| | |
|---|---|
| Title: | Internal Jugular Vein Compression Collar for Novel Symptomatic Treatment of Venous Pulsatile Tinnitus, |
| Short Title | IJV Collar for Pulsatile Tinnitus |
| Drug or Device Name(s): | Q Collar |
| FDA IND | N/A |
| Regulatory Sponsor: | Dr. Brian Sindelar, UNC Department of Neurosurgery |
| eIRB Number: | 21-3127 |
| Protocol Date: | 1/24/2022 |
| Protocol Number: | NCT05441540 |


**Study Principal Investigator**

**Benjamin S. Succop Jr.**
201 S. Elliott Rd
Chapel Hill, NC 27514
Phone 828-443-9726
email: benjamin_succop@med.unc.edu

**Faculty Advisor**
**Dr. Brian Sindelar**
170 Manning Drive
Chapel Hill, NC 27599
Phone 919-966-1374
email: bsind@email.unc.edu

## TABLE OF CONTENTS

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse event |

## ABSTRACT

Context: (Background)
Tinnitus is a medical condition with a wide variety of causes that is characterized by the perception of sound, often described as ringing or buzzing, without an external stimulus. Venous pulsatile tinnitus is a specific subtype of tinnitus with limited treatment options beyond surgical correction of underlying vascular defect. The clinical diagnostic hallmark of venous pulsatile tinnitus is relief of symptoms with light compression of the ipsilateral external jugular vein by the physician.
Objectives: (primary and important secondary objectives)
This study seeks to pilot an evaluation of whether an external jugular vein compression collar approved by the FDA for contact sports can provide symptomatic relief of venous pulsatile tinnitus. Furthermore, the study will pilot quality of life impacts of the device.
Study Design:
This is a non-blinded, interventional, prospective single cohort pilot study in which participants will be asked to evaluate the effect of wearing the collar, if any, on tinnitus symptoms. Secondary effects such as adherence, comfort, and quality of life while wearing the device will also be evaluated.
Setting/Participants:
This study will recruit 20 particpants complaining of pulsatile tinnitus who are patients at the UNC Meadowmont ENT outpatient clinic. Inclusion criteria will include those patients identified to have pulsatile tinnitus without a medical or surgical treatment upon thorough evaluation by the ENT service. Exclusion criteria will be those with non-pulsatile tinnitus, age, cerebral infarction (blockage or narrowing in the arteries supplying blood and oxygen to the brain) or severe head trauma, medical contraindications to restriction of blood outflow via the internal jugular veins, glaucoma, hydrocephalus, recent penetrating brain trauma (within 6 months), known carotid hypersensitivity, known increased intracranial pressure, idiopathic intracranial hypertension, known intracranial vascular malformation, central vein thrombosis, any known airway obstruction, or those not tolerating initial fitting of the collar.

Study Interventions and Measures:
The intervention device is marketed as the Q Collar, a light jugular vein compression device FDA approved for use in contact sports for individuals above the age of 13.
Main study outcomes will be degree of relief upon application of collar, sustainment of relief with home use of the collar, and quality of life metrics administereed at the beginning and end of the study.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title** | Internal Jugular Vein Compression Collar for Novel Symptomatic Treatment of Venous Pulsatile Tinnitus |
| **Funder** | Departmental Funds |
| **Clinical Phase** | Pilot Study |
| **Study Rationale** | Venus pulsatile tinnitus is a subtype of tinnitus that is refractory to medical treatment. Its defining symptom is patient perception of a whooshing sound in time with the heartbeat, and its characteristic diagnostic sign is relief of symptoms when the internal jugular vein is lightly compressed by the physician during examination. This study seeks to apply the defining diagnostic findings to treatment through use of a internal jugular vein compression collar approved by the FDA for contact sports. |
| **Study Objective(s)** | **Primary**<br>• To determine if an internal jugular vein compression collar significantly relieves symptoms of venous pulsatile tinnitus.<br>**Secondary**<br>• To determine quality of life impacts |
| **Test Article(s)**<br>*(If Applicable)* | The Q-Collar is a non-invasive device intended to be worn around the neck of athletes aged 13 years and older during sports activities to aid in the protection of the brain from effects associated with repetitive sub-concussive head impacts. |
| **Study Design** | Interventional single cohort pilot study. Data collected at original visit vai completion of tinnitus intensity and QOL scales, daily during 2-4 week follow up, and at follow up visit. All data collected through REDCAP administered scales into REDCAP password protected database |
| **Subject Population key criteria for Inclusion and Exclusion:** | **Inclusion Criteria**<br>1. Subjects age 18 and older<br>2. Subjects are diagnosed with pulsatile tinnitus<br>3. Subjects are patients at UNC ENT Meadowmont outpatient clinic.<br>**Exclusion Criteria**<br>1. Known risk factors for or existence of intracranial or intraocular hypertension, listed in detail in study protocol. |
| **Number Of Subjects** | 20 |
| **Study Duration** | Each subject's participation will last 2 weeks |

