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Bi-modal stimulation in the treatment of tinnitus: a study protocol for an exploratory trial to optimise stimulation parameters and patient subtyping

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ABSTRACT

Introduction: Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. Bi-modal neuromodulation is emerging as a promising treatment for this condition. The main objectives of this study are to investigate the relevance of inter-stimuli timing and the choice of auditory stimuli for a proprietary bi-modal (auditory and somatosensory) neuromodulation device and to explore whether specific subtypes of patients are differentially responsive to this novel intervention for reducing the symptoms of chronic tinnitus.

Methods and analysis: This is a two-site, randomised, triple-blind, exploratory study of a proprietary neuromodulation device with a pre-post and 12-month follow-up design. Three different bi-modal stimulation parameter sets will be examined. The study will enrol 342 patients, split 80:20 between two sites (Dublin, Ireland and Regensburg, Germany), to complete 12 weeks of treatment with the device. Patients will be allocated to one of three arms using a step-wise stratification according to four binary categories: tinnitus tonality, sound level tolerance (using Loudness Discomfort Level of <60 dB SL as an indicator for hyperacusis), hearing thresholds, and presence of a noise-induced audiometric profile. The main indicators of relative clinical efficacy for the three different parameter sets are two patient-reported outcomes measures, the Tinnitus Handicap Inventory and the Tinnitus Functional Index, after 12 weeks of intervention. Clinical efficacy will be further explored in a series of patient subtypes, split by the stratification variables and by presence of a somatic tinnitus. Evidence for sustained effects on the psychological and functional impact of tinnitus will be followed up for 12 months. Safety data will be collected and reported. A number of feasibility measures to inform future trial design include: reasons for exclusion, completeness of data collection, attrition rates, patient's adherence to the device usage as per manufacturer's instructions and evaluation of alternative methods for estimating tinnitus impact and tinnitus loudness.

Ethics and dissemination: This study protocol is approved by the Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee in Dublin, Republic of Ireland, and by the

Ethics Committee of the University Clinic Regensburg, Germany. Findings will be disseminated to relevant research, clinical, health service and patient communities through publications in peer-reviewed and popular science journals and presentations at scientific and clinical conferences.

Trial registration number; the trial is registered on ClinicalTrials.gov (NCT02669069). The sponsor is Neuromod Devices, Dublin, Republic of Ireland.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The main strength of this study is that it is a large two-site, triple-blinded, randomised trial that will provide exploratory evidence of the relevance of stimulation parameters on the clinical efficacy of different bi-modal stimulation parameters and will inform future trial design.
- The study comprehensively characterises patients for subtyping and this will refine candidature for the intervention.
- Among the limitations of this study are the variability in duration between screening and enrolment and the selection of the investigated stimulation parameters.
- The online recruitment process may inadvertently introduce participant selection bias.

INTRODUCTION

Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. The condition is most commonly referred to as 'ringing in the ears' but symptoms can manifest as buzzing, hissing or sizzling. Tinnitus often coincides with hearing loss and it is commonly believed that hearing loss may be a contributory factor (1). While the exact mechanisms responsible for tinnitus are yet to be fully elucidated, it is believed that the reduction in peripheral auditory input, due to hearing loss, results in pathological behaviours that are misinterpreted as sound within the central auditory systems (2).

Tinnitus has traditionally been treated by means of acoustic stimulation with limited success (3). Systematic reviews highlight a lack of double-blind, randomised, controlled studies or quality clinical evidence supporting the efficacy of acoustic stimulation in treating tinnitus (4). This has lead researchers to investigate approaches to treating tinnitus that go beyond acoustic stimulation.

One approach that has been increasingly investigated in the last decade is invasive and non-invasive neuromodulation of brain structures and networks involved in tinnitus generation (5, 6). Neuromodulation is defined as the process of inhibition, stimulation, modification, regulation, or alteration of electrical activity in the central, peripheral, or autonomic nervous systems (7). It is the science of how electrical stimulation can modulate nervous system functionality for therapeutic benefit.

To date, a limited number of uncontrolled pilot studies have been conducted to assess the safety and initial efficacy of neuromodulation employing cranial nerve stimulation for tinnitus treatment in humans. These have included invasive vagus nerve stimulation (VNS) (8), non-invasive stimulation of the vagus nerve (9, 10) and non-invasive Cervico-Trigeminal Nerve Stimulation (CTNS) (11, 12). While VNS demonstrated promising results in animals (13), human studies have demonstrated mixed results (8, 14, 10). Human studies using non-invasive CTNS have demonstrated promising initial efficacy (11, 12). However, these results should be considered preliminary as the data stems from small pilot studies. The intervention evaluated by Hamilton and colleagues (2016) utilised synchronised auditory and

somatosensory stimulation. However, recent animal research suggests that inter-stimuli timing intervals may play an important part in the effectiveness of bi-modal auditory and somatosensory stimulation on tinnitus (15). This theory is supported by the findings of a recent 20-patient human pilot study (12). Similarly, there is debate in the literature about the choice of auditory stimuli and whether this should stimulate frequency channels associated with sensorineural hearing loss (CTNS approach) or frequency channels not associated with hearing loss (VNS approach) (8, 12). Progression to randomised, controlled trials (RCT) with adequately powered sample size is needed. This study protocol represents the first important step towards that goal.

Hypothesis and aims

The main objectives of the study described here are to investigate the relevance of inter - and intra - stimuli timing and the choice of auditory stimulation in order to optimise bi-modal stimulation parameters for this treatment. Exploratory analyses will be conducted to investigate whether subtypes of patients are differentially responsive to this novel intervention. Safety data will also be collected and reported. Additional feasibility outcomes concern methodological and procedural uncertainties when this novel medical device is prescribed and fitted in a large sample of patients.

METHODS AND ANALYSIS

Trial design

The Treatment Evaluation of Neuromodulation for Tinnitus (TENT) study is a two-site, randomised, triple-blind, exploratory study examining three different bi-modal stimulation parameter sets. The treatment duration is 12-weeks and patients are followed up at 6 weeks, 6 months and 12 months post treatment cessation. TENT will be conducted at two sites:

Wellcome Trust-HRB Clinical Research Facility, St. James's Hospital, Dublin, Ireland and Tinnituszentrum Regensburg, University of Regensburg, Germany. The protocol was independently reviewed and approved by Research Ethics Committees of the Tallaght Hospital/St James' Hospital (Ref: 2016-03-List 11(3)) and the University Clinic Regensburg (Ref: 16-101-0186). The trial sponsor is Neuromod Devices Limited. The trial was registered on ClinicalTrials.gov on 27 January 2016 (Identifier: NCT02669069). The first patient was consented in 22 March 2016 with the last visit planned for May 2018. Our reporting follows standard protocol items for clinical trials defined in the SPIRIT 2013 Statement (16).

Eligibility criteria

Eligible patients will be aged 18-70 years at screening; self-report having experienced tinnitus for more than 3 months and less than 5 years; score between 28 and 76 points on the Tinnitus Handicap Inventory (THI), have a Minimum Masking Level (MML) measurement between 20-80 decibels Hearing Level (dB HL), be able to read and understand English or German (depending on the recruiting centre) and be willing to commit to the duration of the programme.

