Tinnitus Retraining therapy Trial protocol

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Aims/Objectives/Research Question/Hypotheses: The purpose of the Tinnitus Retraining Therapy Trial (TRTT) is to assess the efficacy of Tinnitus Retraining Therapy (TRT) as a treatment for severe debilitating tinnitus in a randomized trial. TRT is a non-medical intervention that uses directive counseling (DC) and sound therapy (ST) to habituate the patient's associated negative emotional reactions to tinnitus, its perception, and ultimately, its impact on the patient's life. Johns Hopkins is the Data Coordination Center (DCC) for this the Tinnitus Retraining Therapy Trial, which will test the efficacy of TRT as a therapy for severely debilitating tinnitus. The DCC will not screen nor have any direct contact with trial participants. Study forms will be keyed by the Clinical Centers into a web-based data management system that uses SSL encryption during transmission of data from Clinical Centers to the DCC. The study forms' data transmitted by the Clinical Centers and received by the DCC are identified by name code and study I.D. only. There are no personal identifiers on these forms.

1. Background and Rationale: Tinnitus is the perception of sound in the absence of a corresponding external sound. The majority of the tinnitus patients report no distress due to the condition, but about 5%, or about 2 million individuals require professional help for the treatment of tinnitus because it significantly impacts their work, normal daily activities, and/or sleep (Jastreboff and Jastreboff, 2000). It is this latter group of severely impaired tinnitus patients who will become study participants in this project.

Previous clinical approaches to patients with debilitating tinnitus have generally been unsuccessful in alleviating the distress caused by the condition (Dobie, 1999). Tinnitus retraining therapy (TRT) is a non-medical intervention that uses DC and low-level ST to habituate the patient's associated negative emotional reactions to tinnitus, its perception and, ultimately, its impact on the patient's life (Gold *et al.*, 2000). The first component of TRT, DC is thought to reduce the relevance of the tinnitus in the patient's life. The second treatment component, ST, acts by reducing the contrast between background neuronal activity and the tinnitus-related neuronal activity, facilitating habituation of the tinnitus perception.

Clinical studies at the University of Maryland, where TRT was pioneered, and elsewhere, suggest that TRT is an effective treatment, (Jastreboff and Jastreboff, 2000, Berry *et al.* (2001, Hazell, 1999), but it is not clear if both DC and ST are necessary for a full treatment effect (Jastreboff and Jastreboff, 2000, McKinney *et al*). There have been no rigorous, controlled clinical trials to test the efficacy of TRT or control for the treatment effects of DC and ST. Current reviews of TRT studies are critical of methodological shortcomings in these studies, including lack of double-blind designs, randomized treatment assignment, and placebo controls (Leal 1998; Philips 2010)..

References:

Berry JA, Gold SL, Frederick EA, Gray WC, Staecker H. Patient-based outcomes in primary tinnitus patients undergoing tinnitus retraining therapy. Presented at the Trilogical Society, Southern Section, Marco Island, FL, Jan, 2001.

Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope*. 1999. 109:1202-11.

Gold SL, Formby C, Gray WC. Celebrating a decade of evaluation and treatment: the University of Maryland Tinnitus & Hyperacusis Center. *Am J Audiol*. 2000. 9:69-74.

Hazell JWP. The TRT method in practice. *Proceedings of the Sixth International Tinnitus Seminar* (p. 92-8). London, UK. 1999.

Jastreboff PJ, Jastreboff MM. Tinnitus Retraining Therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. *Am J Acad Audiol* 2000. 11:162-77.

Leal P, Milne R. Tinnitus retraining therapy. Development and Evaluation committee report No. 83. The Wessex Institute for health Research and Development. At http://www.epi.bris.ac.uk/rd

McKinney CJ, Hazell JWP, Graham RL. An evaluation of the TRT method: *Proceedings of the Sixth International Tinnitus Seminar* (p. 99 – 105). London, UK. 1999a.

Philips JH, McFerran D. Tinnitus Retraining Therapy (TRT) for tinnitus. *Cochrane Database of Sytematic Reviews* Issue 3. Art No. CD007330 DOI: 10.100214651858.CD0037330 pub 2.

2. Participants:

The TRTT will enroll approximately 228 human subjects with debilitating tinnitus, defined as a score of 40 or more on the Tinnitus Questionnaire and with tinnitus of at least one year's duration. Study participants include individuals eligible to receive medical care at a military healthcare facility, including both active and retired military members as well as family members. Special classes of subjects and vulnerable populations will not be included in this trial. Participants will be recruited from participating Clinical Centers (military healthcare facilities) through colleague referral and community recruitment.

