The Statistical Analysis Plan for the Unification of Treatments and Interventions for Tinnitus Patients Randomized Clinical Trial (UNITI-RCT)

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Abstract

Background

Tinnitus is a leading cause of disease burden globally. Several therapeutic strategies are recommended in guidelines for the reduction of tinnitus distress; however, little is known about the potential increased effectiveness of a combination of treatments and personalized treatments for each tinnitus patient.

Methods

Within the Unification of Treatments and Interventions for Tinnitus Patients project, a multicenter, randomized clinical trial is conducted with the aim to compare the effectiveness of single treatments and combined treatments on tinnitus distress (UNITI-RCT). Five different tinnitus centers across Europe aim to treat chronic tinnitus patients with either cognitive behavior therapy, sound therapy, structured counseling, or hearing aids alone, or with a combination of two of these treatments, resulting in 4 treatment arms with single treatment and 6 treatment arms with combinational treatment. This statistical analysis plan describes the statistical methods to be deployed in the UNITI-RCT.

Discussion

The UNITI-RCT trial will provide important evidence about whether a combination of treatments is superior to a single treatment alone in the management of chronic tinnitus patients. This pre-specified statistical analysis plan details the methodology for the analysis of the UNITI trial results.

Trial registration

ClinicalTrials.gov NCT04663828 (https://clinicaltrials.gov/ct2/show/NCT04663828). The trial is ongoing. Date of registration: December 11, 2020. The main RCT analyses will start

by the end of December 2022 and will include data from patients who have finished their treatment by the 19th of December 2022.

Background

Tinnitus is a common condition associated with a high global disease burden. Currently, there is no universal treatment or cure for tinnitus [1]. Different therapeutic strategies are recommended to reduce the burden of tinnitus; however, little is known about the potentially greater efficacy of a combination of treatments compared to single treatments. Moreover, treatment studies in tinnitus research often suffer from methodological shortcomings. Multi-center randomized clinical trials (RCTs) could help to achieve methodologically more robust results. Within the multidisciplinary EU-funded project "Unification of Treatment and Interventions for Tinnitus Patients" (UNITI, [1]), a multicenter randomized clinical trial (UNITI-RCT) is conducted with the aim to compare the effectiveness of single or combinational treatment interventions for tinnitus. In detail, there are 10 different treatment arms, four with single treatments (cognitive behavioral therapy (CBT), sound therapy (ST), structured counseling (SC), or hearing aids (HA)) and six with combinational treatments (CBT and HA, CBT and ST, CBT and SC, ST and HA, ST and SC, SC and HA).

A study protocol for UNITI-RCT has previously been published [1] and the trial has been registered at ClinicalTrials.gov (NCT04663828). The study protocol states that the main goal of UNITI-RCT is to "[...] overcome the shortcomings of previous studies, but also pave the way for personalized medicine approaches in tinnitus. For this purpose, a multi-center parallel-arm superiority RCT, implemented and harmonized among five clinical sites across the EU, combining and investigating selected existing therapies evaluated in the European guidelines for tinnitus [2], is conducted."

The UNITI-RCT is executed in five clinical centers across the EU, with completion expected before the end of 2022. The already published study protocol delineates the rationale and methods of the study, its population plus the respective inclusion and exclusion criteria, the description of outcome measures, collected covariates, and the used interventions. As a follow-up to the study's protocol, this statistical analysis plan (SAP) aims to further describe the statistical techniques in more detail used to address the primary objectives of the RCT. To increase the transparency of data analysis, this plan will be made public before database closure and thus prior to the beginning of data analysis of the main objectives of the UNITI-RCT.

Methods/design

Study objectives

As stated in the study protocol [1], the objectives of the UNITI-RCT are to examine whether:
(1) combination therapy is more effective than a single therapy for the treatment of chronic tinnitus;
(2) the effectiveness of the ten investigated interventions differs from each other;
(3) for the four treatment types (SC, ST, HA, CBT) the combination with another treatment is superior to the treatment alone;
(4) a certain type of intervention either alone or in combination is superior to other treatments;
(5) a combination of treatments targeting both the auditory system and the central nervous system are superior to treatments targeting only either the ear or the brain.
(6) the development of a Decision Support System (DSS), where machine learning will be used to deliver personalized suggestions for interventions aiming to maximize its efficacy.

This SAP describes how objectives 1-5 will be evaluated. All these objectives are testing for superiority of one or several treatment types over the others. The first objective, which focuses on comparing the effects of single and combinatorial treatments in general and independent from the specific intervention, will be considered the main objective to be addressed by UNITI-RCT. The development of the DSS (objective 6) will be described elsewhere.

Table 1: Overview of the planned analyses to address the objectives of the UNITI-RCT.

