Unification of treatments and interventions for tinnitus patients

Proposal No.: 848261

Deliverable D7.1:
First Study Subject Approvals Package

Deliverable No. D19 – WP7

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1 Introduction

The first study subject approvals package will contain the documents about the ethics approvals for the clinical trial at all centres, unless subject to confidentiality.

2 Status of RCT Applications at the respective Ethics Committees

The study protocol for all five UNITI trial cites will be the same. Even though, five ethical approvals for all trial cites are mandatory by the respective Ethical Committees.
To make the work more efficient for the respective Ethical Committees and trial cites, our procedure is to seek ethical approval at the university clinic of the coordinator (University of Regensburg) first and refer to this approval when submitting ethical applications to the remaining four trial cites. The ethical approval by the Ethical Committee of the University of Regensburg has been received on 22.07.2020. Following this approval, the Ethical Committee of Charité, Universitaetsmedizin Berlin has approved the RCT on 02. December 2020. The approvals from the other three Ethical Committees (Athens, Granada and Leuven) are currently processed and will most likely be received by project month 14.

3 Study Information

3.1 Study Protocol

A publication of the study protocol is underway and will be published as an Open Access article as soon as possible.

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria
Primary complaint tinnitus
Chronic tinnitus (for at least 6 months based on history)
Age 18-80 years
Ability to understand and consent to the research / ability to participate (hearing ability, intellectual capacity, no plans for sabbaticals or long-term holidays, no (plans for) pregnancy*)
A score of >22 on the Montreal Cognitive Assessment (MoCa), i.e. adults without mild cognitive impairment
Ability and willingness to use the UNITI mobile applications on their smartphones
A score of ≥ 18 in the Tinnitus Handicap Inventory (THI) of Newman et al. (1996)
Willing to use a hearing aid (if indication)

If a drug therapy with psychoactive substances (e.g. antidepressants, anticonvulsants) exists at the beginning of the therapeutic intervention, it must have been stable for at least 30 days. The therapy should remain constant during the duration of the study, but a necessary change is not an exclusion criterion. Any change in medication is documented in the CRF.
Exclusion Criteria
Objective tinnitus / heartbeat-synchronous tinnitus as primary complaint
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**
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 (but not vestibular migraine)
Serious internal, neurological or psychiatric conditions
Epilepsy or other CNS disorders (brain tumor, encephalitis)
Clinically relevant drug, medication or alcohol abuse up to 12 weeks before study start
Missing written informed consent
Severe hearing loss – inability to communicate properly in the course of the study
One deaf ear

3.3 Informed Consent

The Informed Consent Form was accepted by the Ethics Committees with the proviso that it be adapted to the relevant national and local circumstances. These adaptations will be collected and submitted to the respective ethics committees in January as an amendment to the ICF.

INFORMED CONSENT FORM

Study Title: Unification of treatments and Interventions for Tinnitus Patients – Randomized Clinical Trial

Study Code: UNITI-RCT

Study team (institution):

……

Principal Investigator:

……

Site (City):

……

Contact details:

……

Patient Code:

……

Dear study participant,

thank you very much for your interest in participating in this clinical trial, which will investigate different types of single and combined treatment types for tinnitus. Together with a member of the study team, you will now go through this Informed Consent Form (ICF) which has two parts.

• **Information Sheet** - for information on the progress of the study

• **Certificate of Consent** - for signatures if you agree to take part

If you have any questions or difficulties understanding the following information, please do not hesitate to ask questions.

You will receive a copy of the full Informed Consent Form

PART 1: INFORMATION SHEET - RCT

You are being asked to participate in this clinical research study. Before you decide whether to participate, it is important that you understand why this study is being conducted, what is expected of you as a participant, the potential benefits, risks and inconveniences involved, and how your information and data will be used. Please read this information carefully and if you have any questions, please ask the study team. Before you make a decision regarding your participation, you are welcome to consult with others, such as your family doctor, family and friends. If you do not understand parts of the information presented to you, you are welcome to ask the study team to explain them to you.

Even if you have questions later, please do not hesitate to contact the study team. The contact details of the respective contact persons are listed at the end of this document.

This study is funded by the European Union´s Horizon 2020 research and innovation programme under the grant agreement no. 848261.