Inclusion criteria

- Age 18 years or above
- Primary complaint of continuous, chronic (≥12 months) subjective tinnitus
- TQ score ≥ 40
- Unaided hearing sensitivity bilaterally within the audiometric range from normal to mild hearing loss
- Ability to understand counseling and to comprehend and complete English language questionnaires

Exclusion criteria

- Predisposing disease with tinnitus symptoms amenable to medical or surgical intervention
- Clinical treatment for tinnitus within previous year
- Impaired hearing defined as audiometric thresholds ≥30 DB HL at and below 2,000 Hz and ≥ 40 DB HL at 4,000 Hz
- Evidence of malingering or exaggeration of tinnitus or hearing symptoms
- Active involvement in tinnitus-related litigation (related to disability compensation from the US military)
- Diagnosis of pulsatile tinnitus, somatosounds, or objective tinnitus
- Presence of significant hyperacusis that, based on best clinical judgment, cannot ethically be randomized to, and treated, in the standard of care treatment arm. People with significant hyperacusis, even with the presence of tinnitus, require specific care for hyperacusis that could not be administered within the standard of care treatment arm.
- Presence of fluctuating hearing loss, as reported by the individual, at a level that would interfere with the reliability of testing, based on the best clinical judgment of the examining physician**.**
- Treatment for head or brain trauma (i.e., concussion, blunt trauma, blast injury, or skull fracture) 24 months before being screened or enrolled, or presence of head or brain injury requiring treatment**.**
- Inability to complete audiological testing or clinical trial protocol
- Unable to participate fully in the trial or complete all follow-up visits because of an active or ongoing mental health condition, as assessed by best clinical judgment.
- Unwilling to be randomized
- Drug or alcohol abuse or other condition to hinder compliance with treatment or follow-up procedures
- Unwilling or unable to provide informed consent

Eligible study participants in the TRTT will be randomized to one of 3 treatment arms: 1)TRT (DC and conventional sound generators); 2) partial TRT (DC and placebo sound generator); and 3) SC (standard of care as administered in the military). The primary outcome to be measured in the TRTT will be the difference in scores on the Tinnitus Questionnaire (TQ) from baseline to 18 months follow-

up. There will be three comparisons: 1) TRT versus SC; 2) TRT versus partial TRT, to evaluate the separate effect of sound therapy, under the assumption that placebo sound generator will not provide any meaningful sound therapy beyond that found in SC; and 3) partial TRT versus SC, to evaluate the separate effect of DC. The DCC designed the TRTT to have sufficient power to detect a minimal clinically important difference in the TQ, i.e., a 10 point difference between TRT and SC groups on change in TQ global scores longitudinally assessed over the course of follow-up and a 7-point difference on TQ score by TRT components, DC and ST. Based on a literature survey and consultation with experts, we estimated the variance for the TQ change scores to be 12.5, but also explored the effect of a larger variance of 14.

Using a type I error of 0.05 (divided by three to account for the multiple comparisons) and a two-sided test with Power and Sample Size Calculations (Dupont and Plummer), we estimate that a total of 228 study participants or 76 study participants in each of the 3 groups will be required to yield at least 80% power to detect a 7-point difference for analyses of the TRT components, ST and DC. This sample size will provide for greater than 95% power for the primary analysis (comparison of TRT to SC) and takes into account a 10% drop-out rate. We will still have 80% power to detect an 8-point difference in TQ score is the standard deviation for TQ is as high as 14.

Identities of individual participants will be known only to Clinical Center personnel. All data records entered into the research database will be free of the personal identifiers as specified in section 164.514(b)(2)(i) of the federal Privacy Rule, and identified in the Data Coordinating Center database only by a unique participant ID and an alpha-code. It is possible that indirect identifiers may be included in the database, i.e., variables that could be used in a process of deductive triangulation to identify a participant.

Primary Objectives: Evaluate the efficacy of:

- **TRT** by comparing TRT (Directive counseling (DC) and sound therapy (ST) using conventional sound generators (SGs)) versus usual care;
- **ST** by comparing partial TRT (DC and conventional SGs) versus partial TRT (DC and placebo SGs); and
- **DC** by comparing partial TRT (DC and placebo SGs) versus the standard of care:

in reducing the severity of debilitating tinnitus as measured by change in TQ score from baseline to 18 months post-treatment onset.

Type of study

- Randomized, placebo-controlled (sound therapy), clinical trial
- Multi-center
- Fixed sample sizes

Treatment Groups:

- TRT: DC and conventional NG
- Partial TRT: DC and placebo NG
- Standard of Care (SC)

Treatments

- Directive counseling: Two-hour educational session during which the patient is given information regarding the nature of the tinnitus problem and related problems such as hearing loss and sound intolerance. Visual aids are used in DC to: review the audiological/tinnitus/hyperacusis evaluation; provide instruction on anatomy and physiology of hearing and tinnitus; introduce the Jastreboff neurophysiological model of tinnitus and related concepts of habituation, and describe and recommend the use of ST and environmental sound in the habituation process.

- Conventional SGs: in-the-ear or outside-the-ear devices that generate low-level noise, which is set at the patient's mixing point; (i.e., the noise level that just blends with the study participant's tinnitus).
- Placebo SGs: in-the-ear or outside-the-ear devices that initially generate low-level noise at the patient's mixing point and then systematically decay to silence. The noise levels from the placebo SGs begin to attenuate 40 minutes after the initial setting of the devices and become undetectable 30 minutes later. Placebo NG devices reset to the original mixing point setting when the devices are repositioned outside the patient's ears.
- Standard of Care: Education, assurance, and recommendations as typically delivered in US military medical centers, and based on results of a survey of military study audiologists.