Objective	**Description of comparison**	**Contrasted groups**	**Primary Outcome**	**Secondary Outcome**					
1	**Single versus combined**	(CBT, ST, SC, HA) versus (CBT + HA, CBT + ST, CBT + SC, ST + HA, ST + SC, SC + HA)	THI change at final visit (week 12) compared to baseline	THI at interim (week 6) compared to baseline	THI at Follow Up I (week 36) compared to baseline	THI at Follow Up II (week 48) compared to baseline	CGI-I at various time points (interim visit, and follow-ups at weeks 36 and 48)	TFI, Mini TQ, NRS, WHO-QoL Bref, PHQ-9, PHQ9 at various time points (interim visit, and follow-ups at weeks 36 and 48)	Dropouts, Treatment compliance
2	**All ten treatment arms**	CBT, ST, SC, HA, CBT + HA, CBT + ST, CBT + SC, ST + HA, ST + SC, SC + HA versus each other							
3	**SC single versus combined**	SC versus (SC+CBT, SC+ST, SC+HA)							
	ST single versus combined	ST versus (ST+SC, ST+CBT; ST+HA)							
	HA single versus combined*	HA versus (HA+SC, HA+CBT; HA+ST)							

	CBT single versus combined	CBT versus (CBT+SC, CBT+ST, CBT+HA)							
4	**SC versus no SC**	(SC, CBT + SC, ST + SC, SC + HA) versus (CBT, ST, HA, CBT + HA, CBT + ST, ST + HA)							
	ST versus no ST	(ST, CBT + ST, ST + HA, ST + SC,) versus (CBT, SC, HA, CBT + HA, CBT + SC, SC + HA)							
	HA versus no HA*	(HA, CBT + HA, ST + HA, SC + HA) versus (CBT, ST, SC, CBT + ST, CBT + SC, ST + SC)							
	CBT versus no CBT	(CBT, CBT + HA, CBT + ST, CBT + SC) versus (ST, SC, HA, ST + HA, ST + SC, SC + HA)							
5	**Combination of brain and ear targeting treatments**	(CBT + HA, CBT + ST, ST + SC, SC + HA) versus (CBT, ST, SC, HA, CBT + SC, ST + HA)							

Table legend: CBT: cognitive behavior therapy; ST: sound therapy; SC structured counseling; HA: hearing aids (CBT and HA, CBT and ST, CBT and SC, ST and HA, ST and SC, SC and HA). *: only patients from the strata with HA indication are included in this analysis.

Patient population

Each center aims to enroll 100 patients for the RCT, for a total number of 500 patients with chronic subjective tinnitus (ie., lasting for at least six months). At all sites, potential candidates are recruited via media advertising (according to local regulations) as well as on an individual basis at the clinical sites through e.g., information sheets, word of mouth, or conversations with medical staff.

Inclusion and exclusion criteria

Tables 2 and 3 summarize the inclusion and exclusion criteria for UNITI-RCT.

Table 2: Inclusion criteria of UNITI-RCT as specified in the study protocol [1].

Inclusion Criteria
Tinnitus as the primary complaint
Tinnitus lasting at least 6 months
Age 18-80 years
A score ≥ 18 in the Tinnitus Handicap Inventory at Screening
A score greater than 22 at the Montreal Cognitive Assessment (MoCa)
Ability and willingness to use the UNITI mobile applications [3] on their smartphones
Openness to using a hearing aid (if allocation to the hearing aid stratum)
Ability to understand and consent to the research (hearing ability, intellectual capacity)
Ability to participate in all relevant visits (no plans for e.g., long-term holidays or pregnancy)
Negative pregnancy test at screening (only at the clinical site in Granada due to specific standards of the local ethics committee)
Existing drug therapy with psychoactive substances (e.g., antidepressants, anticonvulsants)

must be stable for at least 30 days at the beginning of the therapeutic intervention. The drug therapy should remain constant during the duration of the study. Necessary changes do not constitute an exclusion criterion per se, but need to be recorded.

Table 3: Exclusion criteria of UNITI-RCT as specified in the study protocol [1].

Exclusion Criteria
Objective tinnitus or heartbeat- synchronous tinnitus as primary complaint
Otosclerosis / acoustic neuroma or other relevant ear disorders with fluctuation hearing
Present acute infections (acute otitis media, otitis externa, acute sinusitis)
Meniere's disease or similar syndromes with the exception of vestibular migraine
Serious internal, neurological or psychiatric conditions
Epilepsy or other central nervous system disorders (brain tumor, encephalitis)
Clinically relevant drug, medication or alcohol abuse up to 12 weeks before study start
Severe hearing loss as defined by the inability to communicate properly in the course of the study
At least one deaf ear
Missing written informed consent
Start of any other tinnitus-related treatments, especially hearing aids, structured counseling, sound therapy (with special devices; expecting long-term effects) or cognitive behavioral therapy in the last 3 months before the start of the study