Potential patients will be excluded if they have pulsatile tinnitus (rhythmical sounds that often beat in time with the heartbeat), tinnitus caused by head or neck injury, or tinnitus resulting from any other neurological condition. Signs of a conductive hearing loss demonstrated by abnormal otoscopy or tympanometry are exclusion criteria; as is a sensorineural hearing loss in either ear of greater than 40 dB HL in at least in one measurement frequency in the range 0.25-1.00 kHz, or of greater than 80 dB HL in at least one measurement frequency in the range 2.0-8.0 kHz. Exclusions also include those patients who began wearing a hearing aid within the last 90 days, those with any type of electro-active implantable device (e.g. vagal nerve stimulator, cochlear implant or a cardio-pacemaker) and those with the following conditions that can be co-morbid with tinnitus: Ménière's disease, Loudness Discomfort Level for sounds presented below 30 dB Sensation Level (SL), Temporomandibular Joint disorder (TMJ) and anxiety determined by a score greater than 120 out of 160 on the State-

Trait Anxiety Inventory (STAI) (17, 18). Moderate to severe dementia as indicated by a score below 20 on the Mini-Mental State Examination (MMSE) (19) will also be sufficient reason for exclusion. A final set of exclusion criteria based on medical history taken at the screening assessment are: oral piercings, pregnancy, involvement in medico-legal cases, history of auditory hallucinations, any current neurological conditions that may lead to loss of consciousness (e.g. epilepsy), current prescription of any drug for a central nervous system pathology and previous use of bi-modal neuromodulation devices.

Intervention

All enrolled patients will receive a proprietary bi-modal auditory and somatosensory neuromodulation device (MBT, Neuromod Devices Ltd., Dublin, Ireland), a CE-marked Class IIa medical device. Auditory stimulation is delivered through high-fidelity circumaural headphones, and comprises of a mixture of a wideband noise and sequences of pure tones. Stimulation of the somatosensory system is delivered electrically using an array of 32 transmucosal electrodes on the tongue. Somatosensory stimulation is delivered in the form of bi-phasic anodic pulses of between 5 and 130μs duration and fixed amplitude. The somatosensory stimulator is arranged so that there is a unique mapping between each electrode in the array and frequencies in the tone sequence. The stimuli for each parameter set across the three arms are outlined in Table 1.

The auditory stimulus intensity is configured uniquely based on each patient's pure-tone audiometric thresholds in the range 0.25 to 8 kHz, and the patient is afforded limited control over the auditory stimulus intensity of -12 dB to +12 dB in 2 dB steps during treatment. For patients with greater than 70 dB HL hearing loss at any frequency, the upper bound of stimulus intensity control is limited for reasons of safety noise dosage. The treatment device reverts to the default stimulus intensities at the start of each new treatment session. Any adjustments made by the patients to the stimulus intensities are logged in the device's memory for subsequent analysis.

The somatosensory stimulus intensity is configured for each patient at enrolment, based on a calibration procedure that ascertains the patient's threshold of perception. The patient is also afforded limited control over the somatosensory stimulus intensity during treatment. The device logs the time and date on which the device is in use by the patient, the duration that the electrode array is in contact with the tongue, and the intensities of both stimuli. Individually configurated devices will be delivered to the investigator sites with a patient's Unique Identifier Code (UIC) numbers marked on each device and its accessories. Investigators will be extensively trained on fitting the device and instructing patients on its use, per the manufacturer's instructions. Patients will be provided with a quick start guide, an Instructions for Use (IFU) manual and a link to an instructional video. Before leaving the clinical sites, patients will complete a 30-minute supervised treatment session to ensure they are comfortable using the device.

Outcomes

Subjective clinical outcome measures to assess tinnitus impact, are the Tinnitus Handicap Index (THI) (20) and the Tinnitus Functional Index (TFI) (21). The THI provides a measure of the psychological impact of tinnitus, 25 items are scored 4/2/0 on a categorical scale corresponding to yes/sometimes/no. The global score of the THI has a value between 0 and 100 with the higher scores indicating greater emotional distress. The TFI assesses a range of functional complaints experienced over the past week (22). Each of the 25 items is assessed on an 11 point Likert scale, the sum of the scores is normalised to give a global score between 0 to 100, with higher scores indicating greater negative functional impact of tinnitus.

Tinnitus loudness is assessed by MML, Tinnitus Loudness Matching (TLM) and Visual Analogue Scale (VAS). MML is a psychoacoustic estimate of the lowest level of broadband noise required to minimally mask the patient's tinnitus (23). The stimulus is normally presented ipsilaterally (tinnitus ear), or if tinnitus is present in both ears the stimulus is presented binaurally or to the ear with the predominate sound. TLM is assessed by

presenting a 1-kHz tone (24) contralateral to the predominant tinnitus ear or if tinnitus is equally loud in both sides or localised in the head, the stimuli will be presented to the ear with better hearing or randomly selected. The stimulus is increased in 1 dB increments until the patient confirms that it is equal in loudness to their tinnitus. Finally, a VAS will be employed for patients to rate the current loudness of their tinnitus, with zero equating to 'not loud at all' and ten equating to 'extremely loud', as the endpoints anchors (25).

Safety data on Adverse Events (AEs) and Serious Adverse Events (SAEs) will be captured throughout the trial. An AE is defined as any unfavourable and unintended sign, symptom or disease, temporarily that may or may not be related to the medical device. It will be rated as minor, major or serious and related or unrelated to the device by the TENT Medical Review Board. An SAE is defined as an AE that led or might have led to the death or serious deterioration in the state of health of a patient Treatment-related AEs are those judged by the Principal Investigator at each site to be possibly caused by the treatment under investigation. The Principal Investigator will remain vigilant for signs of possible treatment-related changes in oral health (e.g. irritations in the oral cavity or discomfort between the tongue tip and dental retainers or metal fillings), and the impact of tinnitus (indicated by the THI and TFI).

Stopping criteria are defined as patients demonstrating a worsening in THI and MML of an increase in THI of 7pts and an increase in MML of 5.3dB. Treatment-related changes in hearing thresholds that are considered an AE are a deterioration from Screening to Endpoint of 15 dB in a minimum of two adjacent test frequencies (0.25-8 kHz) in either ear that cannot be explained by conductive hearing problem or a recent excessive noise exposure.

Additionally, feasibility outcomes include: reasons for exclusion at the screening visit, number of patients who were eligible at the screening appointment but declined to participate further, number of patient withdrawals after device fitting, proportion of incomplete patient datasets at each scheduled visit, patients' compliance with the device usage as per manufacturer's instructions and comparisons of alternative methods for measuring the impact of tinnitus and for estimating tinnitus loudness.

Compliance data will be extracted from log files saved on the device. For feasibility analysis, compliance rate will be expressed as a percentage of logged usage relative to i) the expected compliance as per the intended use for the device (a total of 84 hours over the 12-week period), and to a pre-defined minimum acceptable compliance threshold (defined as at least 3 hours average usage within a 1-week period, corresponding to a sum total of 36 hours of treatment).

Recruitment

Patients are primarily recruited via media advertising and dedicated trial websites in both clinical locations. Advertisements on regional and national radio stations and in regional and national newspapers invite individuals with tinnitus, who are interested in participating in a clinical study for tinnitus, to register their interest on dedicated recruitment websites. The recruitment website provides information on the study and how to proceed with registration. Once they register their interest, candidates will be provided with a UIC and an accompanying Personal Identification Number and be directed to an eligibility assessment website. The eligibility assessment comprises of an online survey, hosted by SurveyGizmo, where those interested can find out about the requirements of participating in the study. Candidates answer a scripted set of general pre-screening questions on age, duration of tinnitus, oral piercings, other current medical conditions including temporomandibular joint disorder and Ménière's disease and involvement in medico-legal cases. This is not part of the formal screening because no personal or medical details will be taken, but it is intended to manage the large numbers of candidates expected to respond to the advertising campaign and anticipated high screen failure rate. Candidates who meet the inclusion criteria at this stage will be provided with a Patient Information Leaflet and Informed Consent via email or post and invited to a screening visit at the local site.

