Multicenter prospective trial of office-based carpal tunnel release with ultrasound guidance (ROBUST)

CLINICAL STUDY PROTOCOL:

No. 90098-TP Revision 01
Dated December 19, 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.

Multicenter prospective trial of office-based carpal tunnel release with ultrasound guidance (ROBUST)

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	**Multicenter prospective trial of office-based carpal tunnel release with ultrasound guidance (ROBUST)**
Purpose	To report the safety and effectiveness of office-based carpal tunnel release with ultrasound guidance (CTR-US) in patients with symptomatic carpal tunnel syndrome (CTS)
Study Design	Multicenter prospective single-arm trial of subjects with symptomatic CTS treated with CTR-US in an office-based setting
Enrollment	A minimum of 140 subjects will be enrolled in the study and treated with CTR-US
Procedure	Unilateral or simultaneous bilateral CTR-US
Visit Schedule	Post-procedure remote subject-reported outcomes evisits: 1-14 days; 1, 3, 6, 12, and 24 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. Median nerve cross-sectional area ≥10 mm^2 in the proximal carpal tunnel region of the target hand measured by diagnostic ultrasound* 5. Prior failure of one or more nonsurgical treatment options (e.g., physical activity modification, bracing, splinting, corticosteroid injection)* 6. Subject agrees to complete follow-up questionnaires over a 24-month period 7. Subject has a valid smart phone number and/or email address to receive and answer follow-up questionnaires
Exclusion Criteria	1. Prior surgery on the target wrist or hand with the exception of (a) trigger finger release or similar minor finger procedure (e.g., digital ganglion cyst removal, foreign body removal) that has clinically recovered, or release for DeQuervain's syndrome (1st dorsal compartment) that has clinically recovered* 2. History of prior surgical CTR in the target hand* 3. History of infection in the target hand* 4. History of prior surgery in the non-target hand, including CTR, within 3 months of enrollment or with persistent symptoms that interfere with normal daily activities or work at the time of consent 5. Planned surgical or interventional procedure on the contralateral hand within 3 months of the target hand procedure date* 6. Corticosteroid injection in the target hand within 6 weeks of study procedure date* 7. Presence of additional process in the target hand requiring additional intervention beyond carpal tunnel release (e.g. neurolysis, mass removal, tenosynovectomy)* 8. Clinically significant degenerative arthritis of the upper limb (shoulder to hand) on the target side* 9. Clinically significant inflammatory disease (including tenosynovitis) of the upper limb (shoulder to hand) on the target side*

	10. Clinically significant trauma or deformity of the upper limb (shoulder to hand) on the target side* 11. Clinically significant vascular disease (including Raynaud's phenomenon) of the upper limb (shoulder to hand) on the target side* 12. Clinically significant neurological disorder (including complex regional pain syndrome) of the upper limb (shoulder to hand) on the target side* 13. Systemic inflammatory disease (e.g., rheumatoid arthritis, lupus) 14. Amyloidosis 15. Chronic renal insufficiency requiring dialysis 16. Diabetes not controlled by a stable dose of medication 17. Uncontrolled thyroid disease 18. Pregnant or planning pregnancy in the next 24 months 19. Workers' compensation subjects 20. Inability to provide a legally acceptable Informed Consent Form and/or comply with all follow-up requirements 21. 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 Note: An asterisk (*) denotes that this criterion must be applied to the target hand for unilateral CTR-US procedures, or to both hands for simultaneous bilateral CTR-US procedures. Clinically significant is defined as likely to interfere with the performance of the procedure in a safe and/or effective manner.
Primary Endpoint	Boston Carpal Tunnel Questionnaire Symptom Severity Scale (BCTQ-SSS) change at 3 months
Secondary Endpoints	• Time to Return to normal daily activities • Time to Return to work among employed subjects • Boston Carpal Tunnel Questionnaire Functional Status Scale (BCTQ-FSS) change at 3 months • Michigan Hand Questionnaire (MHQ) • 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 • Global Satisfaction at 3 months
Principal Investigator:	Ashley L. Pistorio, MD, MS, FACS University of Nevada, Las Vegas 1707 W. Charleston Boulevard, Suite 190 Las Vegas, NV 89102
Study Sponsor and Data Management:	Sonex Health 950 Blue Gentian Road, Suite 200 Eagan, MN 55121 Tel: 888-518-8780 Email: robust-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
CMS	Centers for Medicare and Medicaid Services
CTR	Carpal tunnel release
CTR-US	Carpal tunnel release with ultrasound guidance
CTS	Carpal 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
MHQ	Michigan Hand Questionnaire
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 traditional open or endoscopic approaches [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 [11,16-18] . Because long-term outcomes and complication profiles are generally equivalent among these CTR procedures [19], 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.