Outcomes

The change between the Tinnitus Handicap Inventory (THI) at the final visit and baseline (post - pre) will be used as a primary outcome measure (see Table 1). In addition to the THI, secondary outcome measures are the changes between the final visit and baseline of the tinnitus functional index (TFI [4]), the short version of the tinnitus questionnaire (mini-TQ, [5]), Tinnitus Numeric Rating Scales (NRS, [6]), World Health Organization – Quality of Life abbreviated (WHOQoL-Bref;

https://www.who.int/healthinfo/survey/WHOQOL_BREF.pdf?ua=1), Clinical Global Impression Scale - Improvement (CGI-I, [7]), and Patient Health Questionnaire for Depression (PHQ-9, [9]).

Additional measures which are not defined as primary or secondary outcomes but may be used for sample description and additional analyses include: European School of Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ, [13]), tinnitus sample case history questionnaire (TSCHQ, [14]), Questionnaire on Hypersensitivity to Sound (GUF) [8], Big Five Inventory 2 (BFI-2 [15]), Montreal cognitive assessment (MoCA, also used as inclusion criteria, see above [16]), a short version of the Social Isolation Electronic Survey (Mini-SOISES, [10]), attitudes towards amplification questionnaire (ATAQ) which consists of a subset of questions from the Attitudes towards Loss of Hearing Questionnaire (ALHQ, [11]), Fear of Tinnitus Questionnaire (FTQ [12]), and audiometric and tinnitometric measurements (e.g., tinnitus loudness and frequency, maskability with minimum masking levels, and residual inhibition).

Variables assessment

An overview of all study assessments, and the time points when they were collected is presented in Table 4. The visit window for each study visit was ± 7 days. In addition to the outcome and other clinical measures described above, the assessment included voluntary blood sampling, auditory brainstem response (ABR) and auditory middle-latency responses (AMLR) and recording of concomitant treatment/medication. The collected ABR and AMLR data and blood samples will be addressed in additional analyses to the one described here. Safety measures are otological examination, audiometry, comorbidities, and adverse effects.

Table 4: Overview of assessments for the UNITI-RCT.

	Pre-screening	Screening	Baseline	Treatment start	Interim visit	Final visit = end of treatment	Follow-up	Additional follow-up
ICF	**A[a]**	**A**						
Eligibility criteria	**A**	**A**	**A**					
ESIT-SQ			**A**					
TSCHQ			**B**					
Mini TQ	**A**	**A**	**A**		**A**	**A**	**A**	**B**
Tinnitus numeric rating scales		**A**	**A**		**A**	**A**	**A**	**B**
TFI		**A**	**A**		**A**	**A**	**A**	**B**
THI	**A**	**A**	**A**		**A**	**A**	**A**	**B**
WhoQol-BREF		**A**	**A**		**A**	**A**	**A**	**B**
BFI-2			**A**					
CGI-I					**A**	**A**	**A**	**B**
GUF		**B**	**B**		**B**	**B**	**B**	**B**
PHQ-D	**A**	**A**	**A**		**A**	**A**	**A**	**B**
Mini-SOISES			**A**		**A**	**A**	**A**	**B**
ATAQ			**B[b]**			**B[b]**		
FTQ			**B**		**B**	**B**	**B**	**B**
MoCA		**A**						
Randomization			**A**					
Blood sampling			**B[c]**					
Otological examination		**A**				**A**	**B**	**B**
Audiometry		**A**				**A**	**B**	**B**
Loudness match		**A**				**A**	**B**	**B**

	Pre-screening	Screening	Baseline	Treatment start	Interim visit	Final visit = end of treatment	Follow-up	Additional follow-up
Pitch match		A				A	B	B
Maskability		A				A	B	B
Residual inhibition		A				B	B	B
ABR			A				B	B
AMLR			A				B	B
Treatment				A	A	A		
Comorbidities		A	A	A	A	A	A	B
Concomitant medication/ treatment		A	A	A	A	A	A	B
Adverse events					A	A	A	B

Table legend: Table reproduced from [1] (CC BY 4.0). Interim visit: week 6; final visit: week 12; follow-up: week 36; additional follow-up: week 48. A = mandatory; B = voluntary; ICF = Informed Consent Form; ESIT-SQ = European School of Interdisciplinary Tinnitus Research Screening Questionnaire; TSCHQ = Tinnitus Sample Case History; Mini-TQ = Mini Tinnitus Questionnaire; TFI = Tinnitus Functional Index; THI = Tinnitus Handicap Inventory; WhoQol-BREF = World Health Organization Quality of Life – abbreviated; BFI-2 = Big Five Inventory-2; CGI-I = Clinical Global Impression Scale – Improvement; GUF = Questionnaire on Hypersensitivity to Sound; PHQ-D = Patient Health Questionnaire for Depression; SOISES = Social Isolation Electronic Survey; ATAQ = Attitudes Towards Amplification Questionnaire; FTQ = Fear of Tinnitus Questionnaire; MoCA = Montreal Cognitive Assessment; ABR = Auditory Brainstem Response; AMLR = Auditory Middle Latency Response.