Patient timeline

The schedule of clinical research activities is illustrated in Table 2 and briefly comprises of seven visits to the clinical site, plus two telephone calls during the period of device usage. The various assessments are completed by a multi-disciplinary team including: Audiologists, Medical Doctors, Physiotherapist, Research Nurses and Research Associates.

The initial objective of the Screening visit is to obtain written informed consent, to determine whether the patient satisfies the remaining eligibility criteria and to obtain initial outcome measures, patient characteristics and audiological profile. This information is employed in the subtype classification of patients, the stratified random allocation process and for device configuration, described below.

At the Enrolment and device fitting visit, a Physiotherapist (Dublin) or Medical Doctor (Regensburg) conducts a comprehensive assessment comprising of a set of 25 pre-defined cranial manipulations designed to diagnose somatic tinnitus (26). We define somatic tinnitus where a patient reports that at least one of the somatic manipulations reliably produces a change in the psychoacoustic characteristics of their tinnitus (e.g. in pitch, loudness, localisation, temporal properties etc). Assessments of outcome measures are repeated at the Enrolment visit. Other elements of the visit include an oral health examination and device training and deployment. After completing an on-site supervised treatment session, patients return home and self-administer the treatment. Patients will be instructed to use the device for two daily 30-minute sessions over a 12-week period. These sessions can be continuous or at different times of the day.

Assessment of outcome measures and safety information are collected at the Interim visit, half way through the 12-week treatment. Compliance will also be assessed and reviewed at the Interim visit. Investigators will review the device usage log. Patients with acceptable compliance will be encouraged to continue and patients with poor compliance will be encouraged to improve. Compliance phone calls will be conducted at weeks 3 and 9 to

encourage patients to continue with device usage and address any technical issues that patients may be having.

The purpose of the End-point visit is to repeat outcome measures assessments, the oral health examination, an exit interview and retrieve the device. Three follow-up visits will be conducted to assess the post cessation effects of this intervention.

Sample size

The study is powered for a between-arm clinically significant difference in the mean THI scores from Baseline to End-point, where the reported clinically significant change in THI is 7 points (27). The assumed sample standard deviation is 12.7 points, as elucidated from a previous study using similar technology (11), resulting in an effect size of 0.55. The sample size calculations were performed using Matlab 2016a, assuming a two-sided significance level of 0.016 (0.05 split equally between the three inter-arm pairwise t-tests), and power of 90%, resulting in a total of 91 patients to be enrolled in each treatment arm, or 114 patients per arm to account for an expected drop-out rate of 20%. In total, 342 patients will be required across the three arms of the study, split 80:20 between the Dublin and Regensburg sites respectively.

Allocation

Eligible patients will be randomised, in equal proportions, between the three parallel arms at the device configuration site by members of the technical team, not investigators (see Figure 1). Stratified randomisation will be performed to balance the influence of several baseline co-variates in the post-hoc analyses. The stratification co-variates are chosen based on the investigator's research objectives, namely to elucidate relative treatment effects on tinnitus patients with varying underlying characteristics. Allocation of patients will be stratified across the three intervention arms according to four binary categories applied in a step-wise

manner: i) tinnitus tonality, ii) sound level tolerance (using Loudness Discomfort Level of <60 dB SL as an indicator for hyperacusis), iii) 'Normo-acoustic' (defined as pure-tone thresholds of 20dB HL or less in all audiometric test frequencies between 0.25 and 8 kHz in both ears), and iv) presence of a noise-induced audiometric profile (defined as a dip in pure-tone hearing thresholds of 10dB or more in any frequency in the 3 to 6 kHz range in any ear). These co-variates are not mutually exclusive, so priority during stratified randomisation will be given to the least prevalent co-variates based on candidate characteristics from the screening phase of the study.

The stratification and randomisation will be performed adaptively (Minimisation) 28), whereby the probability of assignment to a treatment intervention changes as the imbalance within the relevant stratum increases. Dice rolls emulated in Matlab's Mersenne Twister algorithm (version 2016a) will be used with the randomisation seed set to the date each new block of patients is randomised.

Data Management

All data will be collected electronically using a validated electronic Case Report Form (eCRF) application. Patient data collected at all stages of the trial will be entered into the eCRF using UIC's assigned to patients at recruitment phase. All investigators and patients will be blinded to allocation arm and no allocation information will be contained in the eCRF. The data monitors will be able to remotely view the data in the eCRF to monitor safety data.

Statistical Methods

The main indicators of clinical efficacy for the three different parameter sets are two patient-reported outcomes (THI and TFI) after 12 weeks of intervention. Baseline outcome measures are computed as the average scores at the Screening and Enrolment visits. Clinical efficacy will be explored for a series of patient subtypes, split by the stratification variables, while evidence for sustained effects on the psychological and functional impact of

tinnitus will be followed up for 12 months. Additional feasibility measures to inform future trial design include: reasons for exclusion, completeness of data collection, attrition rates, patients' adherence to the device usage as per manufacturer's instructions. These will be collated using descriptive statistics and reported as percentages. We will also evaluate the alternative methods for estimating tinnitus impact and tinnitus loudness, as far as possible using psychometric criteria defined by the COSMIN checklist (29).

Efficacy analyses will focus on investigating i) between-arm changes in the THI and TFI outcome measures from Baseline to End-point, and ii) within-arm changes in THI and TFI outcome measures from Baseline to End-point, for the full cohort and then sequentially testing the subtypes described above using serial gatekeeping to control the family-wise error rate at the 0.05 significance level. The between-arm analyses will be based on an intention-to-treat estimand and tested with multiple regression utilising Baseline scores as a covariate. Missing data will be handled by using Markov chain Monte Carlo multiple imputation methods (Rubin, 2004; Schafer, 1997). The within-arm analyses will be based on a per-protocol estimand and tested with paired two-tailed t-tests. The use of per-protocol estimand will ensure that the changes in outcome measures within a particular treatment arm are reflective of real-use scenarios, i.e. where the patients use the treatment as directed. The threshold for inclusion in the per-protocol analysis is set at the pre-defined minimum acceptable compliance threshold previously described. Additional exploratory efficacy analyses shall be conducted in order to ascertain treatment effects from Baseline to Interim (i.e. 6 weeks of treatment), and to evaluate any sustained efficacy by analysing changes in efficacy outcome measures from End-point to the three Follow-up assessments (i.e. at 18, 36 and 60 weeks after device fitting).

Safety analyses will be performed by evaluating the incidence of adverse events, classified as treatment or non-treatment related, and further sub-classified as Minor, Major and Serious. Adverse events will be recorded proactively, by monitoring significant changes in THI, TFI, MML, hearing thresholds and oral health, and reactively by documenting any

adverse events reported by patients during the study. All adverse events will be analysed for trends, and statistical tests for significant between-arm differences will be conducted.

Efficacy and safety data analysis will be conducted in compliance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomised controlled trials (30) using the SAS software package.

Dissemination

Findings will be disseminated to relevant research, clinical, health service and patient communities through publications in peer-reviewed and popular science journals and presentations at scientific and clinical conferences.

DISCUSSION

This paper outlines the protocol for a multi-site, randomised, triple-blind, exploratory study designed to explore the effects of different bi-modal stimulation parameter sets across a number of tinnitus subtypes in a range of tinnitus clinical subdomains. The results of this study will inform the design of future triple-blind randomised control trials. The main objective is to determine an optimised bi-modal stimulation parameter set, but we will also explore which patient characteristics might best predict therapeutic benefit in that treatment arm. We anticipate that this could lead to improved personalised intervention options for people with chronic subjective tinnitus.