Outcomes

- Primary: Change in TQ global score assessed at the end of treatment at the 18-month follow-up visit (relative to the baseline TQ global score) and change as assessed longitudinally at 3, 6, 12, and 18 months follow-up.
- Secondary
  - Change in TQ sub-scale scores at follow-up
  - Change in Tinnitus Handicap Inventory score at follow-up
  - Change in Tinnitus Functional Index score at follow-up
  - Change in TRT Interview visual analogue scales at follow-up
  - Change in the Digit Symbol Substitution Test at follow-up
  - Change in general health-related quality of life as assessed by the EuroQOL
  - Change in psychoacoustic variables at follow-up, including tinnitus pitch and loudness match, and loudness discomfort level

Blinding

- DC treatment assignment not blinded to treating audiologist
- Treatment assignment blinded to audiologist performing audiometric assessments
- ST treatment assignment blinded to study participant
- ST treatment assignment blinded to treating audiologist
- ST treatment assignment blinded to personnel involved in outcome assessments
- Treatment assignment not blinded to Data and Safety Monitoring Board
- Treatment assignment not blinded to statistician

Randomization

- Equal probability of assignment to any treatment group
- Randomization schedules generated by computer
- Variable block sizes of 3, 6, or 9, randomly selected
- Stratification by Clinical Center
- Allocation concealment: Treatment assignment requested online following completion of all baseline tests and signed informed consent; the Clinical Center accesses the randomization page of the TRTT website which is designed and maintained by the DCC.

Recruitment

- Recruitment period = approximately 30 months
- Recruitment rate = 7 to 8 participants per month (about 1-2 participants per month per Clinical Center)

Data analysis

- Primary analysis by assigned treatment group (intention-to-treat principle)
- Initial descriptive analyses
- Assessment of baseline variables for interaction or confounding

- Use the t-test (or Wilcoxon rank-sum test) to evaluate the differences in change in TQ global score from baseline to the 18 month follow-up visit between the three treatment groups while using the Bonferroni correction for multiple testing.
- Use linear regression to model the association between the change in outcomes (baseline to 18 months) and covariates of interest (treatment and baseline characteristics).
- Graphically summarize the change in outcomes over time by plotting the mean and standard deviation of each outcome for each treatment group for each visit.
- Use Generalized Estimating Equations (GEE) to model the effects of treatment assignment and baseline characteristics upon the outcomes measurements over time.
- Sensitivity analyses and multiple imputation methods will be used to evaluate and adjust for the effect of missing data.
- No planned interim analysis, unless requested by the Data and Safety Monitoring Board

Each potential study participant eligible after initial screening will undergo a baseline eligibility evaluation, and if eligible, a randomization visit, 2 treatment visits, and 4 follow-up visits.

The Baseline Eligibility Visit comprises completion of the following assessments:
1. Tinnitus Questionnaire (TQ), which measures five domains related to the impact of tinnitus on an individual, including psychological distress, intrusiveness, hearing difficulties, sleep disturbances, and somatic complaints.
2. Medical and Tinnitus History, which collects information on tinnitus and medical history, including history of allergies, autoimmune disease, head trauma, and the need for further tests.
3. Beck Depression Index Fast Screen (BDI-FS), which is a measure of depressive symptoms, identifies potential study participants with clinical depression, defined for the TRTT as a score of 4 or greater or endorsement of item # 7 (suicidal thoughts or wishes).
4. Tinnitus Initial Interview Form, which obtains information from participants about their tinnitus, including its etiology, and related hearing sensitivity.
5. Audiological/Tinnitus/Hyperacusis (ATH) examination, conducted for both ears, will include pure-tone thresholds, audiometric speech tests, tympanometry, acoustic reflex measures, and otoacoustic emission screening.
6. Physical examination which is performed to determine whether there is any physical cause for the participant's tinnitus and to record results of any laboratory tests required to confirm eligibility.
7. Laboratory and Other Tests, if deemed necessary by the study otolaryngologist following the physical examination

If the patient is eligible, Study staff will discuss randomization with the Study Participant. If the Study Participant is willing to be randomized to treatment, then s/he will complete the following to provide baseline values for comparison to follow-up. These forms must be completed before the randomization assignment is accessed online:

8. Tinnitus Handicap Inventory, which assesses the functional, emotional, and catastrophic effects of the tinnitus.
9.Tinnitus Functional Index (TFI), which is a tinnitus specific, validated health related quality of life instrument with 25 items and an eight-factor structure including: intrusiveness, reduced sense of control, cognitive interference, sleep disturbance, auditory difficulties (related to tinnitus), relaxation interference, reduced quality of life, and emotional distress. The TFI is more sensitive to change in domains affected by tinnitus than the Tinnitus Reaction Questionnaire (TRQ). The TFI is able to measure additional domains of quality of life affected by tinnitus over and above those measured by the TRQ. Adding an additional 25-item instrument would be too burdensome for the study population, so we replaced the TRQ with the TFI.

10. State-Trait Anxiety Inventory (STAI), which determines the individual's personality trait "anxiety" and is used as a risk factor for treatment efficacy
11. Positive and Negative Affect Schedule (PANAS), which is a measure of a person's feeling and emotions and is used as a risk factor for treatment efficacy
12. Life Events Checklist, which collects information about life events that affect stress and anxiety and is used as a risk factor for treatment efficacy
13. Euro Quality of Life (EQ), which is an instrument used to assess general health-related quality of life. It consists of 5 items assessing difficulty in performing activities of daily living.
14. Digital Symbol Substitution Task (DSST), which is a test of cognitive function that assesses the ability of an individual to focus attention to a task and to recall.
15. Hearing Handicap Inventory, a 10-item form that measure the respondent's perception of hearing impairment and will be used as a risk factor for treatment efficacy.