| | |
|---|---|
| **Study Phases**<br>**Enrollment**<br>**Study Treatment**<br>**Follow-Up** | Participants meeting inclusion/exclusion criteria at UNC Meadowmont will be invited to participate. Those who consent will be fitted with the collar. Then, the at home treatment phase will begin where they report on collar efficacy. Finally, a follow up visit will be conducted to complete exit surveys. |
| **Efficacy Evaluations** | Significant improvement in tinnitus symptoms while wearing collar. |
| **Safety Evaluations** | At intiial visit, team clinician will supervise collar fitting and evaluate for significant pain, discomfort, or adverse effect which will halt participation for that participant and be recorded. During at home study phase, participants will report any adverse effects with their daily recording of symptomatic efficacy. |
| **Statistical And Analytic Plan** | One sided t test on tinnitus intensity while wearing collar vs. while not wearing collar will evaluate primary endpoint of collar relief efficacy. ANOVA analysis of intensity differences will elucidate effect of time, if any. One sided t test will evaluate secondary endpoints of quality of life |
| **DATA AND SAFETY MONITORING PLAN** | Faculty mentor Dr. Brian Sindelar is monitoring all safety related aspects. These include the evaluation of the initial collar fit, collar use education, and reporting of adverse events during at home period. |

## EXAMPLE: TABLE 1: SCHEDULE OF STUDY PROCEDURES

| **Study Phase** | **Screening through EPIC** | **Initial consenting and fitting visit** | **Home Use (Daily for 14 days)** | **Follow up visit** |
|---|---|---|---|---|
| **Visit Number** | **N/A** | **1** | **N/A** | **2** |
| **Study Days** | **0** | **1** | **2-15** | **16** |
| Informed Consent/Assent | | X | | |
| Review Inclusion/Exclusion Criteria | X | | | |
| Demographics/Medical History | | X | | |
| Fit Collar | | X | | |
| Adverse Event Assessment | | X | | |
| QOL Data | | X | | X |
| Symptom Relief Data | | X | X | X |
| Adherence/Usage Data | | | X | |
| Adverse Event Reporting | | | X | |

# 1 BACKGROUND INFORMATION AND RATIONALE

Section 1 should be no more than 3 – 5 pages. Refer the reader to the applicable grant, or attached literature references for more detailed information.

## Introduction

Tinnitus is a medical condition with a wide variety of causes that is characterized by the perception of sound, often described as ringing or buzzing, without an external stimulus.1 It is extremely common, and has a prevalence in the United States ranging from 10% to 15% of the population.2 Persistent tinnitus can have a highly negative impact on quality of life, with individuals suffering from the condition manifesting higher rates of anxiety, depression, and lowered self esteem[3-5]. Pulsatile tinnitus is a specific subtype of tinnitus with limited treatment options. It is defined as a "whooshing" sound that pulsates in rhythm with the patient's heartbeat and generally manifests unilaterally.[6] Pulsatile tinnitus affects over 10% of the total tinnitus population, and it has a variety of both vascular, specifically venous, and nonvascular causes.[7] Unlike traditional tinnitus, medication is ineffective for most causes of pulsatile tinnitus.[8]

The provocative physical exam test for venous pulsatile tinnitus consists of the physician lightly compressing the internal jugular vein ipsilateral to the side of symptoms.[9] For patients with any venous cause of pulsatile tinnitus, symptoms will be relieved upon compression of the ipsilateral internal jugular vein and return when pressure is released by the examiner, a diagnostic finding with 93% sensitivity.[10] Given that the provocative exam finding for venous pulsatile tinnitus is relief of symptoms while compressing the neck, and that in many cases effective treatment options are limited for this condition, it is the goal of this study to test a FDA approved internal jugular vein compression collar as a symptomatic treatment for patients with this condition. By applying and sustaining the compression technique used by physicians on exam, it is hypothesized that this collar will achieve significant, perhaps even complete reduction in patient symptoms.