This study is timely for several reasons. First, completing this exploratory trial will be important in determining any feasibility challenges and will be used to estimate the time, resources and sample size required for a full-scale RCT to answer the definitive question of clinical efficacy. Second, findings from this study could potentially inform the acceptability of bimodal stimulation in the wider population. There is a real need for effective therapeutic options that reduce or alleviate the tinnitus percept instead of simply helping people to manage the cognitive, emotional and behaviour impacts of their symptoms or to accept their

long-term condition (3). Third, low quality clinical trial design and reporting has been identified as a major barrier to developing effective tinnitus therapies and standards of practice have been proposed 31,32, 33). The study design and protocol description is in line with those recommendations.

AUTHORS' CONTRIBUTIONS:

SD, CH, SH and BC conceived of the study. SD, CH, SH initiated the study design. SH provided statistical expertise in clinical trial design. BL, SV and DAH are members of the Science Advisory Board for Neuromod Devices Ltd and contributed to the Clinical Investigation Plan and the Statistical Analysis Plan, on which the protocol is based. BL and BC are Principal Investigators at the two trial sites. All authors contributed to the refinement of the study protocol and approved the final manuscript. SD submitted the manuscript for publication.

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COMPETING INTERESTS STATEMENT

SD, CH, SH, and BC are employees and shareholders of the Sponsor. BL, SV and DAH act as paid consultants for the Sponsor.

DATA SHARING STATEMENT

The data from this study will not be shared publicly shared.

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	Auditory stimulation	Temporal relationship with somatosensory stimulation
Arm 1	Sequence of tones, mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are synchronous with the tones
Arm 2	Sequence of tones, mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are asynchronous with the tones
Arm 3	Sequence of tones mixed with a broadband noise with the spectral range outside the regions normally associated with sensorineural hearing loss	Somatosensory pulses are uncorrelated and asynchronous with the tones

Table 1 Stimulation parameter set for the three parallel arms

	Screening	Enrolment and fitting	Post-allocation				Follow-up	Follow-up	Follow-up
	Screening	Enrolment	*Telephone call*	*Interim visit*	*Telephone call*	*Endpoint visit*			
TIMEPOINT**	*wk-6 to 10*	*wk1*[1]	*wk3*[1]	*wk6*[1]	*wk9*[1]	*wk12*[1]	*wk18*[1]	*wk36*[1]	*wk60*[1]
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Training on how to use the device		X							
Review of device usage data log with participant				X					
Encourage compliance		X	X	X	X				
Return device						X			
INTERVENTIONS:									
Arm 1			◆—	—	—◆				
Arm 2			◆—	—	—◆				
Arm 3			◆—	—	—◆				
ASSESSMENTS:									
Medical history	X								
Previous or concomitant medications/illnesses		X[2]		X		X	X	X	X
Tinnitus location & tonality	X[3]	X[2]		X		X	X	X	X
Audiometric tests of hearing	X[3,4]								
Loudness Discomfort Level	X[3]					X			
Mini-Mental Stat Examination	X								
Somatic assessment		X							
Oral assessment		X				X			
Regensburg Insomnia Scale		X				X			
State-Trait Anxiety Inventory	X			X		X			
Tinnitus Functional Index	X	X		X		X	X	X	X
Minimum Masking Level	X	X		X		X	X	X	X
Tinnitus Loudness Matching	X	X		X		X	X	X	X
Tinnitus Handicap Inventory	X	X		X		X	X	X	X
Visual Analogue Scales (loudness and intrusiveness)	X					X	X	X	X
Adverse events		X[2]		X		X	X	X	X
Clinical Global Impression (loudness and intrusiveness)				X		X			
Device usability questionnaire						X			
Hyperacusis questionnaire[5]								X	

Table 2. Schedule of Assessment

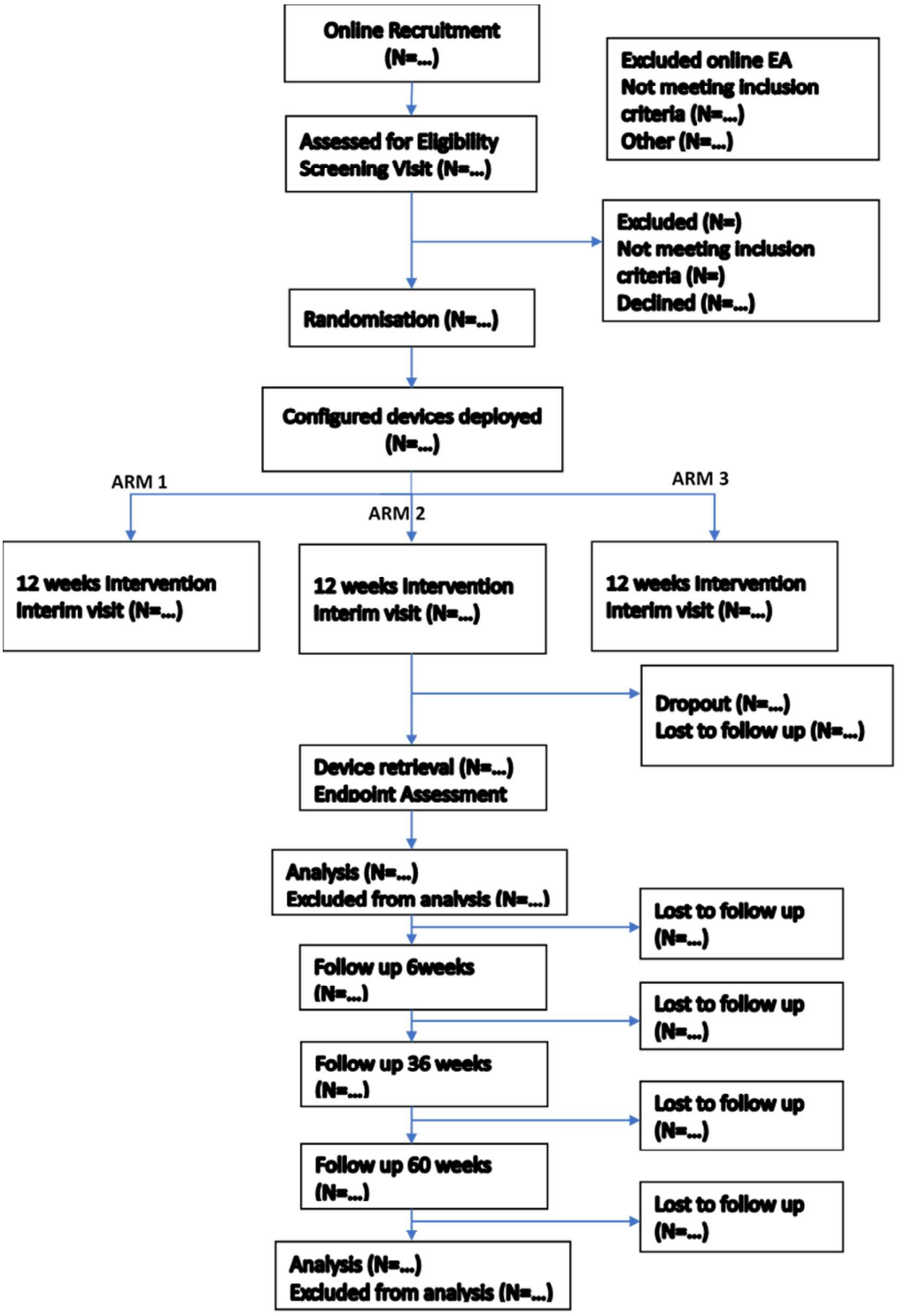

Figure 1 Anticipated flow of participants through the TENT study

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

***while these items are not described in the manuscript they are addressed in our protocol, the study has been designed in line with GCP, SPIRIT and ISO14155 guidelines.**

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Not reported in manuscript*
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not reported in manuscript
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12, 13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not reported in manuscript
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not reported in manuscript
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not reported in manuscript
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9, 14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not reported in manuscript
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not reported in manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Not reported in manuscript
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not reported in manuscript
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not reported in manuscript
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported in manuscript

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Bi-modal stimulation in the treatment of tinnitus: a study protocol for an exploratory trial to optimise stimulation parameters and patient subtyping

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Title: Bi-modal stimulation in the treatment of tinnitus: a study protocol for an exploratory trial to optimise stimulation parameters and patient subtyping

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Running Title: Bi-modal stimulation in the treatment of tinnitus

Keywords: Tinnitus, Bi-modal stimulation, neuromodulation

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ABSTRACT

Introduction: Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. Bi-modal neuromodulation is emerging as a promising treatment for this condition. The main objectives of this study are to investigate the relevance of inter-stimuli timing and the choice of auditory stimuli for a proprietary bi-modal (auditory and somatosensory) neuromodulation device and to explore whether specific subtypes of patients are differentially responsive to this novel intervention for reducing the symptoms of chronic tinnitus.