1. WHAT IS THE PURPOSE OF THE STUDY?

Tinnitus is the perception of noise or ringing without the presence of an external source of sound. It is a very common problem and many people are suffering from this condition. Although much progress has been made, there is currently no curative treatment for tinnitus available. Different manifestations of tinnitus make it difficult to find a treatment that benefits all those affected. However, in some people particular treatments appear to alleviate tinnitus-related suffering. The aim of this study is not only to compare commonly used tinnitus treatments (sound therapy, cognitive behavioural therapy, hearing aids or structured counseling) among each other, but also to investigate the effect of certain treatments in combination (e.g., hearing aids together with structured counseling). Moreover, we want to find out, which people are more likely to benefit from a certain type of treatment (single or combination).

2. DO I HAVE TO TAKE PART?

Your participation in the study is voluntary. You decide whether you want to participate or not. If you decide to participate, you are free to cancel your participation in the study at any time and without giving reasons. However, if you decide to withdraw from the study, we ask you to seek advice from the study team or the responsible staff doctor and attend one of the early termination visits. This will in no way affect your medical care in the future.

The study team can also decide to take you off the study at any time. The reasons that might cause your treatment to be stopped include, but are not limited to:

- The study team decides that the study treatment is not helping you or that it is not safe for you to continue treatment with the study treatment
- You start a treatment with another therapy for tinnitus
- You are unable to comply with the study requirements
- You are positive for COVID-19 and the study team considers that your condition will jeopardize your health condition
- The study is stopped by the study site or by <<insert name of country regulatory body>> or another regulatory body
- The study is stopped or paused by the study team or the principal investigator due to new safety data from other participating subjects on the study

3. PROCEDURE OF THE STUDY OR WHAT WILL HAPPEN IF I DECIDE TO TAKE PART?

We want to compare frequently used tinnitus treatments and investigate the effect of certain treatments in combination. We also want to find out which persons are more likely to benefit from a certain type of treatment (single or combination treatment). To do this, we will divide participants into two groups based on their hearing test (level of hearing loss). If your degree of hearing loss shows a need for a hearing aid, you will be placed in a group for hearing aid indication, which does not mean that you will receive a hearing aid. Within this group, participants are then randomly (by chance) assigned to one of 10 treatments (hearing aids, sound therapy, structured counseling, cognitive behavioral therapy as a single treatment or as combinational treatment with a maximum of two simultaneous treatments). If the degree of your hearing loss shows that you have no indication for a hearing aid, you will be included in the group without hearing aid indication. Within this group, participants are then also randomly (by chance) assigned to one of 6 treatments (sound therapy, structured counseling, cognitive behavioral therapy as a single treatment or as combinational treatment with a maximum of two simultaneous treatments). The study team will be looking after you and the other participants very carefully during the study. If there is anything that concerns you or makes you feel uncomfortable about this study, please talk to the study team.

Regardless of the treatment you will receive, there are 3 phases in this study: Screening period, treatment period and follow-up period as shown in **Figure 1**. There will be a minimum of 4 visits (+ one additional voluntary visit), each lasting about 2 hours.

Screening/ Baseline Period

Study procedures

In order to participate in this study, there is a need to clarify during a so-called Screening if you are eligible for participation. After a successful (online) pre-screening, the study team and the responsible staff will:

- ask you to sign the informed consent form.
- ask you to fill in some questionnaires and do some tests that are relevant for study participation.
- will perform an assessment of your cognitive abilities (MoCA test).
- confirm that you are eligible for the study (or that you are not eligible).

If you are considered as eligible to participate, the study team and the responsible staff will:

- ask you to fill in some health-related questionnaires.
- evaluate your tinnitus condition via specific questionnaires.
- make an examination of your ear.
- perform a hearing test.
- will make some more clinical tests for tinnitus: tinnitus loudness, tinnitus pitch, tinnitus maskability, residual Inhibition (short-term tinnitus suppression after sound stimulation).
- will perform measures of acoustic evoked potentials (measurements of auditory pathway activity via electrodes placed on the head).
- record your full medical history, including your prior treatments and medical problems you may have had. Also, which of treatments are carried out during the course of the study.
- review any medicines you are taking, including any over the counter medicines, herbal supplements, and herbal/natural remedies. Also, which of them are taken during the course of the study.
- ask you to give a small quantity of blood to measure biomarkers. A biomarker is a biological molecule that is a sign of a normal or abnormal condition. Some biomarkers may help predict how well someone will respond to a specific treatment for a disease. <u>This part is optional. You do not have to give your consent to genetic testing to take part in this study.</u>
- randomize you to a treatment group.

