can occur with mOCTR may also occur with CTR-US.

9.2 POTENTIAL BENEFITS

The data obtained from this study will be used to document the safety and effectiveness of UltraGuideCTR and compare it to mOCTR. The data derived from this study may benefit individuals with CTS in the context of a shared-decision making process when contemplating CTR. In addition, subjects potentially could directly benefit from participation in this study. UltraGuideCTR is designed to provide relief from CTS through a less invasive approach than mOCTR. Previous publications reported that patients may experience significant symptom relief and return to activities within 3-5 days post-procedure, which is faster than typically reported for mOCTR.

10. DATA ANALYSIS

This is a multicenter, randomized, controlled trial designed to evaluate the safety and effectiveness of CTR-US compared to mOCTR in treating subjects with symptomatic CTS. Eligible subjects will be randomized (2:1) to receive CTR-US (n≈80) or mOCTR (n≈40).

10.1 SAMPLE SIZE JUSTIFICATION

The results of the power analysis provided a sample size consisting of 102 evaluable subjects. Group sample sizes of 68 and 34 achieve 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.60 and alpha is 0.05 using a two-sided two-sample equal-variance t-test with a 2:1 randomization allocation. To account for reasonable subject attrition, 120 subjects (n≈80 CTR-US, n≈40 mOCTR) will be enrolled in the trial.

10.2 ANALYSIS POPULATIONS

The primary statistical analyses will be performed on a modified intention-to-treat population, which will be comprised of all subjects who meet all study eligibility criteria, are subsequently randomized, and receive their assigned treatment. Randomized subjects who withdraw from the study prior to treatment or who receive the incorrect treatment will not be included in the modified intention-to-treat population.

10.3 DURATION VARIABLES

Study day 0 is the day the subject receives CTR-US or mOCTR. Postoperative study day will be calculated relative to day 0 as follows:

Study Day = (Date of Event – Date of Treatment)

10.4 ANALYSIS WINDOWS

Study data will be categorized into discrete, contiguous reporting windows to ensure that all available data are included in the analyses. The analysis windows for this study are defined below:

Study Visit	Target Days	Analysis Window
Treatment	0	0
2 weeks	14	7-22
1 month	30	23-60
3 months	90	61-135
6 months	180	136-270
12 months	365	271-450

10.5 **DATA ANALYSIS METHODS**

Baseline data will be analyzed using descriptive statistics. Continuous data will be summarized using mean and standard deviation for normally distributed data, median and interquartile range for non-normally distributed data, and counts and percentages for categorical data. For categorical variables, percentages will be calculated based on non-missing data.

The percentage of patients in each treatment group that return to normal daily activities within 3 days postoperatively, and the percentage of employed patients in each treatment group that return to work within 3 days postoperatively will be reported and compared using the Fisher's exact test. These outcomes will also be reported as the median and interquartile range in each treatment group. Due to the likelihood that the data distribution may be positively skewed, the nonparametric Mann-Whitney U test will be the statistical test used to assess these endpoints.

Differences between the CTR-US and mOCTR groups with respect to longitudinally measured continuous outcomes (i.e. BCTQ-SSS, BCTQ-FSS, Numeric Pain Scale, EQ-5D-5L) will be analyzed using mixed model analysis and adjusting for the baseline score.

Adverse events will be reported using counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method. The incidence of AEs in each group will be calculated on a per-subject basis and analyzed using Fisher's exact test.

Statistical analyses will be performed using a two-sided hypothesis test at a 5% level of significance. No adjustments for multiplicity are planned. Missing data imputation will not be performed.

11. STUDY RESPONSIBILITIES AND MANAGEMENT

This study will be performed in accordance with all requirements set forth in the U.S. regulations, 21 Code of Federal Regulations (CFR) Parts 812, 50, 54, and 56, the Declaration of Helsinki, and any other applicable local laws, regulations, or guidelines.

11.1 INVESTIGATOR RESPONSIBILITIES

Each investigator will be responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, IRB requirements, and applicable laws and regulations. Investigators may not begin enrollment until the Sponsor or its designee receives and approves (when necessary) the following documents:

- Signed Investigator Agreement
- Financial disclosure forms for all participating investigators
- IRB roster (or IRB registration number from the Office of Human Research Protection)
- IRB protocol and ICF approvals
- Investigators' current curricula vitae and medical license
- Signed Site Delegation Log

It is acceptable for Investigators to delegate one or more of the above functions to a Co- or Sub-Investigator, or a trained Research Coordinator; however, the Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each study site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations (e.g., Health Insurance Portability and Accountability Act (HIPAA) in the U.S.). Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate IRB and the Sponsor.

11.2 SUBJECT ENROLLMENT PROCESS

All study candidates must appropriately consent to participate in the study, as administrated by qualified study site personnel using an IRB and Sponsor-approved informed consent form (ICF) prior to beginning any aspect of the study procedure or tests that are not standard of care for the site. Investigational sites will be required to document the consent process within each enrolled subject's medical record.

11.3 **INSTITUTIONAL REVIEW BOARD**

Investigators must submit the study protocol to the Institutional Review Board (IRB) and obtain the IRB's written approval before being allowed to conduct and participate in the study. Each Investigator is responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc. Investigators will provide the Sponsor with copies of such approvals and reports.