Screening and Baseline measurements as well as treatment start can be performed on the same day. In this case, all measurements are only performed once. The baseline should be maximum 4 weeks before the treatment start; otherwise, baseline measures should be repeated (without ESIT-SQ, TSCHQ, BFI-2, ATAQ, electrophysiological measurements).

*Declaration of consent (ICF) can be digital for the pre-screening.

**Only for participants who were allocated to a single or combinational treatment with HA.

***Blood samples can be taken at any time point before treatment start

Intervention

Treatment conditions

The main objective of the UNITI RCT is to investigate the effects of four different interventions (SC, ST, HA, CBT) and the combinations of these interventions (CBT + HA, CBT + ST, CBT + SC, ST + HA, ST + SC, SC + HA). Internal standard operation procedures were developed, and workshop training was conducted to ensure harmonization among the participating clinical sites with regard to the procedure, technical equipment, and training of the research staff. A full description of each of the four treatments is available in the study protocol [1].

Randomization and blinding

Eligible participants are randomly allocated to one of ten treatment arms of single or combinational treatments (see Figure 1). In the first step, patients will be stratified into two groups according to the severity of their tinnitus distress as measured by the THI. Participants with a THI score greater or equal to 48 are allocated to a “high distress” group, whereas participants with a smaller than 48 are allocated to a “low distress” group. This stratification was performed to capture the tinnitus disorder subtype, which is marked by high tinnitus-related distress[17]. In the second step, the two subgroups of low and high tinnitus distress will be further stratified based on their degree of hearing loss into a subgroup with and without hearing aid indication. This results in four stratification groups, namely: HA indication & low tinnitus distress, HA indication & high tinnitus distress, no HA indication & low tinnitus distress, and no HA indication & high tinnitus distress (cf. Figure 1). An equal ratio of 25 patients per group per clinical site is intended, resulting in a total number of 100

patients per site. Subsequently, in each center, patients are assigned to one of the ten treatment arms according to predefined randomization tables to have appropriate ratios for the planned primary analysis/contrasts (e.g., single vs. combinatory treatment).

Figure 1: Randomization scheme as shown in the study protocol. Figure reproduced from [1] (CC BY 4.0).