If the treatment starts later than 4 weeks after the Baseline Period, all measures are repeated again (except two specific questionnaires about your tinnitus, acoustic evoked potentials and examination of the ear).

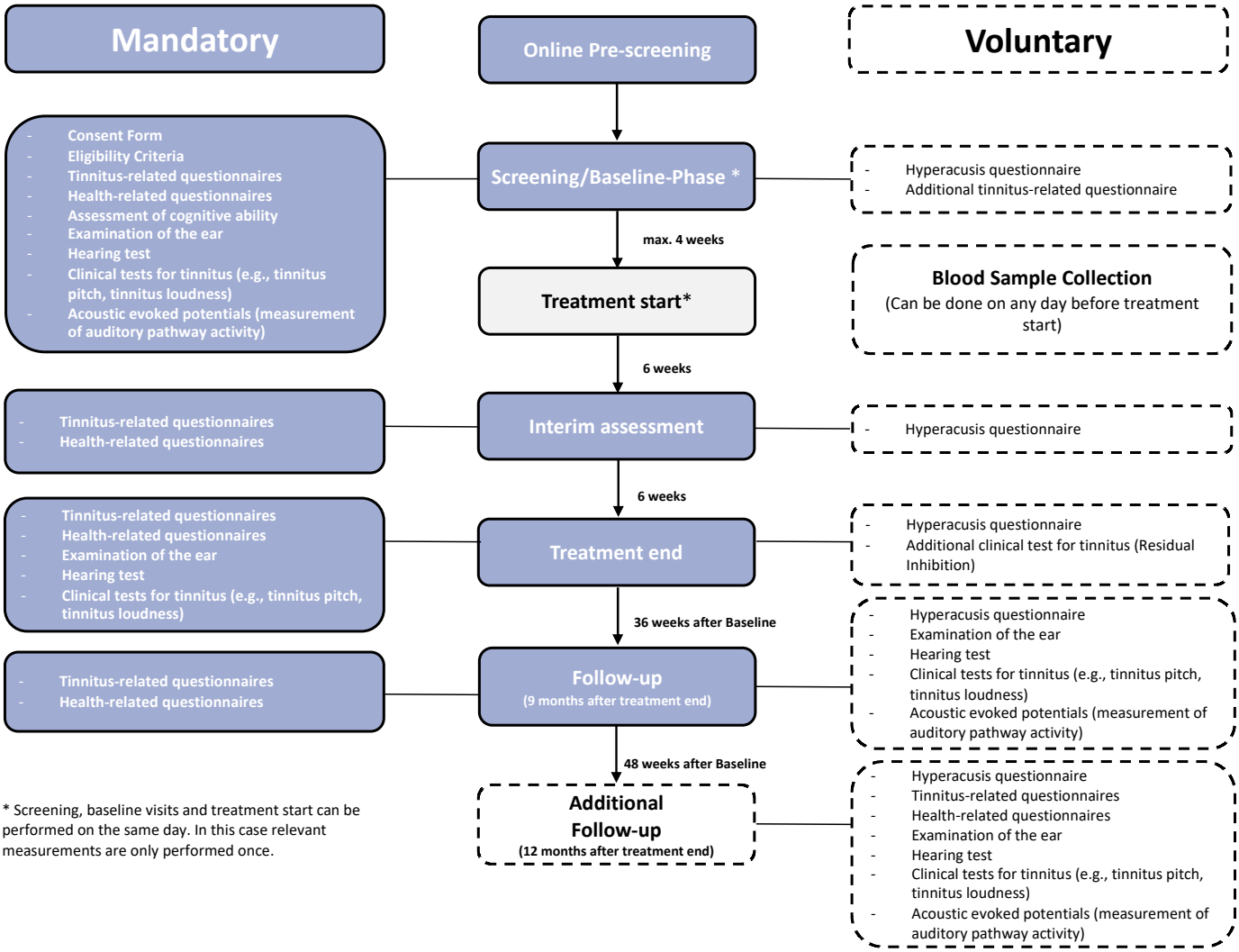

Figure 1 – Flow chart Assessments

Treatment Period

The treatment period will last 12 weeks. During the treatment period you will be asked to visit the clinic 3 times.

Study procedures

Treatment Start: During the baseline visit you will be randomized to a specific treatment. The study team will

- the study team will explain you the particular treatment in more detail.
- update your full medical history,

Interim Visit: During the interim assessment (6 weeks after treatment start) the study team will

- ask you to fill out some health- and treatment-related questionnaires.
- evaluate your tinnitus condition via specific questionnaires.
- update your full medical history.
- ask you for adverse events occurred.