## 1.1 Name and Description of Investigational Product or Intervention

The current FDA approved internal jugular vein compression collar, marketed as the Q collar, is manufactured by Q30 Innovations Home. It is designed to be worn around the neck of individuals aged 13 and older. It functions by lightly compressing the internal jugular vein's bilaterally, safely increasing intracranial volume and intracranial pressure. The FDA approved neck collar device is made of a thermoplastic elastomer that is specifically fitted to an individual to provide mild internal jugular vein compression.[11] The product was developed and confirmed with ultrasonography to confirm appropriate fit and compression of the vein based on an athlete's neck circumference.[12]

## 1.2 Findings from Non-Clinical and Clinical Studies

(This section is only applicable for drugs, biologics and devices)

### 1.2.1 Non-Clinical Studies

The landmark paper by Smith et al. (2012) and Turner et al. (2012) demonstrated significant reduction in axonal injury following internal jugular vein compression in a rodent concussion model and this catapulted the translatable research specifically in concussion mitigation.[13] Interestingly during rodent behavioral testing in the application to blast concussive injury, a potential protective benefit of IJV compression against hearing injury was discovered by the faculty preceptor of this project, Dr. Brian Sindelar, and his team.[14-15] Through conversations with the student researcher and with colleagues at UNC otolaryngology, including faculty attending Dr. Matthew Dedmon, the collar was identified as a potential intervention for venous pulsatile tinnitus.

### 1.2.2 Clinical Studies

The use of jugular compression collars (Q-collar) during physical activity has recently been shown to reduce white matter alterations associated with head impact exposure in male and female athletes in sports including football, hockey, and soccer. Ongoing trials have demonstrated improvements in concussion biomarkers through clinical and radiographic measures.[13, 16-17]

## 1.3 Relevant Literature and Data

Pulsatile Tinnitus: Overview, Pathophysiology, Diagnosis

Pulsatile Tinnitus is the auditory perception of rhythmic noises in time with the heartbeat.[18] It can be either vascular or nonvascular in origin, and vascular presentations are divided into venous and arterial etiologies.[19] In vascular etiologies, the symptomatic presentation is a consequence of turbulence in vasculature near the cochlea, hence the synchronization with pulse.[20] This condition can have significant adverse effects on patient quality of life, leading to insomnia, difficulty concentrating, impaired audition, and mental health deterioration.[21] Venous abnormalities are the most common causes of pulsatile tinnitus, particularly structural and flow abnormalities in one or multiple intracranial or extracranial venous structures secondary to intracranial hypertension or anatomical variation.[22] Non-invasive imaging is an effective means of diagnosing pulsatile tinnitus, successfully identifying relevant phenomena in 40% to 70% of cases.[23-24] Furthermore, physical exam alone can distinguish venous causes from other ideologies of pulsatile tinnitus.[9] Specifically, relief of symptoms upon temporary manual neck compression of the ipsilateral IJV detects venous etiology with 93% sensitivity, a finding that is replicated with less sensitivity by a Valsalva maneuver or by turning the patient's head toward the side lateralizing with pulsatile tinnitus.[9-10]

Etiologies of Venous Pulsatile Tinnitus

Venous pulsatile tinnitus is caused by a broad differential of specific etiologies. All etiologies involve disturbed flow of an internal jugular vein and/or one of the veins or sinuses that drain into it.30 The turbulent flow is conducted by the skull base and mastoids to the cochlea, resulting in the perception of pulsating sound.[25-26] Broadly, these etiologies and their treatments can be classified by location of the abnormality: the lateral sinuses, emissary veins, jugular bulb, and internal jugular vein.[10] For cases in which the underlying etiology cannot be identified and corrected, there are few options for symptomatic

management. Cognitive behavioral therapy, meditation, and sound machines have all been employed for symptomatic management with limited success.[11]

*Surveys and Scales:*
The Tinnitus Handicap Inventory (THI) is a 25-item validated survey that evaluates the degree of impact a patient's tinnitus has on their quality of life.[27] It is currently the first line survey for systemic impacts of tinnitus and is attached at the end of this proposal. In addition, NIH validated patient reported outcome measurement information system (PROMIS) questionnaires on anxiety, depression, physical function, and satisfaction will be administered before and after the treatment period to evaluate the collar's broader impact on patient quality of life (see end of proposal).[28] Additionally, a custom tinnitus intensity scale modeled after the numerical pain scale with be used to assess relief. Lastly, a single item Likert scale inquiring about use of the collar when symptoms present will be applied to evaluate adherence.