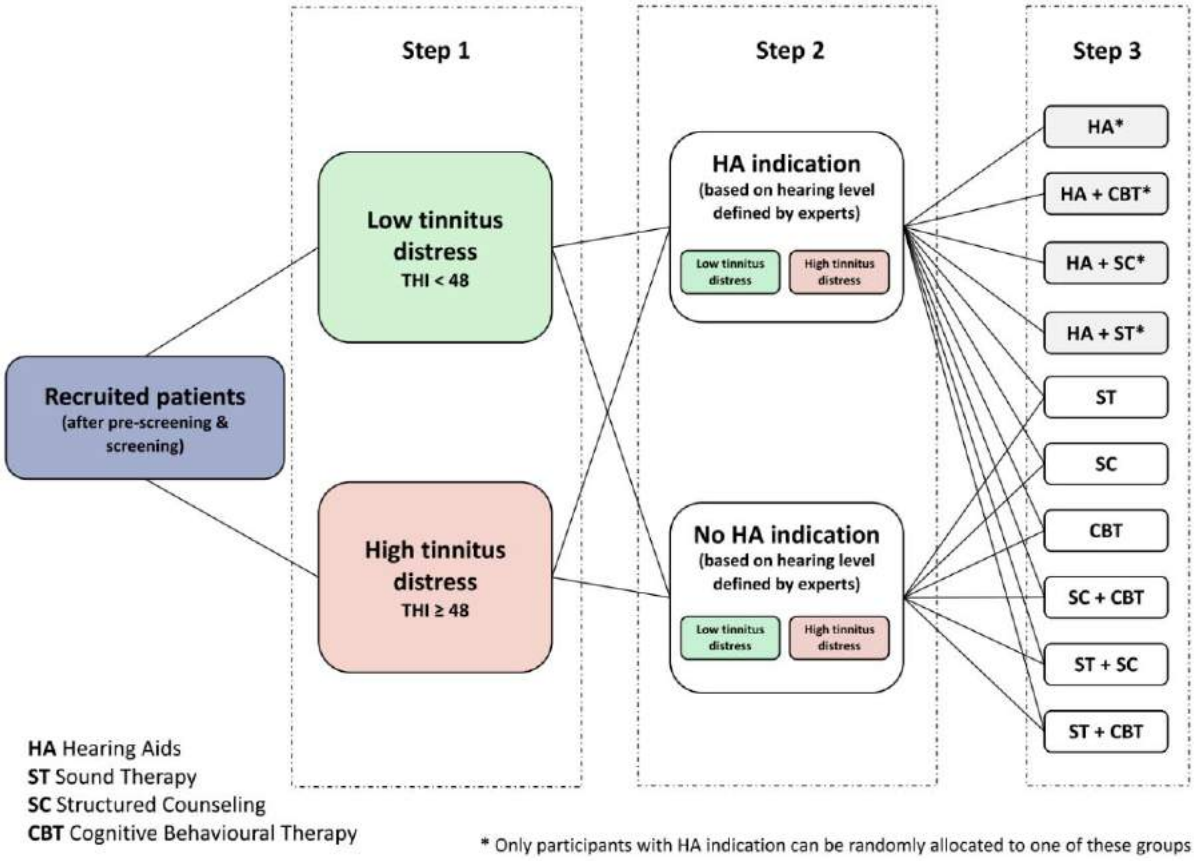

Table 5 shows the expected allocation of patients to each of the ten treatment arms considering the proportional ratios of the planned analysis.

Table 5: Expected randomization per center and per treatment.

	randomized allocation of patients in Athens	randomized allocation of patients in Berlin	randomized allocation of patients in Granada	randomized allocation of patients in Leuven	randomized allocation of patients in Regensburg	Total
HA	12	12	12	12	12	60
ST	12	12	12	12	12	60
SC	12	12	12	12	12	60
CBT	12	12	12	12	12	60
HA + CBT	4	4	4	4	4	20
HA + SC	4	4	4	4	4	20
HA + ST	6	6	6	6	6	30
SC + CBT	12	12	12	12	12	60
ST + SC	14	14	14	14	14	70
ST + CBT	12	12	12	12	12	60
Total	100	100	100	100	100	500

The randomization of patients takes place at each clinical site and is monitored centrally. A specific interactive web response system (IWRS) is used to support each clinical site with the randomization of their patients. This facilitates the management of many patients from different sites located in several countries and the monitoring of the multicentric study with a complex design. The distribution across the four strata is centrally monitored during the

randomization process. If a recruited and eligible participant quits the RCT participation before randomization, this participant is considered a screening failure. In case an eligible participant is already randomized to a treatment group and quits study participation, this patient is considered a dropout.

The local clinical staff will enter clinical data into a central tinnitus database [6]. Patient-specific data as well as treatment types will be stored with specific pseudo-anonymized codes. The data analysis team (see section timing of analysis) will only have access to the blinded treatment codes stored in the database and will therefore be blinded to the type of treatment participants received. The statistical analysis team will have the treatment codes unblinded only after the analysis is completed by the project coordinators (SSch and WS).

General principles of statistical analysis

A p-value of < 0.05 will be considered statistically significant and parameter estimates will be presented with two-sided 95% confidence intervals.

Sample size calculation

A sample size of 500 participants has been calculated based on conservative estimates of the effect size from previous clinical trials delivering CBT, SC, and ST, with the aim to achieve enough statistical power to address objective 1; see the study protocol [1]. Each of the five centers will recruit 100 patients. An equal ratio between the four strata (HA yes, THI ≥ 48; HA no, THI ≥ 48; HA yes, THI < 48; HA no, THI < 48) is intended for each study site.

Timing of analysis

An initial data exploration is conducted during data collection to ensure the integrity (i.e., the overall completeness and accuracy) of the data stored in the database. No interim analyses are planned. Data preparation, such as data cleaning (e.g., standardizing variable names,

encoding categorical variables as factors) and munging will take place for each center after the final visit of the last patient is recorded, as well as plausibility checks. Exploratory data analysis with graphical methods (e.g., histograms, bar-plots, scatterplots, graphical exploration of missing values) will also be conducted for each center after the final visit of the last patient is recorded. The initial and exploratory data analysis, as well as the analysis of the main results, will be carried out by the statistical analysis team [JS, SG, CJ, UN, MSp, ME, NW, LB] with the pseudo-anonymized treatment code, and therefore treatment blindness will be preserved. The main RCT analyses will start by the end of December 2022 and will include data from patients who have finished their treatment by the 19th of December 2022. Secondary outcome analysis is planned to occur when the 48-week follow-up period has been reached for participants included in the primary outcome analysis.

Data sets to be analyzed

The intention-to-treat (ITT) population includes all participants randomized regardless of compliance with the study protocol. Unless otherwise specified, the main analyses will be conducted on an intention-to-treat basis.

Sensitivity analysis: A per-protocol analysis will be conducted to detect potential effects from non-compliance. It will include all subjects who met the requirements for treatment compliance (as described below). The main analysis will be repeated in the per-protocol population to test the robustness of the primary ITT analysis.