Final Visit: During the Final Visit (12 weeks after treatment start), which is also the end of your treatment, the study team will:

- ask you to fill out some health- and treatment-related questionnaires.
- evaluate your tinnitus condition via specific questionnaires.
- update your full medical history.
- ask you for adverse events occurred.
- make an examination of your ear.
- perform a hearing test.
- will make some more clinical tests for tinnitus: tinnitus loudness, tinnitus pitch, tinnitus maskability.
- ask you, if you want to participate in further voluntary clinical tests for tinnitus: residual inhibition (short-term tinnitus suppression after sound stimulation).

Follow-up Period

During the follow up period you are asked to visit the clinic 2 times as shown in **Figure 1**.

Study procedures

Follow up: The 1st follow-up visit will be performed 9 months after your baseline visit and the study team will:

- ask you to fill out some health-related questionnaires
- evaluate your tinnitus condition via specific questionnaires
- update your full medical history.
- ask you for adverse events occurred.
- ask you, if you want to participate in further voluntary measurements:
    - examination of your ear
    - hearing test
    - some more clinical tests for tinnitus: tinnitus loudness, tinnitus pitch, tinnitus maskability, residual Inhibition (short-term tinnitus suppression after sound stimulation).
    - measures of acoustic evoked potentials (measurements of auditory pathway activity via electrodes placed on the head).

Additional follow up: The 2nd follow up visit will be performed 12 months after your baseline visit. This is a voluntary visit, during this visit the study team will:

- ask you to fill out some health-related questionnaires.
- evaluate your tinnitus condition via specific questionnaires.
- make an examination of your ear.
- perform a hearing test.
- will make some more clinical tests for tinnitus: tinnitus loudness, tinnitus pitch, tinnitus maskability, residual Inhibition (short-term tinnitus suppression after sound stimulation).
- will perform measures of acoustic evoked potentials (measurements of auditory pathway activity via electrodes placed on the head).
- update your full medical history.
- ask you for adverse events occurred.

Additional assessment via mobile applications

The study team will ask you if you want to participate in an additional voluntary assessment. Thereby, you have to answer several tinnitus-related questions via a specific app on your smartphone on a daily basis (5-10 minutes per day).

4. WHAT DO I HAVE TO DO?

If you agree to take part in this study, you must have the tests and measures described above performed at the designated times before, during and after your treatment and come to the clinic at the times agreed with the study team. It is important that you follow all instructions from the study team or the responsible staff. In addition to the above, you must:

- provide accurate and complete information about your medical history and your present condition.
- inform the study team immediately if you believe you have symptoms of COVID-19.
- inform the study team about any new side effect, injury, or symptom you experience. Inform the study team about any changes in current medical conditions. This information should be reported to the study team between study visits by using the contact numbers on the first page of this information sheet.
- inform the study team about any other prescription or over the counter medicines, vitamins, herbal supplements or herbal/natural remedies you are taking before and during the study. Check with the study team before starting any new medications or treatments.
- be able to complete the study:
    - no plans for a sabbatical or long-term holiday

- if you are a female – no current pregnancy or plans in the near future. The treatment will not affect you or the baby, but please inform the study team about it.

5. WHAT ARE THE POSSIBLE SIDE EFFECTS, RISKS AND DISCOMFORTS OF TAKING PART?

It is not expected that you will have more side effects than those you might experience from current clinical practice.

As with any tinnitus investigation there is a possibility of a slight increase of tinnitus since participants will pay more attention to their tinnitus. If you experience a severe long-term deterioration of your tinnitus, please inform the study team and not quit the treatment by yourself.

During the study, you will be asked to give a small quantity of blood. The procedure is as usual and it is not expected any risk by this injection. However, the study team will follow you closely and keep track of any unwanted effects or any problems.

In order to get as much information about you and your tinnitus as possible many different questionnaires and measures will be conducted. This can sometimes be very time-consuming and demanding. But we are well aware of this and trying to find a good balance for any participant.

6. HOW WILL I BENEFIT FROM TAKING PART?

It is hoped that the new treatment will help you with your tinnitus suffering, but this cannot be guaranteed and there may not be any direct benefit for you. Information from this study may help researchers understand tinnitus and develop new tests and treatments to help other patients with this condition.

7. WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If important new information on the study treatment becomes available which may affect your decision to be in the study, the study team will promptly tell you. As a result of such new information, the study team might recommend that you leave the study. He/she will explain the reasons for this and will talk to you about how best to manage your condition.

8. WHAT ARE THE COSTS OF TAKING PART?

There are no costs for you if you take part. You will receive the treatment at no cost and there will be no charges for study visits, tests or procedures. You will not be paid

for being in this study. If you will be randomized to the group that will be given a hearing aid you are allowed to keep this device after the completion of the study.

9. HOW WILL MY PERSONAL DATA BE USED AND PROTECTED?

Your personal data is protected by all applicable data protection and privacy laws, which include EU Regulation 2016/679.

To get the answers we need from the research described in this document, we have to collect personal information about you and your health. This includes information collected at your clinic during this study and also information that is already in your medical records. Besides information about your health we need information such as your age and gender. Results from the tests and examinations mentioned in the section “Procedure of the study or what will happen if I decide to take part ” are also included as part of your personal information. The collected data will then be uploaded in an international tinnitus database for collaborating researchers and stored according to EU data security and privacy settings. No personalized data will be stored in the database.

All collected data will be treated strictly confidential within the legal framework. All information concerning your personal data is made anonymous, only the local study team at the study site will know who you are. Your name will be replaced by an Identifier Code and only selected members of the study team have access to this code. Health authorities and people helping the study team/ principal investigator to run the study, including members of ZEINCRO group will be allowed to see your personal information, but they will not know who you are unless they are study inspectors.

The study information from this study must be kept for at least 10 years (§ 13 GCP-V). The results will be used to learn about tinnitus and different treatment methods. They can also be used to answer other questions including the safety of treatment. The use of your coded personal data for these purposes is based on your consent, on legal requirements concerning the performance of research studies and on public interest.

The results of this study will be published, for example, in medical journals or online, but you will not be mentioned in a way that would allow the public to find out who you are. Researchers, such as those from other companies and universities, may ask to use information from this study, including your information and samples, for other medical, health or scientific research. Researchers may combine the results from this study with results from other studies. Any disclosure of study data for scientific purposes will only be made in an anonymous form, i.e. no conclusions can be drawn about you as an individual, and in accordance with this document. You have the right to object to the use of your data for this additional research for reasons specific to you. If you wish to object to such use, please contact the study team.

Your coded study data information will not be sent outside the European Economic Area (EEA).

You may request to see the information collected about you. If you believe that any of this information is incorrect, you can write to the study team to ask them to change or remove the incorrect information. You can also request that we may limit the use of your personal information. If you change your mind about participating, we will not be able to remove the personal information that was collected for this study before you stopped participating. If you have questions about how we use your personal information or if you would like a copy of the Binding Corporate Rules, please contact the study team first. You can also contact the responsible data protection officer:

Last Name/ First Name: <<insert name of country-specific name >>

Contact details:

If you are not satisfied with the answers you receive, or in the event of violations, you have the right to complain to the relevant supervisory authority

<<insert name of country-specific complaint office>>

The blood samples that you may provide will be used for specific analyses during this study. You will not receive copies of the results. If you decide to stop participating in this study, your study-coded information and samples we have already collected will continue to be used in the manner you agreed to at the beginning of the study.

Your samples are analyzed in another country (Spain, Sweden). The coded samples are stored there under secure conditions.

In the event of a breach of the use of your personal data, you will be notified immediately in accordance with the applicable legislation of such a breach concerning

With respect to the handling of your personal data we refer to the information sheet for data protection, which will be discussed with you separately.

10. BIOLOGICAL SAMPLES

This study involves the collection of biological samples such as blood. Blood will be collected for genetical analysis. For example, to identify a potential biomarker for tinnitus/ response to a certain treatment. Regardless, if you do agree or not agree to give blood for the above-mentioned analyses, you will be able to participate in this study.

If you are interested in giving a blood sample, please inform the study team member or the responsible staff so they can give you the specific ICF related to blood sampling.

11. WHAT OTHER INFORMATION WILL BE AVAILABLE?

A description of this clinical trial will be available on clinicaltrials.gov as required by National and International Law and no personal data will be public.

12. WHOM SHOULD I CONTACT IF I NEED MORE INFORMATION OR HELP?

If you have any questions or need clarifications for this study or in case of any side effects, feel free to contact the principal investigator whose contact details are on the first page of this document.