### 1.4 Compliance Statement

This study will be conducted in full accordance with all applicable University of North Carolina Research Policies and Procedures and all applicable Federal and state laws and regulations All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with University of North Carolina IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

The purpose of the study is to determine the preliminary efficacy of an internal jugular vein compression collar for treating pulsatile tinnitus. Pilot data, if demonstrative of efficacy, will be used to apply for a multicenter grant.

### 2.1 Primary Objective (or Aim)

The primary objective of this study is to determine if an internal jugular vein compression collar can relieve symptoms of venous pulsatile tinnitus.

### 2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Determine if the collar effect varies with time
- Evaluate changes in quality of life as a result of collar use
- Compare home use with in clinic use

## 3 INVESTIGATIONAL PLAN

### 3.1 General Schema of Study Design

Before contact: Screen for eligibile participants through EPIC
First Visit: Consent, collect voluntary demographic and QOL data, fit collar, educate on use, evaluate symptom relief
Home Use:

### 3.1.1 Screening Phase

Potential subjects will be screened using the protocol inclusion and exclusion criteria through EPIC. A limited waiver has been requested for this information..

### 3.1.2 First Visit: Consent, Fitting, Education, Evaluation, Scales

During the first visit, potential participants identified through screening will be invited by a member of the study team to participate. If they agree, they will fill out consent forms, demographics, and preliminary QOL scales through REDCAP, as well as a baseline tinnitus intensity scale. At this point, a clinicial research team member not associated with their care will supervise fitting of the collar. The patient will be monitored for 10 minutes for adverse effects, then asked to complete the scale once more. Lastly, the patient will be educated on fitting and use of the collar, specifically not to use for more than 4 hours daily nor while sleeping, given the collar with its packaging and its instructions, and sent home for home use.

### 3.1.3 At Home Use (2 weeks)

Through a REDCAP link to their email or mobile device, the participants will daily record length of time using collar, average tinnitus intensity with and without collar, and any discomfort/adversity with collar use for 14 days consecutively.

### 3.1.4 Second Visit: Re-evaluation and Exit Scales

The participant will undergo refitting of the collar and evaluation of symptomatic relief under medical supervision once again. The participant will then complete QOL surveys again and an exit survey. This concludes participation.

## 3.2 Study Duration, Enrollment and Number of Sites

### 3.2.1 Duration of Subject Study Participation

16 days: 1 day for consent, fitting, and initial evlauation; 14 days for at home use, and 1 day for follow up.

### 3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately 1 investigative site in the United States. This site is the UNC Meadowmont ENT outpatient clinic.
Recruitment will stop when approximately 20 subjects are recruited. It is expected that approximately 22 subjects will be enrolled to produce 20 evaluable subjects.

## 3.3 Study Population

### 3.3.1 Subject Inclusion Criteria

1) Male or female age 18 years and older
2) Diagnosis of venous pulsatile tinnitus
3) Patient at UNC ENT Meadowmont Clinic

### 3.3.2 Subject Exclusion Criteria

- Increased presence of acid in the body or excessive blood alkalinity
- Open head injury (including in or around the eye) within the past six months
- Pseudotumor cerebri (false brain tumor)
- Presence of brain or spinal shunt
- Known seizure disorder
- Known airway obstruction
- Increased likelihood of blood clotting (coagulation)

- Skin injury, rash, or other abnormality on or around the neck
- age <18
- unable to provide written consent,
- history of neurological deficits,
- previous cerebral infarction (blockage or narrowing in the arteries supplying blood and oxygen to the brain)
- severe head trauma
- medical contraindications to restriction of blood outflow via the internal jugular veins
- glaucoma (narrow angle or normal tension - increased pressure in the eyes),
- hydrocephalus (increased fluid on the brain)
- recent penetrating brain trauma (within 6 months),
- known carotid hypersensitivity
- known increased intracranial pressure
- idiopathic intracranial hypertension
- known intracranial vascular malformation (e.g. aneurysm, arteriovenous malformation, cavernoma)
- central vein thrombosis
- not tolerating initial fitting of collar.
- Known pregnancy (this is not a direct contraindication but is being made out of an abundance of caution)
- Inability to speak or comprehend English (this pilot study does not have funding for translators)

# 4 STUDY PROCEDURES

## 4.1 Study Treatment Phase

Pre consent: identification of eligility according to inclusion/exclusion factors by chart review

### 4.1.1 Visit 1 (at Meadowmont ENT clinic visit)

- Explanation of Study
- Invitation to participate
- Consenting of participant
- Tinnitus intensity and quality of life scales through REDCAP
- Fitting of collar
- Evaluation of pain or discomfort
- 10 minute observation of patient with fitted collar
- Readministration of tinnitus intensity scale
- Education on collar use and misuse (emphasis on no more than 4 hours daily and only while awake
- Transfer of collar and materials to participant