Methods and analysis: This is a two-site, randomised, triple-blind, exploratory study of a proprietary neuromodulation device with a pre-post and 12-month follow-up design. Three different bi-modal stimulation parameter sets will be examined. The study will enrol 342 patients, split 80:20 between two sites (Dublin, Ireland and Regensburg, Germany), to complete 12 weeks of treatment with the device. Patients will be allocated to one of three arms using a step-wise stratification according to four binary categories: tinnitus tonality, sound level tolerance (using Loudness Discomfort Level of <60 dB SL as an indicator for hyperacusis), hearing thresholds, and presence of a noise-induced audiometric profile. The main indicators of relative clinical efficacy for the three different parameter sets are two patient-reported outcomes measures, the Tinnitus Handicap Inventory and the Tinnitus Functional Index, after 12 weeks of intervention. Clinical efficacy will be further explored in a series of patient subtypes, split by the stratification variables and by presence of a somatic tinnitus. Evidence for sustained effects on the psychological and functional impact of tinnitus will be followed up for 12 months. Safety data will be collected and reported. A number of feasibility measures to inform future trial design include: reasons for exclusion, completeness of data collection, attrition rates, patient's adherence to the device usage as per manufacturer's instructions and evaluation of alternative methods for estimating tinnitus impact and tinnitus loudness.

Ethics and dissemination: This study protocol is approved by the Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee in Dublin, Republic of Ireland, and by the

Ethics Committee of the University Clinic Regensburg, Germany. Findings will be disseminated to relevant research, clinical, health service and patient communities through publications in peer-reviewed and popular science journals and presentations at scientific and clinical conferences.

Trial registration number; the trial is registered on ClinicalTrials.gov (NCT02669069). The sponsor is Neuromod Devices, Dublin, Republic of Ireland.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The main strength of this study is that it is a large two-site, triple-blinded, randomised trial that will provide exploratory evidence of the relevance of stimulation parameters on the clinical efficacy of different bi-modal stimulation parameters and will inform future trial design.
- The study comprehensively characterises patients for subtyping and this will refine candidature for the intervention.
- Among the limitations of this study are the variability in duration between screening and enrolment and the selection of the investigated stimulation parameters.
- The online recruitment process may inadvertently introduce participant selection bias.

INTRODUCTION

Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. The condition is most commonly referred to as 'ringing in the ears' but symptoms can manifest as buzzing, hissing or sizzling. Tinnitus often coincides with hearing loss and it is commonly believed that hearing loss may be a contributory factor (1). While the exact mechanisms responsible for tinnitus are yet to be fully elucidated, it is believed that the reduction in peripheral auditory input, due to hearing loss, results in pathological behaviours that are misinterpreted as sound within the central auditory systems (2).

Tinnitus has traditionally been treated by means of acoustic stimulation with limited success (3). Systematic reviews highlight a lack of double-blind, randomised, controlled studies or quality clinical evidence supporting the efficacy of acoustic stimulation in treating tinnitus (4). This has lead researchers to investigate approaches to treating tinnitus that go beyond acoustic stimulation.

One approach that has been increasingly investigated in the last decade is invasive and non-invasive neuromodulation of brain structures and networks involved in tinnitus generation (5, 6). Neuromodulation is defined as the process of inhibition, stimulation, modification, regulation, or alteration of electrical activity in the central, peripheral, or autonomic nervous systems (7). It is the science of how electrical stimulation can modulate nervous system functionality for therapeutic benefit. Neuromodulation approaches of the central nervous system for the treatment of tinnitus include repetitive transcranial magnetic stimulation, transcranial direct current stimulation and epidural stimulation of temporal, temporoparietal and frontal brain areas. All these approaches have resulted in reduction of tinnitus handicap in a subgroup of patients (8, 9, 10, 11). Targeted modification of central nervous activity by neurofeedback has also been proposed as a therapeutic approach for tinnitus. In addition, a limited number of uncontrolled pilot studies have been conducted to assess the safety and initial efficacy of neuromodulation employing cranial nerve stimulation for tinnitus treatment in humans.

To date, a limited number of uncontrolled pilot studies have been conducted to assess the safety and initial efficacy of neuromodulation employing cranial nerve stimulation for tinnitus treatment in humans. These have included invasive vagus nerve stimulation (VNS) (12), non-invasive stimulation of the vagus nerve (13, 14) and non-invasive Cervico-Trigeminal Nerve Stimulation (CTNS) (15, 16). While VNS demonstrated promising results in animals (17), human studies have demonstrated mixed results (12, 18, 14). Human studies using non-invasive CTNS have demonstrated promising initial efficacy (15, 16). However, these results should be considered preliminary as the data stems from small pilot studies. The intervention evaluated by Hamilton and colleagues (2016) utilised synchronised auditory and somatosensory stimulation. However, recent animal research suggests that inter-stimuli timing intervals may play an important part in the effectiveness of bi-modal auditory and somatosensory stimulation on tinnitus (19). This theory is supported by the findings of a recent 20-patient human pilot study (16). Similarly, there is debate in the literature about the choice of auditory stimuli and whether this should stimulate frequency channels associated with sensorineural hearing loss (CTNS approach) (15) or frequency channels not associated with hearing loss (VNS approach) (12). Progression to randomised, controlled trials (RCT) with adequately powered sample size is needed. This study protocol represents the first important step towards that goal.

Hypothesis and aims

The main objectives of the study described here are to investigate the relevance of inter - and intra - stimuli timing and the choice of auditory stimulation in order to optimise bi-modal stimulation parameters for this treatment. Exploratory analyses will be conducted to investigate whether subtypes of patients are differentially responsive to this novel intervention. Safety data will also be collected and reported. Additional feasibility outcomes concern methodological and procedural uncertainties when this novel medical device is prescribed and fitted in a large sample of patients.

METHODS AND ANALYSIS

Trial design

The Treatment Evaluation of Neuromodulation for Tinnitus (TENT) study is a two-site, randomised, triple-blind, exploratory study examining three different bi-modal stimulation parameter sets. The treatment duration is 12-weeks and patients are followed up at 6 weeks, 6 months and 12 months post treatment cessation. TENT will be conducted at two sites: Wellcome Trust-HRB Clinical Research Facility, St. James's Hospital, Dublin, Ireland and Tinnituszentrum Regensburg, University of Regensburg, Germany. The protocol was independently reviewed and approved by Research Ethics Committees of the Tallaght Hospital/St James' Hospital (Ref: 2016-03-List 11(3)) and the University Clinic Regensburg (Ref: 16-101-0186). The trial sponsor is Neuromod Devices Limited. The trial was registered on ClinicalTrials.gov on 27 January 2016 (Identifier: NCT02669069). The first patient was consented in 22 March 2016 with the last visit planned for May 2018. Our reporting follows standard protocol items for clinical trials defined in the SPIRIT 2013 Statement (20).