You have the right to ask questions at any time about the potential risks of this study. **Your participation in this study is voluntary and can be revoked at any time during the study period without giving reasons and without serious disadvantages for you.**

……	……
Place Date	**Place/Date**
……	……
Participant´s name	**Study team member´s name**
……	……
Participant´s signature	**Study team member´s signature**

PART 2: CERTIFICATE OF CONSENT – UNITI-RCT

Herewith I

Last Name/ First Name:

……

Date of birth:

……

Address:

……

Phone number/ email:

……

agree to participate in the study "**Unification of treatments and Interventions for Tinnitus patients**" at the <<insert name of clinical site>>.

In doing so, I will be randomly assigned to an intervention for tinnitus consisting of single or combinational types of treatment. After one-three screening/baseline visits, I will receive a 12-week long treatment for tinnitus. I agree to complete several tinnitus- and health-related questionnaires as well as clinical measures at up to five different visits with a duration of about 2 hours each (in case screening and baseline are performed on the same day – up to 4 hours).

I hereby confirm that I have been fully informed about the implementation of the UNITI study.

I confirm that I have read and understood the Patient Information Sheet on the conduct of the UNITI study. I had enough time to make a decision and had the opportunity to ask additional questions about participating in the study.

I understand that my participation is voluntary and free of charge, and that I can withdraw my consent at any time without giving any reason, without this having any effect on my future care.

I confirm that I am able and willing to fully complete my participation in this study.

I understand that I must inform the study doctor or the responsible staff before I take a new drug or start a new treatment.

I grant authorized representatives or national/international health authorities (e.g. European Medicines Agency/EMA, US Food and Drug Administration/FDA or national health authorities) free access to my medical files for quality assurance of the clinical trial, provided that my data remain confidential and secret.

I understand that neither I nor my public or private insurance company will incur any costs from the treatment, procedures and tests of the study.

I agree that my study data may be used and shared by the study team/principal investigator (PI) and other researchers for additional research in an anonymous form, without the possibility to draw conclusions about personal information.

I have been informed about the protection of my personal data.

- ☐ I do not want the study doctor to tell my personal doctor that I am taking part in this study.

I understand that after signing, I will be given a copy of this consent form and a copy of the patient information sheet.
I have decided to participate in this study.

…… ……

Place/Date **Participant´s signature**

The study consent conversation was carried out by:

……

Herewith I declare, that methods, aim and procedure as well as potential benefits and risks were fully and comprehensively explained to the above-mentioned participant at the …… (dd-mm-yyyy) in both verbally and written form. I also confirm to handed over a copy of the study information sheet as well as a copy of this signed consent form to the participant.

…… ……

Place/Date **Study doctors´s signature**

Contact informations:

<<insert contact informations>>

INFORMED CONSENT FORM (BLOOD SAMPLING)

Study Title: Unification of treatments and Interventions for Tinnitus patients – Genetic analysis

Study Code: UNITI-Gen

Study team:

……

Principal Investigator:

……

Site:

……

Contact details:

……

Patient Code:

……

Dear study participant,

an optional, but essential part of this study involves the collection of a blood sample from you during the study which will be used to research the genetic component of tinnitus. Before you decide whether to participate in this part of the study we would like to give you some more information to help you to understand why the genetic research is being done, what is involved and how your data will be used. Together with a member of the study team, you will now go through this Informed Consent Form (ICF) which has two parts.

• **Information Sheet** – for information on this research project

• **Certificate of Consent** - for signatures if you agree to take part

If you have any questions or difficulties understanding the following information, please do not hesitate to ask questions.

You will be given a copy of the complete Informed Consent Form

PART 1: INFORMATION SHEET – Genetic Analysis

1. WHY DOES THIS GENETIC RESEARCH MATTER?

Additional genetic analyses for research purposes will be performed on blood samples taken once at treatment period while you are on the study.

Genetic research looks at genetic material, which is in your body, such as in blood cells. Cells are the 'building blocks' of your body. Cells contain a type of molecule called deoxyribonucleic acid (DNA). Your genes are made of DNA. There are other components of genetic material as well, such as RNA (ribonucleic acid). You can think of genetic information as a large instruction book that your body reads to understand how it should be built and function.