### 4.1.2 Between Visit (at home) phase

Patient wears collar for <4 hours total while awake for symptomatic relief as needed

Patient reports daily average tinnitus intensity with and without collar, length of use, and any adverse events through REDCAP email/text link

Continues daily for 14 days

#### 4.1.3 Follow up visit

Reevaluation of tinnitus baseline without collar and with collar under medical supervision

Collection of collar and instruction materials

QOL surveys through REDCAP

Qualitative Exit Survey on collar

## 4.2 Subject Completion/Withdrawal

Example: Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, development of exclusion criteria, or adverse events  The Investigator or the Faculty Advisor may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons.  It will be documented whether or not each subject completes the clinical study. If the Faculty Advisor becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

#### 4.2.1 Early Termination Study Visit

Subjects who withdraw from the study will have all records deleted from the REDCAP database except for adverse events, which will be reported by the Faculty Advisor to the IRB.

# 5 STUDY EVALUATIONS AND MEASUREMENTS

## 5.1 Screening and Monitoring Evaluations and Measurements

### 5.1.1 Medical Record Review

Diagnosis of venous pulsatile tinnitus

Inclusion/Exclusion criteria

Year of Birth

Time since diagnosis (chronicity of current disease)

### 5.1.2 Physical Examination

- Date of birth
- Gender
- Race

## 5.2 Efficacy Evaluations

### 5.2.1 Diagnostic Tests, Scales, Measures, etc.

- Primary endpoint: symptom relief
    - Tinnitus aural intensity scale before and after collar administration at each visit and once daily for with collar and without collar intensity
- Secondary endpoint: QOL Impact
    - Tinnitus Handicap Index (Once at beginning of study, once at end)
    - Patient Reported Outcome Measurement Information System (PROMIS) scales in depression, anxiety, physical function, and satisfaction
- Secondary endpoint: Temporality
    - Aural intensity scale submissions will be plotted and compared over time course of study
- Secondary endpoint: Homes vs. clinic use
    - Supervised tinnitus intensity scale measurements will be compared to at home measurements to evaluate if perception of symptomatic intensity varies with environment

## 5.3 Safety Evaluation

Example: Subject safety will be monitored by observation and intervention of adverse events during the physician-supervised fitting period at the beginning of the study and by education of the participants to discontinue use of the collar with any significant change in physical well-being or onset of new symptoms and immediate reporting of that occurrence to the PI and Faculty Advisor through the REDCAP link.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Primary Endpoint

The primary efficacy endpoint will be the change in tinnitus intensity with and without the collar averaged within participants for each completion and across participants the study and

## 6.2 Secondary Endpoints

Secondary endpoints will include the following:

- The change in participant quality of life
- The effect of time on symptomatic relief
- The effect of medical supervision on symptomatic relief
- Adverse events (none are expected; however, the unlikely occurrence will be tabulated or a lack thereof shall be reported)

## 6.3 Statistical Methods

### 6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### 6.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects who complete the study.
The primary efficacy endpoint will be the change in tinnitus intensity with and without the collar, averaged within and across each patient's completion of the tinnitus scales. This means that there will be 16 paired collar and no collar measurements per patient, one at each clinic visit and one each day during the 14 day intervening period. The significance of this change will be evaluated using a unidirectional t-test.
Secondary endpoints will include the following:

- Temporality of symptom relief
    - Subjects with and without collar scores will be averaged for each day of the study, ANOVA testing will evaluate for the presence of a significant time component.
- Supervised vs. unsupervised use
    - The mean relief recorded at the first and second visit will be averaged and compared avross patients with the mean relief recorded during at home use using a bidirectional t test.
- QOL impacts
    - Evaluated for each scale using bidirectional t test

### 6.3.3 Safety Analysis

Adverse events are not expected; however, all subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized if at all present. SAEs (if any) will be described in detail.
AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

### 6.4 Sample Size and Power

For the principal endpoint, the tinnitus intensity scale ranges from 1-10. Assuming an average tinnitus intensity of 5 and a standard deviation of plus or minus 2 (such that 95% of the venous pulsatile tinnitus population has tinnitus intensity between 1 and 9). Intensity scale measurements will be averaged across individual submissions and across participants. With 16 paired evaluations per participant and 20 participants total, that creates 320 non collar tinnitus intesnity measures 320 collar intensity measures.
Setting an alpha of p=.05 and a power of 0.8 (beta=0.2), we expect a minimum effect of a 1 point decrease between the no collar and collar measurements. To be conservative, we will preserve the 2 point standard deviation assumed for the baseline measure to apply to the collar relief measure. These parameters allow us to evaluate the viability of our sample size.