Each randomized participant enrolled into the TRTT will be seen for the following visits after randomization:
1. Initial Treatment Visit, which is scheduled within 2 months of randomization, but is allowed to take place on the same day and immediately following randomization. Under circumstances approved by the Steering Committee, the initial treatment visit may take place after 2 months.The initial treatment visit will include the following, as randomly assigned:

- **DC:** The Study Audiologist explains the results of the ATH evaluation, educates the study participant about the anatomy and physiology of the normal auditory system, describes how the central auditory system and higher cortical processes may interpret an auditory signal and how this processing relates to the participant's tinnitus perception, describes the Jastreboff model of tinnitus, and sets goals with and for the individual participant. Visual aids used include a flip-chart presentation specifically designed for the TRTT and a three-dimensional model of the ear. Each participant is counseled individually, along with any family members who may be present during the session. At the Initial Treatment Visit, which usually lasts approximately 2 hours, the Study Audiologist systematically presents information designed to help the Study Participant change the way that he or she views his or her tinnitus and/or hyperacusis (painful sensation to noise), addresses the individual participant's concerns, and recommends strategies to help the participant achieve the long-term goal of habituating the awareness of and annoyance to his or her tinnitus. Sufficient time is allowed to answer the participant's questions and to ensure that he or she understands all information presented and the treatment goal of reducing the impact of tinnitus in the participant's life.

- **Standard of care clinical consultation** is defined as the currently offered treatment for individuals with severe tinnitus by the participating military sites. The protocol for the typical standard of care for tinnitus in the military was determined by conducting a survey of the practice patterns reported by audiologists at military medical centers who had initially agreed to serve as Clinical Centers in the TRTT and includes components of care that are provided by a majority of providers and/or most of the time in cases where a component was usually provided. Visual aids include a flip-chart presentation specifically designed for the TRTT and a three-dimensional model of the ear. During the standard counseling session, the Study Audiologist will explain the results of the ATH evaluation and educate the Study Participant about the anatomy and physiology of the normal auditory system. The counseling session will be patient-driven in that attention will be focused on those aspects that are of most concern to the individual patient (e.g., inability to sleep because of the tinnitus). Sufficient time is allowed to answer the participant's questions and to ensure that he or she understands all information presented and the treatment goal of reducing the impact of tinnitus in the participant's

- **Placement and activation of SGs for study participants assigned to conventional or placebo SGs:** Sound therapy will be achieved through use of a digital equivalent of the Tranquil model sound generator, manufactured by General Hearing Instruments, Inc. (GHI). Both

conventional and placebo SGs will be housed in a non-occluding, in-the ear or outside-the-ear instrument that offers adjustment to a "zero" (fully quiet) noise floor. GHI will provide both the standard and the placebo SG devices. The placebo SG will have specially designed sound properties, closely resembling key properties of the standard SG, and a physical appearance identical to the standard instrument so that neither the Study Audiologist nor the Study Participant will be aware of which sound treatment the participant is receiving. The placement, activation, and orientation to the SGs will take place after the DC session has been completed. Typically, orientation requires about one hour, and includes instruction to the participant on the use and care for the instruments, correct volume settings, schedule of use, and placement and removal of instruments.

2. Second treatment Visit will be scheduled 1 month after the initial treatment visit and will include:

- Reinforcement counseling for either DC or standard of care clinical consultations
- Review of proper placement, use, and maintenance of SGs for participants assigned to TRT or partial TRT

Follow-up visits are scheduled at 3, 6, 12, and18 months after the initial treatment visit. Data collected at Follow-up Visits include the following:

Visit	Questionnaires										
	TQ	**THI**	**TFI**	**BDI**	**FTI**	**DSST**	**STAI**	**PANAS**	**LEC**	**EQ**	**HHI**
3 mo	✓	✓	✓	✓							
6 mo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12 mo	✓	✓	✓	✓							
18 mo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

TQ Tinnitus Questionnaire
THI Tinnitus Handicap Inventory
PANAS Positive & Negative Affect Schedule
LEC Life Events Checklist
DSST Digit Symbol Substitution Task
STAI State-Trait Anxiety Inventory
BDI Beck Depression Index-Fast Screen
FTI Follow-up TRT Interview
HHI Hearing Handicap Inventory
EQ EuroQOL
TFI Tinnitus Functional Index

Visit	ATH Evaluation Measures					
	audiometric pure tone	**speech recognition threshold**	**tinnitus pitch match**	**tinnitus loudness match**	**loudness discomfort level**	**word recognition scores**
1 mo					✓	
3 mo					✓	
6 mo	✓	✓	✓	✓	✓	✓
12 mo	✓	✓	✓	✓	✓	✓
18 mo	✓	✓	✓	✓	✓	✓

Brief data analysis plan and description of the nature of variables to be derived:

Initial analyses will be descriptive in nature, using means, standard deviations, and proportions to describe baseline characteristics of the sample for all participants combined and by intervention group. Distributions of continuous variables will be examined for symmetry, and transformations will be considered for seriously skewed variables. For continuous variables, one-way analyses of variance will be used to compare the intervention groups on demographic and other baseline characteristics; the purpose is to assess comparability among the randomly assigned groups. For dichotomous or other categorical variables, chi-square tests will be used to compare intervention groups, and enrolled/excluded groups. Pearson correlation coefficients will be calculated to assess the strength of the associations among the various outcome measures, and to examine associations of other covariates with outcome measures; such potential confounding variables will be considered for inclusion in secondary analyses involving regression models. All primary analyses will be based on the "intention to treat" principle.