All humans have the same instruction book in their body but some words or letters may be different from one person to the other. Some of those differences have no effect on your health, like hair or eye color; but others can influence the likelihood of developing a disease or affect how medicine to treat a certain disease will work. If genetic analyses are done, they may involve all or part of your genetic information. Some genetic information is inherited from your parents and some genetic information is only found in your body and cannot be passed on from generation to generation.

We ask you and other participants in this study to provide blood samples because we want to investigate how genetic differences between people and their disease can affect the way people respond to the treatment used in this study. In other words, we want to identify genetic factors that may be responsible for the occurrence/expression and severity of your tinnitus and for your response to a particular treatment

The blood samples collected are sent to specific laboratories (Granada, Spain; Stockholm, Sweden) for specific analysis (in accordance with EU data protection legislation). The genetic test will not bring you any direct personal benefit and the results will not be available to you, your family or your doctor and will not affect your treatment. We will only use your samples for the purpose set out in this document. Blood collection is completely voluntary for you

If you decide not to take a blood sample, this has no influence on your participation in the study.

If you withdraw your consent after taking a sample but before your blood sample is analysed, the study team will arrange for the sample to be destroyed.

If you withdraw your consent after your blood sample has been analysed, the study team/principal investigator will make all reasonable efforts to destroy your blood sample and any extracted DNA, and your data will not be included in any future analysis or research, but the study team/principal investigator (PI) is under no obligation to destroy the existing analysis of this study.

2. WHAT WILL HAPPEN IF I DECIDE TO TAKE PART IN THIS GENETIC RESEARCH?

If you would like to provide a blood sample for genetic research, we will take about 12 ml of blood from you at any time point during the study. DNA will be extracted from your sample. In this process, most of the original blood sample will be used, but a small amount may be kept as a “backup” in case there are of problems with the analysis of your DNA.

The DNA and the remaining sample will be sent from the respective study centres to the above-mentioned two laboratories in Spain and Sweden according to current regulations, where it will be stored and analysed under secure conditions.

DNA and/or the blood sample will be kept for up to 5 years after the main study is completed and then it will be destroyed.

The genetic analyses are carried out exclusively in the two laboratories mentioned above. These laboratories are obliged to comply with the agreements in this Informed Consent.

3. WHAT ARE THE POSSIBLE MEDICAL RISKS OF TAKING PART?

Blood collection poses only a minimal risk because all the material used is sterile. Nevertheless, in rare cases an infection can occur. Temporary pain at the injection site, a haematoma ("bruise") or reddening of the skin may also occur

4. HOW WILL I BENEFIT FROM TAKING PART?

You will have no direct benefit from this research. However, this research may contribute to the better understanding of tinnitus condition and its treatment. This genetic research may eventually lead to improvements in diagnosis and treatment.

5. DO I HAVE TO TAKE PART?

Your blood sample is voluntary. You will receive the same treatment and care in the study, regardless of whether you give blood of this genetic research or not. If you decide not to give blood, you can still participate in the study.

6. DO I RECEIVE A PAYMENT FOR TAKING PART?

You will not be paid for taking part in this research.

7. WILL I BE ABLE TO SEE MY RESULTS OF THE GENETIC RESEARCH?

This genetic study is for research purposes only. You will therefore not be able to view the results of your genetic testing.

8. DO I HAVE RIGHTS TO THE RESULTS FROM THE GENETIC RESEARCH?

You have no rights to the information from the genetic test. All information derived directly or indirectly from this genetic research, and all patents, diagnostic tests, pharmaceuticals or biological products developed directly or indirectly as a result of

this genetic research are the sole property of the study team/principal investigator (PI) (and its successors, licensees and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be made directly or indirectly as a result of this genetic research. However, in signing this form and donating a blood sample for genetic research, you have the same rights as described in the Information Sheet for the main study.

9. HOW WILL MY GENETIC AND PERSONAL DATA BE USED AND PROTECTED?

This genetic research will be carried out with a high degree of confidentiality. Your blood sample will be labelled with the same code that is given to you in the study. No personal identifiers such as your name or date of birth will be recorded on the sample.

The results of this genetic research will not be linked to your identity. Personal identifying data (source data) will be stored separately from the data collected in the study in a secure location. In order to verify the proper conduct of the genetic research and the entire study, the responsible regulatory authorities may request access to your study documents including the original data (source data). The regulatory authorities can also verify that this genetic research has been carried out properly and can access your medical records and learn your identity for this purpose.