Eligibility criteria

Eligible patients will be aged 18-70 years at screening; self-report having experienced tinnitus for more than 3 months and less than 5 years; score between 28 and 76 points on the Tinnitus Handicap Inventory (THI), have a Minimum Masking Level (MML) measurement between 20-80 decibels Hearing Level (dB HL), be able to read and understand English or German (depending on the recruiting centre) and be willing to commit to the duration of the programme.

Potential patients will be excluded if they have pulsatile tinnitus (rhythmical sounds that often beat in time with the heartbeat), tinnitus caused by head or neck injury, or tinnitus resulting from any other neurological condition. Signs of a conductive hearing loss demonstrated by abnormal otoscopy or tympanometry are exclusion criteria; as is a sensorineural hearing loss in either ear of greater than 40 dB HL in at least in one measurement frequency in the

range 0.25-1.00 kHz, or of greater than 80 dB HL in at least one measurement frequency in the range 2.0-8.0 kHz. Exclusions also include those patients who began wearing a hearing aid within the last 90 days, those with any type of electro-active implantable device (e.g. vagal nerve stimulator, cochlear implant or a cardio-pacemaker) and those with the following conditions that can be co-morbid with tinnitus: Ménière's disease, Loudness Discomfort Level for sounds presented below 30 dB Sensation Level (SL), Temporomandibular Joint disorder (TMJ) and anxiety determined by a score greater than 120 out of 160 on the State-Trait Anxiety Inventory (STAI) (21, 22). Moderate to severe dementia as indicated by a score below 20 on the Mini-Mental State Examination (MMSE) (23) will also be sufficient reason for exclusion. A final set of exclusion criteria based on medical history taken at the screening assessment are: oral piercings, pregnancy, involvement in medico-legal cases, history of auditory hallucinations, any current neurological conditions that may lead to loss of consciousness (e.g. epilepsy), current prescription of any drug for a central nervous system pathology and previous use of bi-modal neuromodulation devices. Finally, the Principal Investigator does not deem the candidate to be suitable for the study for other reasons not listed above.

Intervention

All enrolled patients will receive a proprietary bi-modal auditory and somatosensory neuromodulation device (MBT, Neuromod Devices Ltd., Dublin, Ireland), a CE-marked Class IIa medical device. Auditory stimulation is delivered through high-fidelity circumaural headphones, and comprises of a mixture of a wideband noise and sequences of pure tones. Stimulation of the somatosensory system is delivered electrically using an array of 32 transmucosal electrodes on the tongue. Somatosensory stimulation is delivered in the form of bi-phasic anodic pulses of between 5 and 130μs duration and fixed amplitude. The somatosensory stimulator is arranged so that there is a unique mapping between each electrode in the array and frequencies in the tone sequence. The stimuli for each parameter set across the three arms are outlined in Table 1.

	Auditory stimulation	Temporal relationship with somatosensory stimulation
Arm 1	Sequence of tones, mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are synchronous with the tones
Arm 2	Sequence of tones, mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are asynchronous with the tones
Arm 3	Sequence of tones mixed with a broadband noise with the spectral range outside the regions normally associated with sensorineural hearing loss	Somatosensory pulses are uncorrelated and asynchronous with the tones

Table 1 Stimulation parameter set for the three parallel arms

The auditory stimulus intensity is configured uniquely based on each patient's pure-tone audiometric thresholds in the range 0.25 to 8 kHz, and the patient is afforded limited control over the auditory stimulus intensity of -12 dB to +12 dB in 2 dB steps during treatment. For patients with greater than 70 dB HL hearing loss at any frequency, the upper bound of stimulus intensity control is limited for reasons of safety noise dosage. The treatment device reverts to the default stimulus intensities at the start of each new treatment session. Any adjustments made by the patients to the stimulus intensities are logged in the device's memory for subsequent analysis.

The somatosensory stimulus intensity is configured for each patient at enrolment, based on a calibration procedure that ascertains the patient's threshold of perception. The patient is also afforded limited control over the somatosensory stimulus intensity during treatment. The device logs the time and date on which the device is in use by the patient, the duration that the electrode array is in contact with the tongue, and the intensities of both stimuli.

Individually configurated devices will be delivered to the investigator sites with a patient's Unique Identifier Code (UIC) numbers marked on each device and its accessories. Investigators will be extensively trained on fitting the device and instructing patients on its use, per the manufacturer's instructions. Patients will be provided with a quick start guide, an Instructions for Use (IFU) manual and a link to an instructional video. Before leaving the clinical sites, patients will complete a 30-minute supervised treatment session to ensure they are comfortable using the device.

Outcomes

Subjective clinical outcome measures to assess tinnitus impact, are the Tinnitus Handicap Index (THI) (24) and the Tinnitus Functional Index (TFI) (25). The THI provides a measure of the psychological impact of tinnitus, 25 items are scored 4/2/0 on a categorical scale corresponding to yes/sometimes/no. The global score of the THI has a value between 0 and 100 with the higher scores indicating greater emotional distress. The TFI assesses a range of functional complaints experienced over the past week (26). Each of the 25 items is assessed on an 11 point Likert scale, the sum of the scores is normalised to give a global score between 0 and 100, with higher scores indicating greater negative functional impact of tinnitus.

Tinnitus loudness is assessed by MML, Tinnitus Loudness Matching (TLM) and Visual Analogue Scale (VAS). MML is a psychoacoustic estimate of the lowest level of broadband noise required to minimally mask the patient's tinnitus (27). The stimulus is normally presented ipsilaterally (tinnitus ear), or if tinnitus is present in both ears the stimulus is presented binaurally or to the ear with the predominate sound. TLM is assessed by presenting a 1-kHz tone (28) contralateral to the predominant tinnitus ear or if tinnitus is equally loud in both sides or localised in the head, the stimuli will be presented to the ear with better hearing or randomly selected. The stimulus is increased in 1 dB increments until the patient confirms that it is equal in loudness to their tinnitus. Finally, a VAS will be

employed for patients to rate the current loudness of their tinnitus, with zero equating to 'not loud at all' and ten equating to 'extremely loud', as the endpoints anchors (29).

Safety data on Adverse Events (AEs) and Serious Adverse Events (SAEs) will be captured throughout the trial. An AE is defined as any unfavourable and unintended sign, symptom or disease, temporarily that may or may not be related to the medical device. It will be rated as minor, major or serious and related or unrelated to the device by the TENT Medical Review Board. An SAE is defined as an AE that led or might have led to the death or serious deterioration in the state of health of a patient Treatment-related AEs are those judged by the Principal Investigator at each site to be possibly caused by the treatment under investigation. The Principal Investigator will remain vigilant for signs of possible treatment-related changes in oral health (e.g. irritations in the oral cavity or discomfort between the tongue tip and dental retainers or metal fillings), and the impact of tinnitus (indicated by the THI and TFI).

Stopping criteria are defined as patients demonstrating a worsening in THI and MML of an increase in THI of 7pts and an increase in MML of 5.3dB. Treatment-related changes in hearing thresholds that are considered an AE are a deterioration from Screening to Endpoint of 15 dB in a minimum of two adjacent test frequencies (0.25-8 kHz) in either ear that cannot be explained by conductive hearing problem or a recent excessive noise exposure.

Additionally, feasibility outcomes include: reasons for exclusion at the screening visit, number of patients who were eligible at the screening appointment but declined to participate further, number of patient withdrawals after device fitting, proportion of incomplete patient datasets at each scheduled visit, patients' compliance with the device usage as per manufacturer's instructions and comparisons of alternative methods for measuring the impact of tinnitus and for estimating tinnitus loudness.