The primary outcome variable will be change in the TQ score. We will use spaghetti plots for initial exploratory analyses and longitudinal data analyses as our primary analytic method. Indicator variables will identify group and their coefficients in the models represent the primary focus on group differences. Adjustment for covariates such as age and sex can easily be accounted for in this class of models. Mean TQ scores will be compared between two treatment groups using Generalized Estimating Equations (GEE). The basic model will include terms to account for effects of Clinical Center, Audiologist, treatment group, personality traits as measured by the STAI and PANAS, and perceived hearing impairment as measured by the HHI. Similar models will also be run for the secondary objectives. Other personality characteristics of interest, including age, gender, and minority status will also be included. We will also explore whether treatment with TRT or its components differentially impacts individuals with hyperacusis in conjunction with tinnitus versus those with only tinnitus, and whether and by how much initial tinnitus severity affects treatment efficacy.

For the secondary efficacy analyses looking at the difference between TQ score at baseline and 18 months, we will compare TQ mean scores at 18-month in the treatment phase among treatment groups using Analysis of Covariance (ANCOVA), adjusting for baseline TQ scores, heterogeneity of tinnitus status in the patient population, and important baseline covariates and variables that may be unbalanced at baseline (even with randomization) and are potentially related to TQ score. We will also use GEE for this analysis.

The secondary outcome variables are the same for both the primary objective and the secondary objectives. For both the objectives, all of the longitudinally assessed variables (for example, subscales of TQ, THI, TFI, TRT-VAS, DSST, and LDL) will be treated as the TQ score (primary efficacy outcome analysis) using GEE. The respective mean scores will be compared between corresponding treatment groups (as described in the previous section) over the entire treatment phase. Both the differences in mean responses between treatment groups and the rate of change over time will be of interest in these analyses.

When a patient's data are not available, we will compare participants who are lost to follow-up by with those who complete the study on baseline characteristics and treatment assignment to assess characteristics of those who do not complete the study. We will address missing data by applying a consistent missing value strategy, multiple imputation, as appropriate to the analyses of the primary and the secondary outcome measures. Since GEE procedures analyze only reported data we will compare its results with the imputation methods for consistency. This comparison is a form of sensitivity analysis.

Screening for eligibility and assignment to study group: Screening will be completed either in person or over the telephone at participating Clinical Centers. If the potential participant is willing to be considered for enrollment in the TRTT, then the Clinical Coordinator or the Clinical Center Director asks him or her to schedule a Baseline Eligibility Visit.

Participants presenting at the Baseline Eligibility Visits will undergo informed consent to allow the evaluation for the TRTT, and if eligible, randomization to treatment. It is expected that all clinical center institutions will also require the participant to sign a HIPAA (Health Insurance Portability and Accountability Act) authorization form.

Eligibility status is determined by evaluating the results of the laboratory, medical and audiological/tinnitus/hyperacusis examinations at the conclusion of the Baseline Eligibility Visit. The Clinical Center Director will further discuss participation in the randomized trial with eligible study participants and answer any and all questions related to participation in the study. If the potential participant is willing to consider enrollment, then a Randomization Visit is scheduled. Participants choosing to participate will be randomized to treatment. Randomization takes place when Clinical Center staff accesses the randomization page of the TRTT website, maintained by the Data Coordinating Center, to obtain a randomization assignment by entering the Study Participant's identification number and matching alpha-code. At this time the TRTT inclusion and exclusion criteria will be reviewed to ensure that the person to be entered is actually eligible to participate, that all baseline forms have been completed, and that informed consent has been obtained. Randomization will be stratified by Clinical Center. The system will provide the randomized treatment assignment. The participant has an equal probability of assignment to one of three groups: 1) TRT; 2) Partial TRT or 3) Standard of care.

We will use a placebo SG developed by the TRTT in order to determine the separate effects of the two components of TRT: DC and sound therapy. By comparing study participants assigned to partial TRT (DC and placebo SG) with those assigned to full TRT (DC and conventional SG), we will be able to determine the effect of sound therapy alone. By comparing partial TRT (DC and placebo SG) with the standard of care, we will be able to determine the effect of DC alone. In both cases, we make the assumption that the placebo SG does not provide meaningful sound therapy beyond that which occurs in the standard of care group. Use of the placebo SG will not deny study participants any type of sound therapy that is currently recommended in the military for individuals with tinnitus. Study Audiologists will not know whether the SG is a conventional or a placebo SG. Given that numerous studies show that the size of treatment effect is larger when the treatment assignment is not blinded (Pildal, J et al. Int. J. Epidemiol. 2008 37:422) we believe that it is necessary to blind study participants and audiologists as much as possible to estimate the true treatment efficacy. We will probably not be able to blind study participants to the type of counseling session to which they have been assigned. The study participant may guess the treatment assignment through the treatment session content, and the treating study audiologist obviously will not be blinded. To partially overcome this limitation, the study will require a second audiologist, who will remain blinded to the type of counseling session administered, to conduct all audiometric/tinnitus/hyperacusis testing and administer study questionnaires to study participants for completion at follow-up.

Participants in the control group will receive the standard of care for debilitating tinnitus as currently administered in military healthcare facilities.