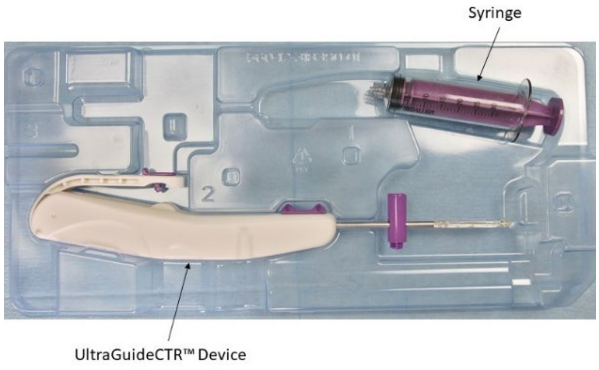
In recent years, multiple studies have demonstrated the feasibility of using ultrasound to perform CTR through even smaller incisions while maintaining or even improving visualization of the carpal tunnel region, including its at-risk neurovascular structures. During CTR with ultrasound guidance (CTR-US), 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 visually using US. To date, a total of 22 clinical studies have been published reporting results on over 2,100 hands in over 1,650 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 [20-32]. Among these over 2,100 hands, there were no major neurovascular complications, and the clinical success rate was >95%.

Historically, CTR procedures were performed in a hospital or an ambulatory surgery center (ASC). However, due to advancements in technology, greater patient demand, and concerns about growing healthcare costs, there is a distinct trend from performing CTR procedures in a hospital or ASC to an office-based setting. A recently published prospective single-center study demonstrated the feasibility of CTR-US when performed in an office-based setting [33.] The

improvement in CTS symptoms following office-based CTR-US was statistically significant and clinically important over 1 year of follow-up and no intraoperative complications or reoperations were reported. However, it remains unclear whether these results are reproducible across multiple practices treating patients with office-based CTR-US in real-world practice. Thus, the objective of this prospective multicenter trial is to evaluate the safety and effectiveness of office-based CTR-US in a large cohort of patients (n=140) with symptomatic CTS followed for 2 years 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 of the carpal tunnel, 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 device is derived from the APEX-CTR post market registry [32]. 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 about 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 electrodiagnostic 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 all 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 Boston Carpal Tunnel Symptom Severity and Functional Status Scores (BCTQ-SSS and 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) [34]. The BCTQ is a CTS specific questionnaire consisting of 11 symptom severity questions (BCTQ-SSS) and 8 functional status questions (BCTQ-FSS). Scoring for the BCTQ- SSS and BCTQ-FSS ranges from 1 to 5, with higher scores indicating more severe symptoms and more severe disability,

respectively [35]. Minimal clinically important differences (MCIDs) for the postoperative change in patient-reported outcomes were 15 points for QDASH [36], 1.14 points for BCTQ-SSS [37], and 0.74 points for BCTQ-FSS [37]. 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 [38,39]. 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 formed the basis for the 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 staged bilateral CTR-US procedures, and 54 simultaneous bilateral CTR-US procedures. 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 returning 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 returning 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.

A recent study by Bergum and Ciota [33] demonstrated the feasibility of CTR-US when performed in an office-based setting. This was a prospective single-center study that evaluated 1-year outcomes in patients treated with office-based CTR-US. Among 88 patients (123 hands) with 1-year follow-up data, 29 patients (57 hands) were treated with simultaneous bilateral procedures, 18 patients (25 hands) were treated with staged bilateral procedures, and 41 were treated with a unilateral procedure. All office-based procedures were successfully completed with local anesthesia and no intraoperative complications occurred.