Compliance data will be extracted from log files saved on the device. For feasibility analysis, compliance rate will be expressed as a percentage of logged usage relative to i) the expected compliance as per the intended use for the device (a total of 84 hours over the 12-week period), and to a pre-defined minimum acceptable compliance threshold (defined as at

least 3 hours average usage within a 1-week period, corresponding to a sum total of 36 hours of treatment).

Recruitment

Patients are primarily recruited via media advertising and dedicated trial websites in both clinical locations. Advertisements on regional and national radio stations and in regional and national newspapers invite individuals with tinnitus, who are interested in participating in a clinical study for tinnitus, to register their interest on dedicated recruitment websites. The recruitment website provides information on the study and how to proceed with registration. Once they register their interest, candidates will be provided with a UIC and an accompanying Personal Identification Number and be directed to an eligibility assessment website. The eligibility assessment comprises of an online survey, hosted by SurveyGizmo, where those interested can find out about the requirements of participating in the study. Candidates answer a scripted set of general pre-screening questions on age, duration of tinnitus, oral piercings, other current medical conditions including temporomandibular joint disorder and Ménière's disease and involvement in medico-legal cases. This is not part of the formal screening because no personal or medical details will be taken, but it is intended to manage the large numbers of candidates expected to respond to the advertising campaign and anticipated high screen failure rate. Candidates who meet the inclusion criteria at this stage will be provided with a Patient Information Leaflet and Informed Consent via email or post and invited to a screening visit at the local site.

Patient timeline

The schedule of clinical research activities is illustrated in Table 2 and briefly comprises of seven visits to the clinical site, plus two telephone calls during the period of device usage. The various assessments are completed by a multi-disciplinary team including: Audiologists, Medical Doctors, Physiotherapist, Research Nurses and Research Associates.

	Screening	Enrolment and fitting	Post-allocation				Follow-up	Follow-up	Follow-up
	Screening	Enrolment	*Telephone call*	*Interim visit*	*Telephone call*	*Endpoint visit*			
TIMEPOINT	***Wks 0 to 10***	***wk1***	***wk3***	***wk6***	***wk9***	***wk12***	***wk18***	***wk36***	***wk60***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Training on how to use the device		X							
Review of device usage data log with participant				X					
Encourage compliance		X	X	X	X				
Return device						X			
INTERVENTIONS:									
Arm 1			←	—	→				
Arm 2			←	—	→				
Arm 3			←	—	→				
ASSESSMENTS:									
Medical history	X								
Previous or concomitant medications/illnesses		X		X		X	X	X	X
Tinnitus location & tonality	X	X		X		X	X	X	X
Audiometric tests of hearing	X								
Loudness Discomfort Level	X					X			
Mini-Mental Stat Examination	X								
Somatic assessment		X							
Oral assessment		X				X			
Regensburg Insomnia Scale		X				X			
State-Trait Anxiety Inventory	X			X		X			
Tinnitus Functional Index	X	X		X		X	X	X	X
Minimum Masking Level	X	X		X		X	X	X	X
Tinnitus Loudness Matching	X	X		X		X	X	X	X
Tinnitus Handicap Inventory	X	X		X		X	X	X	X
Visual Analogue Scales (loudness and intrusiveness)	X					X	X	X	X
Adverse events		X		X		X	X	X	X
Clinical Global Impression (loudness and intrusiveness)				X		X			
Device usability questionnaire						X			
Hyperacusis questionnaire								X[1]	X[2]

Table 2. Schedule of Assessment, [1] Dublin, [2] Germany

The initial objective of the Screening visit is to obtain written informed consent, to determine whether the patient satisfies the remaining eligibility criteria and to obtain initial outcome measures, patient characteristics and audiological profile. This information is employed in the subtype classification of patients, the stratified random allocation process and for device configuration, described below.

At the Enrolment and device fitting visit, a Physiotherapist (Dublin) or Medical Doctor (Regensburg) conducts a comprehensive assessment comprising of a set of 25 pre-defined

cranial manipulations designed to diagnose somatic tinnitus (30). We define somatic tinnitus where a patient reports that at least one of the somatic manipulations reliably produces a change in the psychoacoustic characteristics of their tinnitus (e.g. in pitch, loudness, localisation, temporal properties etc). Assessments of outcome measures are repeated at the Enrolment visit. Other elements of the visit include an oral health examination and device training and deployment. After completing an on-site supervised treatment session, patients return home and self-administer the treatment. Patients will be instructed to use the device for two daily 30-minute sessions over a 12-week period. These sessions can be continuous or at different times of the day.

Assessment of outcome measures and safety information are collected at the Interim visit, half way through the 12-week treatment. Compliance will also be assessed and reviewed at the Interim visit. Investigators will review the device usage log. Patients with acceptable compliance will be encouraged to continue and patients with poor compliance will be encouraged to improve. Compliance phone calls will be conducted at weeks 3 and 9 to encourage patients to continue with device usage and address any technical issues that patients may be having.

The purpose of the End-point visit is to repeat outcome measures assessments, the oral health examination, an exit interview and retrieve the device. Three follow-up visits will be conducted to assess the post cessation effects of this intervention.

Sample size

The study is powered for a between-arm clinically significant difference in the mean THI scores from Baseline to End-point, where the reported clinically significant change in THI is 7 points (31). The assumed sample standard deviation is 12.7 points, as elucidated from a previous study using similar technology (11), resulting in an effect size of 0.55. The sample size calculations were performed using Matlab 2016a, assuming a two-sided significance level of 0.016 (0.05 split equally between the three inter-arm pairwise t-tests), and power of 90%, resulting in a total of 91 patients to be enrolled in each treatment arm, or 114 patients

per arm to account for an expected drop-out rate of 20%. In total, 342 patients will be required across the three arms of the study, split 80:20 between the Dublin and Regensburg sites respectively.

Allocation

Eligible patients will be randomised, in equal proportions, between the three parallel arms (see Figure 1). Stratified randomisation will be performed to balance the influence of several baseline co-variates in the post-hoc analyses. The stratification co-variates are chosen based on the investigator's research objectives, namely to elucidate relative treatment effects on tinnitus patients with varying underlying characteristics. Allocation of patients will be stratified across the three intervention arms according to four binary categories applied in a step-wise manner: i) tinnitus tonality, ii) sound level tolerance (using Loudness Discomfort Level of <60 dB SL as an indicator for hyperacusis), iii) 'Normo-acoustic' (defined as pure-tone thresholds of 20dB HL or less in all audiometric test frequencies between 0.25 and 8 kHz in both ears), and iv) presence of a noise-induced audiometric profile (defined as a dip in pure-tone hearing thresholds of 10dB or more in any frequency in the 3 to 6 kHz range in any ear). These co-variates are not mutually exclusive, so priority during stratified randomisation will be given to the least prevalent co-variates based on candidate characteristics from the screening phase of the study.

The stratification and randomisation will be performed adaptively (Minimisation) (32), whereby the probability of assignment to a treatment intervention changes as the imbalance within the relevant stratum increases. Dice rolls emulated in Matlab's Mersenne Twister algorithm (version 2016a) will be used with the randomisation seed set to the date each new block of patients is randomised.

Data collection methods

All data will be collected electronically using a validated electronic Case Report Form (eCRF) application. Patient data collected at all stages of the trial will be entered into the eCRF using UIC's assigned to patients at recruitment phase. All investigators and patients will be blinded to allocation arm and no allocation information will be contained in the eCRF. The data monitors will be able to remotely view the data in the eCRF to monitor safety data.