No participant will be removed from the study for any reason. Therapy is expected to have been completed before the end of the study. The counseling treatment options within the TRTT take place during the first and second treatment visits and it is expected that all participants will receive counseling, either DC or standard of care. Reinforcement counseling may continue as needed throughout the course of the trial, but usually does not extend past one year. It is possible that participants withdrawing before the end of the study may not receive the full scope of counseling as designated by assignment group within the TRTT, but even if a participant withdraws from the study,

s/he will continue to receive standard military medical care. SGs are provided to the study participants assigned to TRT or partial TRT at the first treatment visit, and will not be returned even if the participant withdraws before the end of the trial.

Study participants will continue to receive usual medical care within the military medical facilities. The only circumstance which might require additional care that is related to the participant's tinnitus is the possibility of onset of depression. Clinical Centers will monitor study participants at each follow-up visit for the onset of depression by repeated measures of the Beck Depression Index Fast Screen over the course of the TRTT. Any participant with a score of 4 or greater or endorsement of item # 7 (suicidal thoughts or wishes) on this instrument will be referred by Clinical Center Directors to an appropriate health care provider.

The projected TRTT sample size is 228, or 76 participants per treatment group based on a smallest clinically meaningful difference in TQ score of 7. The table below illustrates the sample size sensitivities to changes in the expected differences in TQ scores and to a larger standard deviation (14 instead of 12.5) at power of 80, 90, or 95%.

Difference in TQ score	**Power (SD = 12.5)**			**Power (SD = 14)**		
	80%	**90%**	**95%**	**80%**	**90%**	**95%**
10	113	147	**173**	140	**180**	**217**
8	173	**223**	270	**217**	280	337
7	**228**	290	350	283	363	437

Study results will not be reported to study participants until the conclusion of the study. Draft letters describing the results of the study will be prepared jointly by the Data Coordinating Center Director and Study Chair and distributed to Clinical Centers. They, in turn, will distribute copies of these letters describing study results to Study Participants.

Data sent to the Data Coordinating Center will identify study participants only through use of a study assigned ID and alpha-code. The only personal identifier that will be collected is birth date, which, although stored in the database, will be converted to age for all analyses. Data forms at Clinical Centers will be disposed of according to local IRB procedures, which include provisions for maintaining participant confidentiality. Typically Clinical Centers are required to maintain study records from 3 to 7 years after completion of the study.

Study participants will be recruited at Clinical Centers through colleague referral and military community recruitment. Investigators at each center will be responsible for disseminating information about the TRTT to referring physicians. The Data Coordinating Center and Study Chair's office will assist through development of study recruitment materials. Study-wide materials include:

- A set of standard instructional slides for use in training venues to educate new referring physicians and clinical staff about the TRTT, the clinical trial protocol, and entry requirements for Study Participants.
- A study brochure for prospective participants describing tinnitus, the goals and methods of TRTT, and the need for a clinical trial. The brochure will be designed to have multi-cultural appeal to enhance the recruitment of women and minority groups. The brochure has not yet been developed, but will be submitted for approval to the Institutional Review Board before distribution to Clinical Centers.
- A study poster
- A TRTT Facebook page as an additional recruitment tool. Our Facebook page will not allow messaging. It will contain our logo, list eligibility criteria and briefly describe the TRTT clinical trial. Interested persons could click links on our Facebook page to connect to detailed TRTT

content on the clinicaltrials.gov website and to the public page of the TRTT website (http://www.trtt.org). Persons who click the Facebook link to the public page of the TRTT website will see a map with enrolling sites. By clicking on this map, persons will see contact information (email or phone numbers) for their nearest enrolling site.

At this time, we do not plan to use general media advertisements because the population is restricted to military personnel and their families. It is expected that the study brochure will be publically available in the Clinical Center audiology clinical setting for any potential study participant. Copies of the study brochure will also be distributed to referring physicians to give to individuals who may be eligible and have expressed interest in learning more about the TRTT. Posters will be displayed only within military medical settings.

After screening, but immediately prior to the Baseline Eligibility Visit, the Clinical Coordinator or Study Audiologist will meet with the prospective study participant, provide further details of the TRTT, including details of randomization, treatment regimens, potential risks, and benefits, and describe required medical and audiological evaluations. The Study Audiologist will discuss participation in the randomized trial with eligible study participants and answer any and all questions related to participation in the study. To enroll in the study, participants must understand the study design and protocol, the possible risks and benefits or treatment, and that the intention of the Study Audiologist is to administer the randomized treatment as assigned. Both the Study Audiologist and the participant must be willing for the individual to enter the study, receive the randomly assigned treatment and be followed per study protocol. The informed consent process is begun by giving the potential Study Participant the Informed Consent (prepared by the Center Director and approved by the local Institutional Review Board and the Data and Safety Monitoring Board). The detailed informed consent form is read by the Clinical Center Director or Clinical Coordinator to the potential Study Participant in the presence of a family member or friend if possible. Sufficient time is allowed to answer all of the potential Study Participant's questions concerning the trial and proposed therapy. Participants will be advised during the consent procedure and at the onset of the study that they are free to withdraw at any time without fear of penalty of any kind. A signed, dated, and witnessed Informed Consent Statement must be obtained before the potential Study Participant is evaluated at the Baseline Eligibility Visit for the TRTT. A copy of the completed (signed, dated and witnessed) informed consent form is given to the Study Participant, and the original form is filed at the Clinical Center. The Clinical Coordinator will also ask the prospective study participant to sign a HIPAA authorization (depending on local Institutional Review Board requirements) before proceeding to the examinations in the Baseline Eligibility Visit to assess eligibility.