Subject disposition

The flow of participants through the clinical trial stages will be shown with a diagram following the guidelines of the Consolidated Standards Of Reporting Trials (CONSORT) [18]. This will include, for each of the centers the number of participants who were screened, excluded, randomized, dropped out before treatment start (reported per treatment arm), began

the intended treatment, dropped out during treatment (reported per treatment arm), completed treatment, and were analyzed for the main objective (reported per treatment arm). Additionally, protocol deviations will be presented alongside reasons.

Participant characteristics

Baseline participant characteristics will be presented descriptively in a standardized manner as shown in Tables 7 and 8. Participants will be described based on age, sex, education attainment (ESIT-SQ), PHQ-9 scores, THI scores, TFI scores, Mini-TQ scores, WHOQoL-Bref scores, hearing loss (audiometry), and clinical tinnitus characteristics (ESIT-SQ). Descriptive analysis will consist of mean scores followed by standard deviations, as well as medians followed by minimum and maximum values for continuous variables, and frequencies followed by percentages for discrete variables. Descriptive analysis will be available for baseline, interim (6 weeks after baseline), and final visits (12 weeks after baseline). Raw data will also be reported on a longitudinal mean plot together with 95% confidence intervals.

Treatment compliance/adherence and protocol deviations

Compliance with treatment protocols is defined for each treatment arm separately. For combined treatments, failing to meet the criteria for one of the arms is sufficient to identify a patient as failing to comply with the protocol. Table 6 summarizes the definitions for each of the arms. For CBT, meeting one of the two criteria presented below is sufficient to identify a patient as non-compliant.

Table 6: Definitions of non-compliance with treatment protocols.

Treatment	Definition of non-compliance with treatment protocol

CBT	1) Missing the first and second CBT session 2) participating in less than 6 of the 12 CBT sessions
ST	1) having not played at least once each of the four stimuli categories
SC	1) Not having completed the first six chapters of the SC
HA	1) having used HA for less than 4 hours per day, on average, according to data logging

Table legend: CBT = cognitive behavior therapy, ST = sound therapy, SC = structured counseling, HA = hearing aid.

The number and percentage of participants compliant with treatment will be presented per treatment group. Compliance is determined by App-use log files (SC, ST), hearing aid log files (HA), and participation in treatment sessions (CBT). Acceptable compliance will be defined as ≥50% of the recommended intervention (participation in ≥6 CBT sessions including the first two, using HA 4 or more hours per day, on average, according to data logging, having completed at least the first 6 chapters of SC and having played at least once each of the four ST stimuli categories). Withdrawal from/compliance with the randomized intervention will be summarized using the following variables:

- Number of treatment discontinuations;
- Number of patients who decided to continue with study visits even though they canceled their treatment;
- Discontinuation reasons (where available);
- Compliance with the intervention (in percent), as described above;

All cases of protocol deviations will lead to an exclusion of the respective participant from the main analysis. A list of deviations will be presented in a table including the treatment arm and details of the deviation. Protocol deviations are defined as any deviations from the study

protocol [1], non-compliance with inclusion/exclusion criteria as checked during the standard visits (interim and end of treatment visits), non-compliance with treatment protocols, or errors in study conduct.

Concomitant therapies

Type and frequency of concomitant medication and treatment will be categorized and presented descriptively.

Main analysis

Linear regression models will be used to address the main objective of UNITI-RCT by using the difference in the THI between baseline and final visit and adjusting for treatment received (see below). Post-hoc comparisons will then be carried out to identify potential differences in the change in the THI across groups. For objective (1), UNITI-RCT's main objective, a covariate identifying whether the patient received a combined or single treatment will be added to the model. For objectives (2) and (4), the treatment received will be added to the model as a covariate. For objective (3), four models will be developed comparing participants who received one of the single treatments with combined treatments. For objective (5), a covariate will be included in the model identifying whether the patient got an ear-mediated treatment (HA, ST, HA + ST), a brain-mediated treatment (CBT, SC, CBT + SC), or a combination of the two (HA + SC, HA + CBT, ST + SC, ST + CBT). Table 1 provides a summary of the contrasts used for assessing each objective. Effect estimates will be reported with p-values and 95% confidence intervals. The assumptions for linear regression will be tested using diagnostic plots. If the assumptions are violated, transformations will be performed depending on the type of violation (e.g., heteroscedasticity: log transformation, non-linearity: quadratic transformations) or non-parametric alternatives will be used instead.

Adjusted analysis

In addition to the model described above, sensitivity analysis will be conducted by adjusting the model for the following covariates: center where the treatment was received, age, gender, educational attainment, hearing loss, and depression according to the PHQ-9 measured during baseline.