Statistical Methods

The main indicators of clinical efficacy for the three different parameter sets are two patient-reported outcomes (THI and TFI) after 12 weeks of intervention. Baseline outcome measures are computed as the average scores at the Screening and Enrolment visits. Clinical efficacy will be explored for a series of patient subtypes, split by the stratification variables, while evidence for sustained effects on the psychological and functional impact of tinnitus will be followed up for 12 months. Additional feasibility measures to inform future trial design include: reasons for exclusion, completeness of data collection, attrition rates, patients' adherence to the device usage as per manufacturer's instructions. These will be collated using descriptive statistics and reported as percentages. We will also evaluate the alternative methods for estimating tinnitus impact and tinnitus loudness, as far as possible using psychometric criteria defined by the COSMIN checklist (33).

Efficacy analyses will focus on investigating i) between-arm changes in the THI and TFI outcome measures from Baseline to End-point, and ii) within-arm changes in THI and TFI outcome measures from Baseline to End-point, for the full cohort and then sequentially testing the subtypes described above using serial gatekeeping to control the family-wise error rate at the 0.05 significance level. The between-arm analyses will be based on an intention-to-treat estimand and tested with multiple regression utilising Baseline scores as a covariate. Missing data will be handled by using Markov chain Monte Carlo multiple imputation methods 34,35). The within-arm analyses will be based on a per-protocol estimand and tested with paired two-tailed t-tests. The use of per-protocol estimand will

ensure that the changes in outcome measures within a particular treatment arm are reflective of real-use scenarios, i.e. where the patients use the treatment as directed. The threshold for inclusion in the per-protocol analysis is set at the pre-defined minimum acceptable compliance threshold previously described. Additional exploratory efficacy analyses shall be conducted in order to ascertain treatment effects from Baseline to Interim (i.e. 6 weeks of treatment), and to evaluate any sustained efficacy by analysing changes in efficacy outcome measures from End-point to the three Follow-up assessments (i.e. at 18, 36 and 60 weeks after device fitting).

Safety analyses will be performed by evaluating the incidence of adverse events, classified as treatment or non-treatment related, and further sub-classified as Minor, Major and Serious. Adverse events will be recorded proactively, by monitoring significant changes in THI, TFI, MML, hearing thresholds and oral health, and reactively by documenting any adverse events reported by patients during the study. All adverse events will be analysed for trends, and statistical tests for significant between-arm differences will be conducted.

Efficacy and safety data analysis will be conducted in compliance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomised controlled trials (36) using the SAS software package.

Dissemination

Findings will be disseminated to relevant research, clinical, health service and patient communities through publications in peer-reviewed and popular science journals and presentations at scientific and clinical conferences.

DISCUSSION

This paper outlines the protocol for a multi-site, randomised, triple-blind, exploratory study designed to explore the effects of different bi-modal stimulation parameter sets across a number of tinnitus subtypes in a range of tinnitus clinical subdomains. The results of this study will inform the design of future triple-blind randomised control trials. The main objective

is to determine an optimised bi-modal stimulation parameter set, but we will also explore which patient characteristics might best predict therapeutic benefit in that treatment arm. We anticipate that this could lead to improved targeted intervention options for people with chronic subjective tinnitus.

This study is timely for several reasons. First, completing this exploratory trial will be important in determining any feasibility challenges and will be used to estimate the time, resources and sample size required for a full-scale RCT to answer the definitive question of clinical efficacy. Second, findings from this study could potentially inform the acceptability of bimodal stimulation in the wider population. There is a real need for effective therapeutic options that reduce or alleviate the tinnitus percept instead of simply helping people to manage the cognitive, emotional and behaviour impacts of their symptoms or to accept their long-term condition (3). Third, low quality clinical trial design and reporting has been identified as a major barrier to developing effective tinnitus therapies and standards of practice have been proposed (37, 38, 39). The study design and protocol description is in line with those recommendations.

AUTHORS' CONTRIBUTIONS: SD, CH, SH and BC conceived of the study. SD, CH, SH initiated the study design. SH provided statistical expertise in clinical trial design. BL, SV and DAH are members of the Science Advisory Board for Neuromod Devices Ltd and contributed to the Clinical Investigation Plan and the Statistical Analysis Plan, on which the protocol is based. BL and BC are Principal Investigators at the two trial sites. All authors contributed to the refinement of the study protocol and approved the final manuscript. SD submitted the manuscript for publication.

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COMPETING INTERESTS STATEMENT: SD, CH, SH, and BC are employees and shareholders of the Sponsor. BL, SV and DAH act as paid consultants for the Sponsor.

DATA SHARING STATEMENT: The data from this study will not be shared publicly shared.

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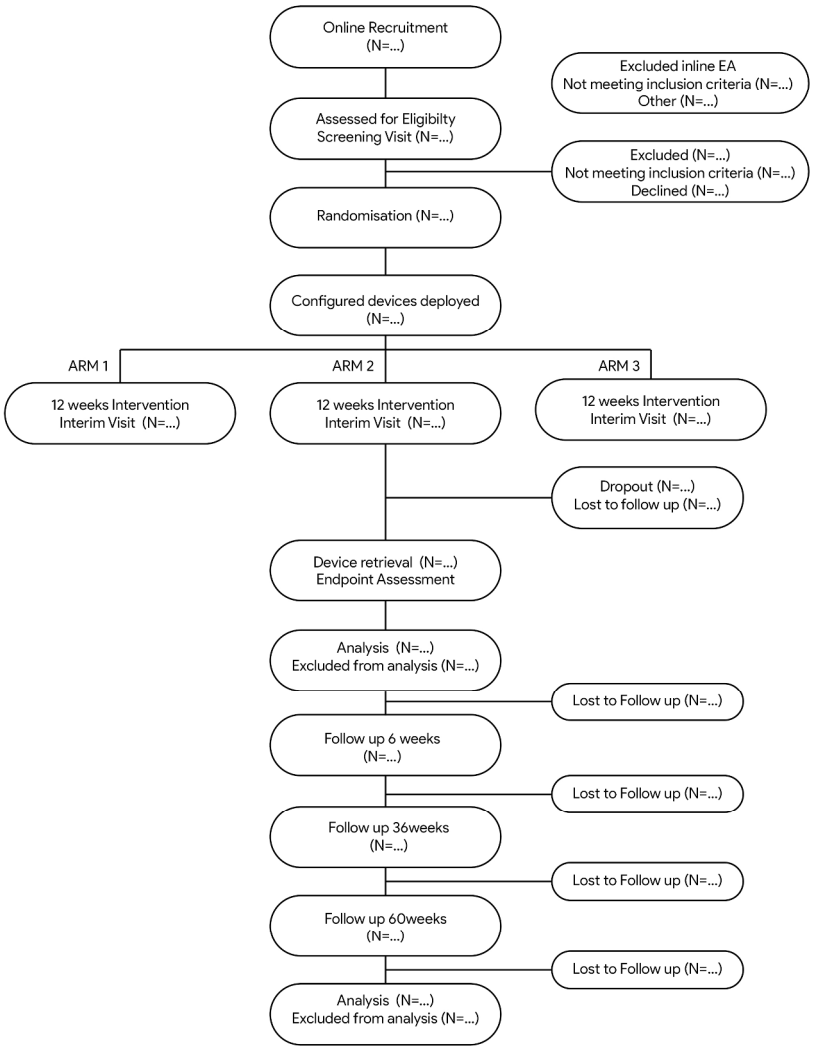
Figures:

Figure 1: Anticipated flow of participants through the TENT study



Anticipated flow of participants through the TENT study

209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

***while these items are not described in the manuscript they are addressed in our protocol, the study has been designed in line with GCP, SPIRIT and ISO14155 guidelines.**

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Not reported in manuscript*
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not reported in manuscript
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12, 13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not reported in manuscript
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not reported in manuscript
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not reported in manuscript
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9, 14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not reported in manuscript
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not reported in manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Not reported in manuscript
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not reported in manuscript
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not reported in manuscript
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported in manuscript

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.