Mean BCTQ-SSS scores decreased by 1.2 (SE 0.07) points at 2 weeks, 1.3 (SE 0.07) points at 1 month, 1.6 (SE 0.09) points at 3 months, and 1.7 (SE 0.08) points at 1 year ($p<0.001$ at each follow-up interval). Mean BCTQ-FSS scores decreased by 0.6 (SE 0.06) points at 2 weeks, 0.9 (SE 0.07) points at 1 month, 1.1 (SE 0.07) points at 3 months, and 1.2 (SE 0.07) points at 1 year ($p<0.001$ at each follow-up interval). Mean QDASH scores decreased by 14 (SE 2) points at 2 weeks, 23 (SE 2) points at 1 month, 27 (SE 2) points at 3 months, and 32 (SE 2) points at 1 year ($p<0.001$ at each follow-up interval). No neurovascular injuries, tendon injuries, infections or significant post-surgical wound complications occurred, and there were no recurrences or reoperations reported in the study. One patient developed complex regional pain syndrome without evidence of nerve injury, which was promptly recognized and successfully treated. This patient ultimately had CTR-US performed on the contralateral hand.

The purpose of this prospective multicenter study is to determine the safety and effectiveness of CTR-US when performed in an office setting.

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 physicians experienced in the diagnosis and treatment of CTS, including CTR-US. Each investigator 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 conducted a minimum of 10 procedures using CTR-US prior to treating subjects in the clinical trial.

6.2 SUBJECT SELECTION

Patients with suspected CTS in one or both hands 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. Median nerve cross-sectional area ≥10 mm2 in the proximal carpal tunnel region of the target hand measured by diagnostic ultrasound*
5. Prior failure of one or more nonsurgical treatment options (e.g., physical activity modification, bracing, splinting, corticosteroid injection)*
6. Subject agrees to complete follow-up questionnaires over a 24-month period
7. Subject has a valid smart phone number and/or 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 (a) trigger finger release or similar minor finger procedure (e.g., digital ganglion cyst removal, foreign body removal) that has clinically recovered, or release for DeQuervain's syndrome (1st dorsal compartment) that has clinically recovered*
2. History of prior surgical CTR in the target hand*
3. History of infection in the target hand*
4. History of prior surgery in the non-target hand, including CTR, within 3 months of enrollment or with persistent symptoms that interfere with normal daily activities or work at the time of consent
5. Planned surgical or interventional procedure on the contralateral hand within 3 months of the target hand procedure date*
6. Corticosteroid injection in the target hand within 6 weeks of study procedure date*

7. Presence of additional process in the target hand requiring additional intervention beyond carpal tunnel release (e.g. neurolysis, mass removal, tenosynovectomy)*
8. Clinically significant degenerative arthritis of the upper limb (shoulder to hand) on the target side*
9. Clinically significant inflammatory disease (including tenosynovitis) of the upper limb (shoulder to hand) on the target side
10. Clinically significant trauma or deformity of the upper limb (shoulder to hand) on the target side*
11. Clinically significant vascular disease (including Raynaud's phenomenon) of the upper limb (shoulder to hand) on the target side*
12. Clinically significant neurological disorder (including complex regional pain syndrome) of the upper limb (shoulder to hand) on the target side*
13. Systemic inflammatory disease (e.g., rheumatoid arthritis, lupus)
14. Amyloidosis
15. Chronic renal insufficiency requiring dialysis
16. Diabetes not controlled by a stable dose of medication
17. Uncontrolled thyroid disease
18. Pregnant or planning pregnancy in the next 24 months
19. Workers' compensation subjects
20. Inability to provide a legally acceptable Informed Consent Form and/or comply with all follow-up requirements
21. 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

Note: An asterisk (*) denotes that this criterion must be applied to the target hand for unilateral CTR-US procedures, or to both hands for simultaneous bilateral CTR-US procedures.

Clinically significant is defined as likely to interfere with the performance of the procedure in a safe and/or effective manner.

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 receive CTR-US within the trial. 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 baseline electronic patient reported outcomes completion, validated questionnaires must be repeated to ensure accuracy of baseline condition at the time of procedure.

7. SUBJECT ENROLLMENT

Subjects meeting all study inclusion/exclusion criteria after their screening evaluation will receive CTR-US. Only subjects who receive CTR-US will be considered enrolled in the study. If a subject has a CTR with a method other than CTR-US they will not be considered enrolled in the study. Eligible patients who do not receive treatment will be discontinued from the trial.