11.4 **INFORMED CONSENT FORM**

The Sponsor will provide a template informed consent form (ICF) to each study site for IRB submission. The template may be modified to suit the requirements of the individual study site, but the Sponsor must pre-approve all changes to the ICF prior to initial submission to the IRB.

Each Investigator or assigned designee must administer this approved ICF to each prospective study subject and obtain the subject's signature or a legally approved designee's signature along with the date of consent prior to enrollment in the study. The ICF must be obtained in accordance with the applicable guidelines on 21 CFR 50, 52 and 56, the Declaration of Helsinki, ISO 14155 or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and be informed that withdrawal from the study will not jeopardize their future medical care. A copy of their signed ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the TUTOR study ICF.

11.5 **CASE REPORT FORM**

The Sponsor will provide standardized case report forms (CRFs) for each individual subject. The CRFs will be electronic (EDC, 21 CRF Part 11 compliant), and will be used to record study data, and are an integral part of the study and subsequent reports.

The electronic CRFs for individual subjects will be provided by the Sponsor via a web portal. After the data has been submitted, reviewed, and centrally monitored, corrections will be initiated via automatic data queries and/or manual data queries answered by appropriate study site personnel. The Investigator will provide his/her electronic signature on the appropriate eCRFs in compliance with local regulations.

11.6 **CENTRAL DATABASE**

All subject data will be collected and compiled in a limited access secure electronic data capture system (EDC). Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

11.7 **RECORDS**

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but not limited to:

- All signed agreements
- IRB approval letter(s)
- Approved ICF template
- Records of AEs, including supporting documents
- Records of protocol deviations, including supporting documents
- Records of each subject's case history, including study required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the investigation, relevant medical history, the results of all diagnostic testing, etc.
- Signature authorization and delegation log
- Any other records that applicable regulation requires to be maintained

11.8 **REPORTS**

The table below lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the IRB reporting requirements for their respective site. If applicable regulations or IRB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, IRB	Within 10 working days of knowledge
Death	Sponsor, IRB	Written reports (e.g., via e-mail) within 48 hours
SAE	Sponsor IRB, if required	Within 10 working days of knowledge Per IRB requirement
Device malfunction with clinical sequelae	Sponsor IRB, if required	Within 48 hours via written communication. Return the device to sponsor within 48 hours.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor IRB, if required	Within 5 working days of knowledge Per IRB requirement
Withdrawal of IRB approval	Sponsor	Within 5 working days of knowledge
Annual progress report	Sponsor, IRB	Annually
Final report	Sponsor, IRB	Within 6 months of study completion or termination
Note: Institutional IRBs may require more stringent reporting requirements that those listed in this table.		

11.9 **SPONSOR RESPONSIBILITIES**

Sonex Health is the Sponsor of this study. The Sponsor's responsibilities in the study include:

- Selecting qualified Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Provide study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Provide financial support to each study site.
- Follow/promote all regulatory standards per appropriate regulations for study sites, and other participants, and ensure compliance through central monitoring.
- Retain ownership of all clinical data generated in this study and control the use of the data for appropriate purposes only.
- Review and approve publication of study results in the literature.

11.9.1 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential according to HIPAA regulations. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

11.9.2 Amending the Investigational Study Protocol

Only the study Sponsor can amend the Investigational Protocol. All changes to the Investigational Protocol must be submitted to the IRB for review and approval. Any change that would require alteration to the ICF must receive approval from the applicable IRB prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

11.9.3 Protocol Deviations

A protocol deviation is an unplanned excursion from the protocol that is not implemented or intended as a systematic change. If an investigator failed to perform tests or examinations as required by the protocol or there were failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. These types of deviations are reported to the sponsor and in accordance with the IRB policy.

A Protocol Deviation CRF must be completed by the site for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion / exclusion criteria, not performing required testing, missed follow-up window, etc.). An Investigator must notify the Sponsor and the reviewing IRB of any deviation from the study protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five (5) working days after the emergency occurred.

11.9.4 Site Noncompliance and Nonperformance

Repeat protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

After a site completes all required approvals and training, a site initiation visit will be conducted as a final check of the site readiness. If a site is not able to enroll its first subject 3 months after "Ready to Enroll" status, the Sponsor may elect to terminate the investigational site and allocate the slot to another candidate site.

11.9.5 Device Accountability

The UltraGuideCTR is an FDA 510k cleared device, will be purchased by the investigational sites for use in the study, and does not require device accountability tracking within the study.

12. STUDY MONITORING

The study sponsor is responsible to ensure that proper monitoring of this investigation is conducted. Appropriately trained personnel, appointed by the study sponsor, will perform monitoring. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement
- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing IRB and/or other regulatory agencies

The clinical study will be monitored using electronic central monitoring processes. On-site monitoring may occur as needed. The sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures, if necessary.

A study specific Monitoring Plan will be created and implemented to standardize monitoring activities across centers and to ensure human subject protection and verify data integrity. The monitors shall receive study specific and SOP training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications, and experience to monitor the progress of an investigation. Study monitors may be Sponsor's employees or representatives. All study monitors will be required to follow the Sponsor's monitoring plan and monitoring standard operating procedures (SOPs).

Study closure is defined as a specific date that is determined by study completion and/or regulatory requirements that have been satisfied per the study protocol and/or by decision of the Sponsor. Study closure visits will be conducted via telephone call for all enrolling clinical sites to review record retention requirements with site personnel.

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