Treatment of missing data

Multiple imputation techniques, such as multiple imputation using chained equations (MICE, [19]), will be deployed if data is assumed to be missing at random (MAR) [20]. The key concept of multiple imputation is to use the non-missing observed data to estimate plausible values for the missing data [19]. This method was selected due to its lower estimate bias, especially when compared to other techniques such as the last observation carried forward [21,22]. Multiple imputation will be used to account for participants with missing outcome values as part of the ITT analysis.

Analysis of safety outcomes

Between-group analysis of safety outcomes will be presented descriptively, as outlined in the study protocol [1].

Adverse events (AE)

ICD-10 codes will be used for all reported adverse events. Serious adverse events as identified by Good Clinical Practice §3 (6, 8) are described in terms of relatedness to treatment (yes/no) and whether the adverse event was expected (yes/no). Self-reported data are used as primary sources of AE and supported by clinical reports. If the same AE is reported by self-reports and clinical reports, only the former will be presented to avoid duplications. The following medical occurrences will be considered serious adverse events:

- Death;

- Threat to life;
- Requirement for hospitalization or extension of current hospitalization;
- Persistent disability or incapacity;
- Medically relevant events (e.g., allergy).

The number of treatment-related adverse events are reported divided by their relationship to treatment (‘doubtful’, ‘possible’, ‘probably’ and ‘certain’).

Statistical Software

All preprocessing and statistical analysis will be conducted in R. Data wrangling will be done with the “tidyverse” packages [23]. Model assessment will be conducted with the “performance” package [24].

Conclusion

The UNITI trial will be one of the world’s largest tinnitus trials and the first to compare established standard treatments performed alone or in combination. The results of the UNITI trial will provide much-needed evidence to clinicians and are likely to influence international clinical guidelines. The planned statistical analysis is detailed here to provide transparency.

Table 7: Baseline characteristics stratified based on center.

Sample (N=, %)	Athens	Berlin	Granada	Leuven	Regensburg
Age					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Sex					
Female					
Male					
Missing (%)					
Education Attainment (ESIT-SQ A5)					
No school					
Primary (elementary school)					
Lower secondary (middle school)					
Upper secondary (high school)					
University or higher degree					
Missing (%)					
PHQ-9 Score					

Mean (SD)					
Median [Min, Max]					
Missing (%)					
THI Score					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
TFI Score					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Mini-TQ Score					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Physical Health (WHOQOL)					
Mean (SD)					

Median [Min, Max]					
Missing					
Psychological Health (WHOQOL)					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Social Factors (WHOQOL)					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Environment (WHOQOL)					
Mean (SD)					
Median [Min, Max]					
Missing (%)					
Hearing Loss					
None					
Mild					

Moderate					
Severe					
Missing (%)					
Tinnitus Presentation (ESIT-SQ B2)					
Constant					
Intermittent					
Missing (%)					
Tinnitus Duration (ESIT-SQ B3)					
Mean (SD)					
Median [Min, Max]					
Missing (%)					

Table 8: Baseline characteristics stratified based on treatment received.

Sample (N=, %)	CBT	HA	SC	ST	CBT + HA	CBT + SC	CBT + ST	HA + SC	HA + ST	SC + ST
Age										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
Sex										
Female										
Male										
Missing (%)										
Education Attainment (ESIT-SQ A5)										
No school										
Primary (elementary school)										
Lower secondary (middle school)										

Upper secondary (high school)										
University or higher degree										
Missing (%)										
PHQ-9 Score										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
THI Score										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
TFI Score										
Mean (SD)										
Median [Min, Max]										
Missing (%)										

Mini-TQ Score										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
Physical Health (WHOQOL)										
Mean (SD)										
Median [Min, Max]										
Missing										
Psychological Health (WHOQOL)										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
Social Factors (WHOQOL)										
Mean (SD)										

Median [Min, Max]										
Missing (%)										
Environment (WHOQOL)										
Mean (SD)										
Median [Min, Max]										
Missing (%)										
Hearing Loss										
None										
Mild										
Moderate										
Severe										
Missing (%)										
Tinnitus Presentation (ESIT-SQ B2)										
Constant										
Intermittent										

Missing (%)										
Tinnitus Duration (ESIT-SQ B3)										
Mean (SD)										
Median [Min, Max]										
Missing (%)										