7.1 PROCEDURE

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

1. Using real-time US visualization, identify relevant anatomical structures within the carpal tunnel.
2. Dissect synovial tissue from the undersurface of the TCL.
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, including the safety of surrounding structures.
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).

Patients may undergo unilateral or simultaneous bilateral CTR-US procedures in this trial. The decision of which procedure to undergo will be made based on the clinical diagnosis and by shared decision-making between the patient and physician.

7.2 PROCEDURE LOCATION

All CTR-US procedures will be performed in-office. Per the Place of Service Codes set forth by the Centers for Medicare & Medicaid Services (CMS), in-office is defined as a location, other than a hospital, skilled nursing facility (SNF), military treatment facility, community health center, State or local public health clinic, or intermediate care facility (ICF), where the health professional routinely provides health examinations, diagnosis, and treatment of illness or injury on an ambulatory basis [40].

7.2.1 Post-treatment Assessments

Postoperative patient care instructions will be standardized 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".

7.2.2 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	24 months
Demographics	√									
Ultrasound median nerve cross-sectional measurement [1]	√									
CTS-6[2]	√									
Procedure		√								
Adverse events		√	√	√	√	√	√	√	√	√

[1]Required for all treated hands.
[2]Measured on both hands

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	24 months
Demographics	√								
Medical history	√								
BCTQ-SSS [1]	√			√[2]	√	√	√	√	√
BCTQ-FSS	√			√[2]	√	√	√	√	√
MHQ	√			√[2]	√	√	√	√	√
EQ-5D-5L	√			√[2]	√	√	√	√	√
Numeric Pain Scale [1]	√	√	√	√	√	√	√	√	√
Procedure		√[1]							
Return To Activities				√	√	√	√	√	√
Return To Work[3]				√	√	√	√	√	√
Pain Medication	√	√	√	√	√	√	√	√	√

[1]Measured on all treated hands.
[2]Collected only at 14-day evaluation
[3]Employed subjects only

7.2.3 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.

7.2.4 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.

7.3 SUBJECT WITHDRAWAL FROM STUDY

7.3.1 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.

7.3.2 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.

7.3.2.1 Prior to 3 months eVisit following ROBUST 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.

7.3.2.2 After 3 months eVisit :

- <u>Subjects Treated with Unilateral CTR-US in ROBUST</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-US in the contralateral hand is still not eligible for enrollment in ROBUST.
    - Surgery in the Study Target Hand –
        - Subjects who have subsequent surgery on the ROBUST 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

- Subjects Treated with Simultaneous Bilateral CTR-US in ROBUST - Subjects who have subsequent surgery on either 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.

7.3.3 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 24-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.

8. OUTCOMES

8.1 PRIMARY ENDPOINT

The primary endpoint of the study is 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 includes a symptom severity score (BCTQ-SSS) and a functional status score (BCTQ-FSS). The BCTQ-SSS consists of 11 symptom severity questions. 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 change in BCTQ-SSS score at the 3-month follow-up relative to baseline will represent the primary endpoint of the study.

8.2 SECONDARY ENDPOINTS

8.2.1 Time to Return to Normal Daily Activities

Time to return to normal daily activities will be ascertained 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. Time to return to normal daily activities postoperatively will represent a secondary endpoint of the study. 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.

8.2.2 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 any capacity (full or limited). Reminders will be sent to the subjects either by email or text messaging to minimize the risk of missing data. Time to return to work 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.

8.2.3 BCTQ-FSS Change at 3 Months

The BCTQ-FSS 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 change in BCTQ-FSS score at the 3-month follow-up relative to baseline will represent a secondary endpoint of the study.

8.2.4 MHQ Change at 3 Months

The Michigan Hand Questionnaire (MHQ) is a validated, hand-specific questionnaire consisting of 37 questions in 6 domains:

- overall hand function
- activities of daily living
- work performance
- pain
- aesthetics
- satisfaction

The raw score for each of the six domains is converted to a score ranging from 0-100, with 100 being the best score for each domain with the exception of the pain domain for which 100 = maximal pain. An overall MHQ score can be obtained by reversing the pain domain score (pain = 100 minus pain score), summing the scores for all six domains, then dividing by six. MHQ scores may be reported as overall scores or scores by each domain. For example, previous studies have documented a minimally clinically important difference of 13 for the overall function, 23 for the pain, and 8 for work domains. The MHQ has also been validated to use in patients with bilateral hand symptoms, such as bilateral CTS. The change in the total MHQ score as well as each of its 6 domains score at the 3-month follow-up relative to baseline will represent secondary endpoints of the study.