$$n_g \doteq (z_{\alpha/2} + z_{\beta})^2 \frac{\sigma_1^2 + \sigma_2^2}{(\mu_1 - \mu_2)^2}$$

Where n is the number of analyses that will allow our minimum effect size to be significant
Substitution lends us the following
$n_g = (1.96+ 0.8416)^2*(2^2+2^2)/(2)^2$
$n_g = 15.86$

Not only is our overall study well in exceeding the number of intensity measurement differences needed to measure a significant effect; we will be able to assess the significant effect within each participant, given that each participant will complete both the with and without collar scales a total of 16 times. This gives our study strong internal and external validity.

### 6.5 Interim Analysis

Not planned. Significant safety adverse events would lead to termination of study.

# 7 STUDY DEVICE (STUDY DEVICE OR OTHER STUDY INTERVENTION)

## 7.1 Description

### 7.1.1 Usage

The collar can be worn while awake for no more than 4 hours daily by participants who meet the inclusion/exclusion criteria. This point shall be educated to participants who enroll.

### 7.1.2 Treatment Compliance and Adherence

The daily scales completed by participants during the at home period will contain reminders of the safety and adherence stipulations of the collar

### 7.1.3 Safety

Subject safety will be monitored by observation and intervention of adverse events during the physician-supervised fitting period at the beginning of the study and by education of the participants to discontinue use of the collar with any significant change in physical well-being or onset of new symptoms and immediate reporting of that occurrence to the PI and Faculty Advisor through the REDCAP link.

# 8 SAFETY MANAGEMENT

## 8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

## 8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

# 9 STUDY ADMINISTRATION

## 9.1 Treatment Assignment Methods

There will be no randomization or blinding of participants.

## 9.2 Data Collection and Management

All data will be collected and stored in a password-protected redcap database available only to access by study personnel. All study personnel are trained and certified in HIPAA. Data collection will occur through individualized links to REDCAP database administered on secure clinic iPad during visits or sent to participant phone/email during home phase.

## 9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. Data and records will not be used for any purpose other than conducting the study. All data and records will be stored in password protected REDCAP database.

No identifiable data will be used for future study without first obtaining IRB approval or determination of exemption.

## 9.4 Regulatory and Ethical Considerations

### 9.4.1 Data and Safety Monitoring Plan

The faculty advisor will oversee all aspects of safety monitoring. These include the supervised fitting and collar education under observation of research team position and the reporting of any adverse events during the at home phase.

The faculty advisor will monitor and review the study progress, subject safety, and the accuracy and security of the emerging data.

### 9.4.2 Risk Assessment

Not Greater than Minimal:

- Psychological
  - Wearing the collar might be embarrassing for some patients. This is averted through a flexible at home protocol in which they are only asked to wear the collar on an as needed basis for symptomatic relief and report their efficacy. Patients will be allowed to withdraw from the study at any time.
- Confidentiality
  - Any study has potential consequences a breach of confidentiality, this study will avoid those consequences through maintenance of the data in a password protected REDCAP database accessible only to the research team, all of whom are HIPAA certified.
- Discomfort
  - The device is FDA approved for contact sports, and there are no adverse risks for the indicated population. However there is a possibility that patients will feel discomfort when wearing it. Care will be made to ensure the fitting is optimize the patient's needs. Possibility of mild discomfort if collar used incorrectly; this will be averted by counseling patients to not use the collar while sleeping and by fitting the collar correctly to the neck circumference of the subject at the initial visit.

### 9.4.3 Potential Benefits of Trial Participation

Direct Benefits: Immediate symptom and quality of life improvement while wearing the collar during the study.
Indirect Benefits: contributing to widespread approval and access of color are used for venous pulsatile tinnitus population if effective in relieving symptoms by generating pilot data that will be used to justify clinical trials.

### 9.4.4 Risk-Benefit Assessment

Given that the device is approved by the FDA in a different setting, that is, contact sports, and given that use of the device in this application will follow all FDA recommendations regarding duration, use, and contraindications, we anticipate minimal risk to participants in the study. The benefits for participants are high given that it is likely the Color will be effective based on the principle of its use aligning directly with the chief diagnostic physical exam findings of this condition, that is, relief of symptoms upon light compression of the internal jugular vein. Therefore, in light of these observations, and given the fact that this condition has limited treatment options outside of surgery, we determine it worthwhile to proceed with the study.