The set of your information collected in the study will be used together with the results of this genetic examination. This may include information about your tinnitus, your health, or your response to the treatment you received in the study. To keep this information confidential, personal information (such as name, address, social security number) will be removed and tracked using only a code number

The joint analysis of the genetic data and the other study data is necessary to achieve the objectives of this genetic study. The results of this genetic examination, such as the differences in your DNA compared to other people, will only be made available to the members of the study team conducting the genetic examination and will be kept under safe conditions at all times. Your sample will be analysed in the laboratory of the ENT Clinic Virgen de las Nieves and the Centre for Genomics and Oncological Research GENYO in Granada, Spain and in the Physiology and Pharmacology Laboratory of the Karolinska Institute in Stockholm, Sweden. All effluents are carefully monitored and no attempt is made to identify you from the available data.

In addition to this genetic examination and with the aim of improving science, patient care and public health, the study team/principal investigator (PI) and the organisations designated by him/her may carry out further research in the future, sharing summary results (e.g. genetic differences of groups of people with a disease) from this genetic examination with other researchers, such as hospitals, academic organisations or health insurance companies. The researchers exchange the results of this genetic analysis by posting them in scientific databases where they can be combined with the results of similar studies to learn more about health and disease. Researchers can use this information only for health-related research purposes. Researchers can see summary results that include your data, but they cannot see your individual data or information that identifies you personally. The results of this genetic research may also be published in scientific journals, but no information that identifies you personally will be included.

The study team/principal investigator (PI) will not disclose individual genetic data to persons who are not part of the study team.

Specific information on data handling in the context of this study can be found in a separate document on data protection.

10. CAN I WITHDRAW MY CONSENT?

You can withdraw your consent to use your sample in genetic research at any time.

If you withdraw your consent after taking a sample but before your blood sample is analysed, the study team will arrange for the sample to be destroyed.

If you withdraw your consent after your blood sample has been analysed, the study team/principal investigator will make all reasonable efforts to destroy your blood sample and any extracted DNA, and your data will not be included in any future analysis or research, but the study team/principal investigator (PI) is under no obligation to destroy the existing analysis of this study.

PART 2: CERTIFICATE OF CONSENT – Genetic Analysis

Herewith I

Last Name/ First Name:

……

Date of birth:

……

Address:

……

Phone number/ email:

……

agree to give a blood sample for genetic analysis in the course of the study "**Unification of treatments and Interventions for Tinnitus Patients**" at the <<insert name of clinical site>>.

I hereby confirm that I have been fully informed or educated about the genetic analyses carried out in the UNITI study.

I confirm that I have read the patient information sheet on genetic research and understand its contents. I had enough time to make a decision and had the opportunity to ask additional questions about participation in the research project.

I understand that my participation and sample donation is voluntary and that I may withdraw my consent at any time without affecting my future care.

I agree that the data collected in the course of the genetic research, including the information collected in the UNITI study (e.g. about my tinnitus, my state of health and response to treatment), may be used as described in the genetic research information sheet as part of this consent form. This does not waive any rights I may have under current legislation.

I consent to this data being processed and analyzed in the laboratories belonging to the UNITI Study Consortium (Stockholm, Sweden, Karolinska Institutet and Granada, Spain, Centre for Genomics and Oncological Research GENYO), as described in the section "How will the genetic data and my personal data be used and protected?

I understand that in order to verify the proper conduct of genetic research, the medical study records may be inspected by the relevant regulatory authorities. I will grant access to the records to those responsible.

I agree that the results of this genetic study may be shared by the study team/principal investigator (PI) with other researchers in summary form (study code) for future health research purposes.

I understand that after signing, I will be given a copy of this consent form and a copy of the patient information sheet.

I agree that the genetic sample I donate and the data collected in the UNITI study may be used as indicated in this document.

…… ……

Place/ Date **Participant´s signature**

The study consent conversation was carried out by:
……

Herewith I declare, that methods, aim and procedure as well as potential benefits and risks were fully and comprehensively explained to the above-mentioned participant on …… (dd-mm-yyyy), in both verbally and in written form. I also confirm to have handed over a copy of the study information sheet as well as a copy of this signed consent form to the participant.

…… ……

Place/Date **Study team member´s signature**

Contact information:

<<insert contact information>>

4 Registration of the RCT at Clinicaltrials.gov

The RCT has been registered at clinicaltrials.gov in Dec 2020 under NCT no. 04663828

https://clinicaltrials.gov/ct2/show/NCT04663828?term=NCT04663828&cond=Tinnitus&draw=2&rank=1