8.2.5 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 change in Numeric Pain Scale score at the 3-month follow-up relative to baseline will represent a secondary endpoint of the study.

8.2.6 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 change in EQ-5D-5L score at the 3-month follow-up relative to baseline will represent a secondary endpoint of the study.

8.2.7 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 will represent a secondary endpoint of the study.

8.2.8 Global Satisfaction

Subjects will be asked to rate their satisfaction with the carpal tunnel release procedure and how likely they are to recommend their carpal tunnel release procedure to a friend or colleague.

8.2.9 Additional Outcomes

Additional outcomes of the study will include:

- BCTQ-SSS change at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- BCTQ-FSS change at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- MHQ change at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- Numeric Pain Scale change at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- EQ-5D-5L change at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- Device- or procedure-related AEs at 2 weeks, 1 month, 6 months, 12 months, and 24 months
- Serious device- or procedure-related AEs at 2 weeks, 1 month, 3 months, 6 months, 12 months, and 24 months

9. ADVERSE EVENTS

An Adverse Event (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.

9.1 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.

9.2 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.

9.3 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.

9.4 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.

9.5 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.

9.6 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.

9.7 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.

9.8 RISK-BENEFIT ANALYSIS

9.8.1 Risk Analysis

Complications and risks that exist for other CTR treatments may also exist for carpal tunnel release using UltraGuideCTR and real-time ultrasound guidance. UltraGuideCTR 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.

9.8.2 Potential Benefits

The data obtained from this study will be used to document the safety and effectiveness of UltraGuideCTR when performed in an office-based setting. 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. Treatment with UltraGuideCTR and real-time ultrasound guidance in an in-office setting may potentially allow for rapid return to work and normal daily activities, as well as avoidance of general anesthesia and the costs associated with treatment in a hospital or ambulatory surgery center.

10.DATA ANALYSIS

This is a prospective, multicenter, single-arm trial designed to evaluate the safety and effectiveness of office-based CTR-US in treating subjects with symptomatic CTS.

10.1 SAMPLE SIZE JUSTIFICATION

This study will enroll a minimum of 140 subjects who will receive office-based CTR-US. This sample size provides adequate statistical power for the evaluation of the primary endpoint given the assumptions below:

- Primary endpoint: BCTQ-SSS change at 3 months
- Statistical test: Linear mixed model
- Two-tailed alpha: 0.05
- Standard deviation change in BCTQ-SSS at 3 months: 0.75 points
- Subject attrition: 15%

The results of this power analysis show that a sample size of 100 evaluable subjects provides 90% statistical power to detect a mean change of 0.2 points on the BCTQ-SSS at 3 months. To account for reasonable subject attrition, a minimum of 140 subjects will be enrolled in the trial.

10.2 ANALYSIS POPULATIONS

The primary statistical analyses will be performed on subjects who meet all study eligibility criteria and receive treatment with CTR-US. Subjects who withdraw from the study prior to treatment will not be included in the analysis.

10.2.1 Duration Variables

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

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

10.2.2 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	271-547
24 months	730	548-912

10.2.3 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 primary endpoint will be reported as the mean change in BCTQ-SSS at 3 months relative to baseline. Data will be reported as the mean change and 95% confidence interval. A linear mixed model will be the statistical test used to assess the primary endpoint, which accounts for the correlation inherent with bilateral procedures [41]. The study will be deemed successful if the mean BCTQ-SSS score at 3 months is statistically significantly lower than at baseline, as determined by a p-value less than 0.05 using the linear mixed model.

Time to return to normal daily activities and time to return to work among employed individuals will be reported as the median and interquartile range in each treatment group.

Longitudinally measured continuous outcomes (i.e., BCTQ-SSS, BCTQ-FSS, MHQ, Numeric Pain Scale, EQ-5D-5L) will be analyzed using a linear mixed model.

Adverse events will be reported using counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method. Calculation of AE incidence will be performed on a per-subject basis.

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. Subgroup analyses will be performed for subjects undergoing a unilateral or bilateral simultaneous procedure.

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 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 the 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. An Investigator who fails to perform tests or examinations as required by the protocol or 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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