If the student participant is eligible at the conclusion of the Baseline Eligibility Visit, Clinical Center staff will again discuss the TRTT and answer any and all questions about the study that potential study participants may have. At this time, Study participants may choose to participate in the TRTT or choose not to allow randomization. Participants choosing to participate will be randomized to treatment.

The risks from the baseline examination are the same as those associated with a hearing test and a general medical examination in an ear, nose, and throat doctor's office, including minor discomfort during examination of the head and neck areas, or risks of discomfort associated with phlebotomy, if required. There are no known physical risks to the study participant from participating in this study. There is the risk that treatment may not be effective and a possible corresponding risk of clinical depression if treatment, either the experimental treatment or the standard of care, does not alleviate the debilitating effects of tinnitus. There are no known social, legal, or economic risks associated with the study. All normal and usual procedures in place to minimize any physical risk during the Baseline Eligibility Visit will be maintained. To minimize the consequences associated with clinical depression, we will monitor each participant at each follow-up visit by administration of the Beck Depression Index Fast Screen. Participants in the TRTT with a score of 4 or greater on the BDI-FS or endorsement of item # 7 (suicidal thoughts or wishes) will be immediately referred by Clinical Center Directors to an appropriate health care provider in this circumstance and will continue participation in the study.

To provide maximum levels of confidentiality for study participants, each participant will be assigned an ID and an alpha-code (a secondary ID) at the time of entry into the study. The participant ID and alpha-code will uniquely identify participants and serve as primary keys to define unique participant records in database tables. The ID and alpha-code will appear on all study forms; for forms that are repeated, these identifiers will be coupled with a date designator to differentiate records from different visits. The study participant's identifying information will not be sent to the Data Coordinating Center but kept only at the Clinical Centers. Clinical Centers will be instructed to keep all paper data collection forms in locked filing cabinets or filing cabinets within rooms kept locked at all times.

The benefits to be gained by study participants include collection of detailed information about the extent and severity of their tinnitus and general information about their hearing and health. If it is ultimately determined that one of the treatments in this study is more effective than another treatment, and the participant did not receive this optimum treatment, then at the end of this study s/he will be offered the optimum treatment at no cost, including the sound generator, if found to be efficacious.The proposed study addresses a common medical condition for which conventional medical management only provides limited results. Information obtained from the study will have significant clinical applications in showing whether TRT or either of its components, DC or sound therapy, is effective in alleviating the distress caused by debilitating tinnitus. Cost benefits associated with disuse of ineffective treatment will be realized if TRT or either one of its components is found not to benefit study participants. The outcomes of the study, therefore, will have broad benefits for communities of individuals with severely debilitating tinnitus and their health care providers. This knowledge will be particularly important for the military and Veteran's Administration, which has a higher proportion of individuals with tinnitus than in the general population. In addition, as part of a research endeavor, standardized accessible approaches to the administration of treatment for tinnitus will be developed that can be directly transferable to other health care providers.

The Tranquil sound generator developed and provided by General Hearing Instruments, Inc. is a commercially available device previously approved for the treatment of tinnitus. The placebo device differs only in the setting used to generate the sound and is convertible to an active device by re-setting a switch.

The TRTT will be monitored by a Data and Safety Monitoring Board (DSMB). Members have been selected by the National Institute of Deafness and Other Communication Disorders (NIDCD). The first meeting of the DSMC was a face-to-face meeting and took place on February 18, 2010. The first meeting included a review of the TRTT protocol and proposed informed consent statements. All succeeding meetings take place by conference call at six-month intervals; the committee will receive reports including information on recruitment, data quality and completeness, adverse events, and outcomes at least 14 days before the conference takes place. *Ad hoc* telephone meetings may also be held by the DSMC, if deemed necessary.

The DSMB members include the following:

Jay F. Piccirillo, M.D., Chairman
Department of Otolaryngology-Head and Neck Surgery
Washington University School of Medicine

Judy R. Dubno, Ph.D.
Department of Otolaryngology-Head and Neck Surgery
Medical University of South Carolina

James A. Henry, Ph.D.
Research Career Scientist
National Center for Rehabilitative Auditory Research
VA Medical Center – NCRAR

Jennifer Schumi, Ph.D.
Statistics Collaborative, Inc.

Gordon B. Hughes, M.D. Ex Officio (deceased)
Program Officer, Clinical Trials, NIDCD

Steven Hirschfeld, M.D., Ph.D
Program Officer, Clinical Trials, NIDCD

The DSMB has the responsibility for monitoring all ethical aspects of the study and any statistical analyses of study data, as they are collected, for evidence of harmful or beneficial treatment effects. The DSMB is responsible for safeguarding the interests of the participants and the reliability and validity of the results reported from this research effort. The DSMC will make recommendations to the TRTT Steering Committee and study sponsor, NIDCD, on pertinent trial issues, e.g, participant safety, study protocol, non-performance of a Clinical Center, and whether to stop the trial early for evidence of benefit or harm. The charter is attached to this proposal.

No *a priori* interim analyses or stopping rules are planned to date. However, the DSMB will have the option to request pre-specified interim analyses.