## 9.5 Recruitment Strategy

A HIPAA waiver has been requested for the screening of eligible participants. The PI will then screen EPIC for patients meeting the exclusion and inclusion criteria to identify eligible participants. Recruiting will occur by a member of the study team not responsible for the patient's direct care engaging them during their clinic visit independent of their provider at UNC ENT Meadowmont.

## 9.6 Informed Consent/Assent and HIPAA Authorization

The principal investigator or one of the physician investigators not responsible for the patient's care will approach a patient meeting exclusion and inclusion criteria in person during one of their regular visits at UNC Meadowmont outpatient clinic. This will occur in the examination room after the patient's care provider has stepped out. At this point the patient will be asked about their interest in hearing about and possibly participating in a study that could help their tinnitus. If the patient acquiescence, the team member will then explain the study as well as its potential direct benefits and risks to the patient, emphasizing that the ultimate goal is scientific advancement instead of improved care. If the patient acquiesces, the consent forms and HIPAA form will be shared and explained to them. If they are still willing to participate, they will sign the forms and become a participant.

### 9.6.1 Individuals with Limited English Proficiency

For Spanish speaking eligible to participate, a certified translator either in person or over the phone will be used to help explain the study. Spanish consent forms and HIPAA forms will be provided.

### 9.6.2 Waiver of HIPAA Authorization

A limited waiver of HIPAA has been requested for identifying prospective patients. Prospective patients will be documented in REDCAP and deleted from the study database if they decline participation.

## 10 PUBLICATION

These data will be submitted for publication in a credentialed academic journal relevant to the field of otolaryngology and also submitted to a relevant academic conference for presentation as an abstract/poster. Data will only be published in aggregate, all identifying characteristics will be deleted prior to analysis and publication.

## 11 REFERENCES

[1] Bhatt, Jay M.; Lin, Harrison W.; Bhattacharyya, Neil. Prevalence, Severity, Exposures, and Treatment Patterns of Tinnitus in the United States. JAMA Otolaryngol Head Neck Surg. 2016;142(10):959-965. doi:10.1001/jamaoto.2016.1700

[2] Tunkel, D. E., et al. (2014). Clinical practice guideline: tinnitus. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery, 151(2 Suppl), S1–S40. https://doi.org/10.1177/0194599814545325

[3] Norun Hjertager Krog, Bo Engdahl, Kristian Tambs. (2010) The association between tinnitus and mental health in a general population sample: Results from the HUNT Study, *Journal of Psychosomatic Research* 69(3) 289-298, https://doi.org/10.1016/j.jpsychores.2010.03.008.

[4] Robert L. Folmer, Susan E. Griest (2000) Tinnitus and insomnia. *American Journal of Otolaryngology,* 21(5) 287-293 https://doi.org/10.1053/ajot.2000.9871.

[5] Crocetti, A.; Forti, S., Ambrosetti, U. et al. (2009) Questionnaires to evaluate anxiety and depressive levels in tinnitus patients. *Otolaryngology: Head and Neck Surgery.* 140(3) https://doi.org/10.1016/j.otohns.2008.11.036

[6] Sismanis, Aristidesa,b Pulsatile tinnitus, Current Opinion in Otolaryngology & Head and Neck Surgery: October 2011 - Volume 19 - Issue 5 - p 348-357 doi: 10.1097/MOO.0b013e3283493fd8

[7] Hofmann E, Behr R, Neumann-Haefelin T, Schwager K. Pulsatile tinnitus: imaging and differential diagnosis. Dtsch Arztebl Int. 2013 Jun;110(26):451-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3719451/

[8] Lenkeit CP, Al Khalili Y. Pulsatile Tinnitus. [Updated 2021 Jul 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553153/

[9] Lyu AR, Park SJ, Kim D, Lee HY, Park YH. Radiologic features of vascular pulsatile tinnitus - suggestion of optimal diagnostic image workup modalities.

Acta Otolaryngol 2018;138(2):128– 134. DOI:
10.1080/00016489.2017.1385847

[10] Jun, H. J., & Park, M. K. (2013). Cognitive behavioral therapy for tinnitus: evidence and efficacy. Korean journal of audiology, 17(3), 101–104. https://doi.org/10.7874/kja.2013.17.3.101

[11]Myer GD, Yuan W, Barber Foss KDet al. Analysis of head impact exposure and brain microstructure response in a season-long application of a jugular vein compression collar: a prospective, neuroimaging investigation in American football. Br J Sports Med 2016;50:127685.