References

1. Schoisswohl S, Langguth B, Schecklmann M, Bernal-Robledano A, Boecking B, Cederroth CR, et al. Unification of Treatments and Interventions for Tinnitus Patients (UNITI): a study protocol for a multi-center randomized clinical trial. Trials. 2021;22:875.
2. Cima RFF, Mazurek B, Haider H, Kikidis D, Lapira A, Noreña A, et al. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. Hno. 2019;67:10–42.
3. Vogel C, Schobel J, Schlee W, Engelke M, Pryss R. UNITI Mobile—EMI-Apps for a Large-Scale European Study on Tinnitus. 2021 43rd Annu Int Conf Ieee Eng Medicine Biology Soc Embc. 2021;00:2358–62.
4. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, et al. The Tinnitus Functional Index. Ear Hearing. 2012;33:153–76.
5. Hiller W, Goebel G. Rapid assessment of tinnitus-related psychological distress using the Mini-TQ. International Journal of Audiology. 4AD;600–4.
6. Landgrebe M, Zeman F, Koller M, Eberl Y, Mohr M, Reiter J, et al. The Tinnitus Research Initiative (TRI) database: A new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome. Bmc Med Inform Decis. 2010;10:42.
7. Adamchic I, Tass PA, Langguth B, Hauptmann C, Koller M, Schecklmann M, et al. Linking the Tinnitus Questionnaire and the subjective Clinical Global Impression: Which differences are clinically important? Health Qual Life Out. 2012;10:79.
8. Nelting M, Rienhoff N, Hesse G, Lamparter U. Die Erfassung des subjektiven Leidens unter Hyperakusis mit einem Selbstbeurteilungsbogen zur Geräuschüberempfindlichkeit (GÜF). Laryngo Rhino Otol. 2002;81:327–34.
9. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med. 2001;16:606–13.
10. Schlee W, Hølleland S, Bulla J, Simoes J, Neff P, Schoisswohl S, et al. The Effect of Environmental Stressors on Tinnitus: A Prospective Longitudinal Study on the Impact of the COVID-19 Pandemic. J Clin Medicine. 2020;9:2756.
11. Saunders GH, Cienkowski KM, Forsline A, Fausti S. Normative Data for the Attitudes towards Loss of Hearing Questionnaire. J Am Acad Audiol. 2005;16:637–52.
12. Fuller TE, Cima RFF, Bussche EV den, Vlaeyen JWS. The Fear of Tinnitus Questionnaire: Toward a Reliable and Valid Means of Assessing Fear in Adults with Tinnitus. Ear Hear. 2019;40:1467–77.
13. Genitsaridi E, Partyka M, Gallus S, Lopez-Escamez JA, Schecklmann M, Mielczarek M, et al. Standardised profiling for tinnitus research: The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). Hearing Res. 2019;377:353–9.
14. Langguth B, Goodey R, Azevedo A, Bjorne A, Cacace A, Crocetti A, et al. Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. Prog Brain Res. 2007;166:525–36.
15. Soto CJ, John OP. The Next Big Five Inventory (BFI-2): Developing and Assessing a Hierarchical Model With 15 Facets to Enhance Bandwidth, Fidelity, and Predictive Power. J Pers Soc Psychol. 2017;113:117–43.
16. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al.

The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005;53:695–9.
17. Ridder DD, Schlee W, Vanneste S, Londero A, Weisz N, Kleinjung T, et al. Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). Prog Brain Res. 2021;260:1–25.
18. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. Cochrane Db Syst Rev. 2012;2013:MR000030.
19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377–99.
20. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. Bmc Med Res Methodol. 2017;17:162.
21. Goeij MCM de, Diepen M van, Jager KJ, Tripepi G, Zoccali C, Dekker FW. Multiple imputation: dealing with missing data. Nephrol Dial Transpl. 2013;28:2415–20.
22. Salim A, Mackinnon A, Christensen H, Griffiths K. Comparison of data analysis strategies for intent-to-treat analysis in pre-test–post-test designs with substantial dropout rates. Psychiat Res. 2008;160:335–45.
23. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the Tidyverse. J Open Source Softw. 2019;4:1686.
24. Lüdecke D, Ben-Shachar M, Patil I, Waggoner P, Makowski D. performance: An R Package for Assessment, Comparison and Testing of Statistical Models. J Open Source Softw. 2021;6:3139.

Declarations

Availability of data and materials

All investigators from UNITI-RCT have access to the study data stored in the tinnitus database [6]. Raw data (de-identified) can be provided upon request.

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Ethics approval

Approval for the UNITI-RCT was obtained by the local ethics committees at all investigator clinical sites and all participants provided written informed consent; detailed information can be found in the study protocol [1].

Consent for publication

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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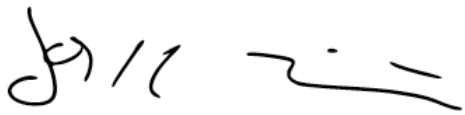
Additional information

- Trial registration: NCT04663828
- SAP Version: 1.0, Date: Dec 19, 2022.
- This document has been written based on information contained in the study protocol, version no. 3., dated November 4, 2021 [1] and the Data Management Plan, version no. 3, dated February 21, 2020 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5cc7abcb5&appId=PPGMS)
- Signatures:

  Signature of person writing the SAP: Jorge Piano Simoes



  Signature of senior statistician responsible: Winfried Schlee

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