Adverse events will be monitored at all study visits, including scheduled and un-scheduled clinical visits, by Clinical Center personnel, and provided to the DMSB every six months at a minimum or more frequently, if requested by the DSMB. Serious adverse events require more immediate reporting. Clinical Center Directors will be required to report any Serious Adverse Events to the Study Chair, Data Coordinating Center Director, and sponsor, NIDCD, within 24 hours of learning of the event for fatal or life-threatening Serious Adverse Events, and 72 hours for other Serious Adverse Events. The Data Coordinating Center will verify that all Serious Adverse Events reported to them have been reported to the NIDCD and also notify the local IRB and all other Clinical Centers of any Serious Adverse Event. Each Clinical Center Director is then responsible for reporting each study-related Serious Adverse Event to their local Institutional Review Board within 7 days.

Any abuse or illegal activities detected during the course of the trial will be reported in accordance with the polices and procedures of Johns Hopkins University and the State of Maryland.

Chair's Office:
C. Craig Formby, PhD, Study Chair. The Chair's Office will be responsible for the overall scientific and administrative aspects of the trial and delivery of all clinical treatments. Responsibilities of the Chair's Office will include clinical training and quality assurance in performing TRT, TRT components, and the Standard of Care (SC) treatments, and the various medical, audiological, and psychoacoustic tests. Study personnel at the Chairman's Office include the Study Chair, TRT and SC Training/Protocol Monitors, Otolaryngologist Training Coordinator, and Administrative Assistant/Meeting Coordinator and Business Manager.

Data Coordinating Center
Roberta W. Scherer, PhD, Director. The Data Coordinating Center oversees scientific aspects of the study design, and serves as the focus of study communications, training and certification of clinical staff in trial procedures, protocol interpretation, data processing, data analysis, and quality assurance activities. The Data Coordinating Center will also be responsible for evaluating adherence to protocol of all data. Staff at the Coordinating Center include the Director of the Coordinating Center, Biostatistician,

Director of Information Management, Co-Investigator, Database Programmer, Statistical Programmer/Analyst, Project Coordinator, Research Assistant, and Administrative Assistant.

Clinical Centers
Directors : Cnthia Eades, MS, Col. Ben Sierra-Irizarry, AuD, Priscilla George, AuD, Shoshannah Kantor, AuD, George Conley, MD, and Cynthia Kirby, AuD. Clinical Centers are responsible for patient recruitment, treatment administration, and follow-up. Clinical Center staff includes at least two Study Audiologists, the Clinical Coordinator, and the Study Otolaryngologist. The Center Director may be either one of the Study Audiologists or the Study Otolaryngologist.

Study Sponsor
The NIDCD funds the TRTT. The Project Officer, Gordon Hughes, MD, serves as a liaison between the sponsor and the TRTT, and provides administrative and fiscal advice;

General Hearing Instruments, Inc. provides the sound therapy devices. GHI will work in coordination with the Study Chair and the Data Coordinating Center to facilitate custom device production and timely return of the completed devices for the double-blind randomized NG assignment for each Study Participant at their Clinical Center. GHI also will provide the necessary software to download and analyze each study participant's NG usage pattern and sound exposure history at follow-up visits.

The primary decision-making body of the TRTT is the Steering Committee, which is a representative body of the investigators. The specific responsibilities, composition, and operating procedures of the Steering Committee include making decisions regarding design issues, study procedures, and allocation of study resources. The Steering Committee reviews study progress and correct deficiencies in data collection or analysis, and acts upon recommendations from the Data Safety and Monitoring Board (DSMB).

The clinical centers are required to provide the Coordinating Center with a copy of their IRB approval notification and approved consent form prior to enrolling participants. We track IRB approval dates at each center, send them reminders about upcoming dates and require submission of renewal of IRB approval notices and approved consent statements. If there is a change to the protocol or consent statement within an approval cycle, we notify all clinical centers via a Policy and Procedure Memorandum (PPM) that is sent via e-mail to the Clinic Center Director and Clinical Coordinator. A complete list of all PPMs and associated materials will be posted on the study website. We require the clinical centers to provide us with the IRB notification for approval of the revised protocol and, if applicable, a copy of the approved revised consent statement before the protocol revision can be implemented.

TRTT Clinical Centers will collect information from participants with their consent. Data will be recorded on paper forms and stored at each study clinic in a secure physical location adhering to the regulations of the local IRB. Data will also be keyed into a web-based data management system that uses SSL encryption during transmission of data from Clinical Centers to the Data Coordinating Center and has security controls on the server, including staff-specific passwords for system access.

The Coordinating Center will track IRB approvals by requiring Clinical Centers to submit IRB approvals and approved consent forms prior to starting the study and renewal documents in order to continue in the study. We will monitor protocol deviations for purposes of quality control, patient safety, training, and reduction of future errors. Protocol deviations will be compiled from several data collection forms, data queries and audits, and site visit findings. The Data Coordinating Center will report serious protocol deviations to the Coordinating Center's IRB and the Data and Safety Monitoring Board. The study clinics will also be asked to report protocol deviations to their local IRBs. Protocol deviation reports will be included in study meeting books as a measure of study clinic performance. If another type of event occurs, e.g., data security is breached, we expect that the Clinical Center director would report that to the Data Coordinating Center and the local IRB. At the Data Coordinating Center we

would evaluate the seriousness of the event in consultation with the TRTT Steering Committee, e.g., were identifiable data lost or stolen, and take appropriate action.