[12] Myer GD, Yuan W, Barber Foss KDet al. The Effects of External Jugular Compression Applied during Head Impact Exposure on Longitudinal Changes in Brain Neuroanatomical and Neurophysiological Biomarkers: A Preliminary Investigation. Front Neurol 2016;7:74.

[13] Smith, David & Bailes, Julian & Fisher, Joe & Robles, Javier & Turner, Ryan & Mills, James. (2011). Internal Jugular Vein Compression Mitigates Traumatic Axonal Injury in a Rat Model by Reducing the Intracranial Slosh Effect. Neurosurgery. 70. 740-6.

[14] Sindelar, B., Shinners, M., Sherman, S., Novak, K., Erickson, K., Patel, V., Kubilis, P., Smith, D., Finan, J., & Bailes, J. E. (2017). Internal Jugular Vein Compression: A Novel Approach to Mitigate Blast Induced Hearing Injury. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 38(4), 591–598. https://doi.org/10.1097/MAO.0000000000001332

[15] Sindelar, B., Shinners, M., Sherman, S., Erickson, K., Patel, V., Kubilis, P., Finan, J. D., & Bailes, J. E. (2017). Reduction in Temporary and Permanent Audiological Injury Through Internal Jugular Vein Compression in a Rodent Blast Injury Model. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 38(8), 1205–1212. https://doi.org/10.1097/MAO.0000000000001500

[16] Myer GD, Barber Foss K, Thomas Set al. Altered brain microstructure in association with repetitive subconcussive head impacts and the potential protective effect of jugular vein compression: a longitudinal study of female soccer athletes. Br. J. Sports Med. 2019;53:1539-51.

[17] Myer GD, Yuan W, Barber Foss KDet al. Analysis of head impact exposure and brain microstructure response in a season-long application of a jugular vein

compression collar: a prospective, neuroimaging investigation in American football. Br J Sports Med 2016;50:127685.

[18] Douglas E. Mattox & Patricia Hudgins (2008) Algorithm for evaluation of pulsatile tinnitus, Acta Oto-Laryngologica, 128:4, 427-431.
DOI: 10.1080/00016480701840106

[19] Evan Kao, Sarah Kefayati, Matthew R. Amans, Farshid Faraji, Megan Ballweber, Van
Halbach, David Saloner. (2017). Flow patterns in the jugular veins of pulsatile tinnitus patients, *Journal of Biomechanics,* (52) 61-67
https://doi.org/10.1016/j.jbiomech.2016.12.008.

[20] Dobie RA. Overview: suffering from tinnitus. In: Snow JB, editor. Tinnitus: theory and management. Lewiston, NY: BC Decker; 2004. pp. 1–7.

[21] Dong C, Zhao PF, Yang JG, Liu ZH, Wang ZC. Incidence of vascular anomalies and variants associated with unilateral venous pulsatile tinnitus in 242 patients based on dual-phase contrastenhanced computed tomography. Chin Med J (Engl) 2015;128(5):581–585.

[22] Sonmez G, Basekim CC, Ozturk E, Gungor A, Kizilkaya E. Imaging of pulsatile tinnitus: a review of 74 patients. Clin Imaging 2007;31(2):102–108.

[23] Vattoth S, Shah R, Curé JK. A compartment-based approach for the imaging evaluation of tinnitus. AJNR Am J Neuroradiol 2010;31(2):211–218.

[24]Amans MR, Haraldsson H, Kao E et al. MR Venous Flow in Sigmoid Sinus Diverticulum.
AJNR Am J Neuroradiol 2018;39(11):2108–2113.
DOI: https://doi.org/10.3174/ajnr.A5833

[25]Eisenman DJ, Raghavan P, Hertzano R, Morales R. Evaluation and treatment of pulsatile tinnitus associated with sigmoid sinus wall anomalies. Laryngoscope 2018;128(Suppl 2):S1– S13. https://doi.org/10.1002/lary.27218

[26] Li B, Cao X, Liu X et al. Interventionai Diagnosis and Treatment of Vasculogeneic Pulsatile Tinnitus. J Otol 2014;9(1):7–15.

[27] Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the Tinnitus Handicap Inventory. Archives of otolaryngology--head & neck surgery, 122(2), 143–148.
https://doi.org/10.1001/archotol.1996.01890140029000

[28] Patient-Reported Outcomes Measurement Information System Database
https://commonfund.nih.gov/promis/index

## APPENDIX

All relevant scales, documents, and figures have been appended to the IRB