


# BMJ Open MinT-trial: Mindfulness versus cognitive behavioural therapy in Tinnitus patients: protocol for a randomised controlled, non-inferiority trial

Maaïke Maartje Rademaker <sup>1,2</sup>, Inge Stegeman,<sup>1,2</sup> Arno Liefstink,<sup>1</sup> Metten Somers,<sup>3</sup> Robert Stokroos,<sup>1,2</sup> Adriana L Smit<sup>1,2</sup>

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For numbered affiliations see end of article.

## Correspondence to

Maaïke Maartje Rademaker; [m.m.rademaker-3@umcutrecht.nl](mailto:m.m.rademaker-3@umcutrecht.nl)

## ABSTRACT

**Introduction** Chronic subjective tinnitus is a condition that affects 5.1% to 42.7% of the population, depending on the definition and studied population. Evidence-based treatment options are limited. Cognitive Behavioural Therapy (CBT) has been proven effective to improve quality of life and to diminish tinnitus distress. Positive short-term effects of mindfulness-based interventions on tinnitus distress have been reported; however, the longer term effects remain to be studied.

**Methods and analysis** We designed a monocentre randomised controlled, non-inferiority trial to compare the effectiveness of mindfulness-based cognitive therapy (MBCT) and CBT in chronic tinnitus patients. Fifty-four patients (≥32 on the Tinnitus Functional Index (TFI), suffering from tinnitus for at least 6 months) will be included in the trial and randomised into one of two intervention groups. One group will receive MBCT, the other group will receive CBT. Our primary objective is to determine whether MBCT is non-inferior to (as good as) CBT on tinnitus distress (TFI) in chronic tinnitus patients at 12 months follow-up after end of therapy. Non-inferiority will be declared if the mean decrease in TFI score for MBCT is no worse than the mean decrease in TFI score in CBT, with statistical variability, with a margin of 13 points. Most secondary objectives (tinnitus severity of problem, tinnitus intrusiveness, quality of life, anxiety, depression, symptoms of psychopathology, perceived tinnitus complaints, coping style (mostly validated questionnaires)) are expected to show non-inferiority to MBCT compared with CBT. We expect a significant difference between MBCT and CBT for mindfulness awareness.

**Ethics and dissemination** This research protocol was approved by the Institutional Review Board of the UMC Utrecht (NL67838.041.18, V.4, April 2019). The trial results will be made accessible to the public in a peer-review journal.

**Trial registration number** NL7745.

## BACKGROUND

Tinnitus is the perception of sound in the absence of acoustic stimulation and is often experienced as a ringing or buzzing sound.<sup>1</sup>

## Strengths and limitations of this study

- This study allows for a comparison between mindfulness-based cognitive therapy (MBCT) and cognitive behavioural therapy (CBT, standard care).
- This is the first high-quality non-inferiority trial to evaluate long-term effects of MBCT in chronic tinnitus patients.
- Multiple outcome measures will be assessed with validated questionnaires, such as but not limited to tinnitus distress, anxiety and depression, coping style and quality of life.
- Differences in the amount of therapy hours, and composition of the group in both treatments will limit generalisability and might influence the outcome.
- Though, CBT for tinnitus and MBCT will be compared, both interventions might entail elements of the other intervention.

Over 70 million people in Europe suffer from some form of tinnitus, which can be chronic and disabling for affected individuals.<sup>2</sup> The perceived distress is caused by tinnitus characteristics such as loudness and severity and by additional complaints such as difficulties in concentration, sleeping problems and feelings of anxiety.<sup>3–5</sup> Quality of life decreases with increasing tinnitus complaints, and patients with severe tinnitus disturbance can experience severe limitations in their day-to-day life.<sup>1,6</sup>

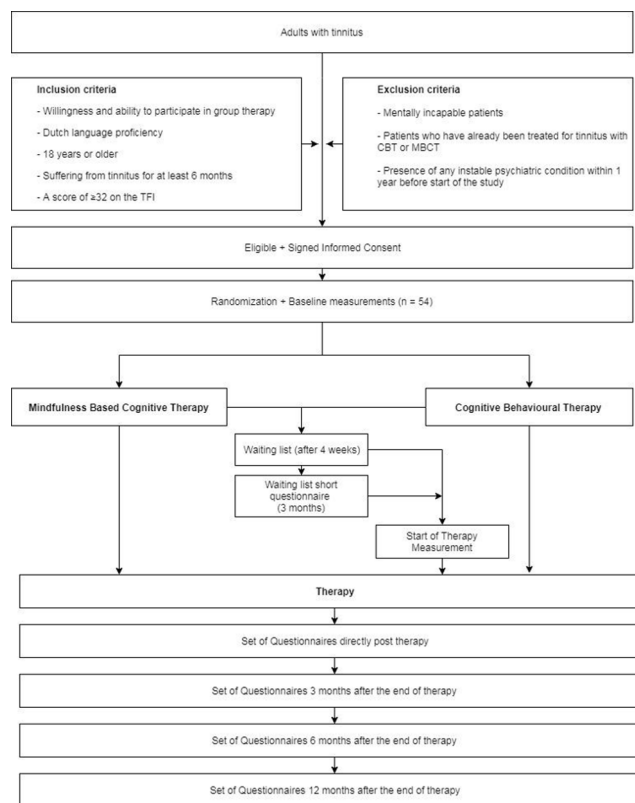
Treatment modalities for tinnitus can be divided in pharmacological and non-pharmacological therapies.<sup>7</sup> So far, no curative treatment has been identified and evidence-based treatment options for tinnitus are limited, which might be related to its heterogeneity, perception of tinnitus and levels of distress.<sup>8</sup>

Cognitive behavioural therapy (CBT) has been proven effective in tinnitus patients to improve quality of life and diminish tinnitus distress.<sup>9 10</sup> In CBT, a structured psychological intervention, patients are taught cognitive and behavioural skills to influence (responsive) thoughts and behaviour. It is based on the idea that people's experiences influence their concepts.<sup>9</sup> Treatment therefore focusses on unhelpful thoughts and behaviour. CBT has developed over the years in regard to techniques and delivery methods. These are most commonly referred to as three 'waves'.<sup>11</sup> While operant learning and conditioning methods are highlighted in 'first wave' methods, in the 'second wave', the attention is more aimed at handling information.<sup>12</sup> More recent developments in CBT, also referred to as 'third-wave', stress acceptance and mindfulness.<sup>13</sup>

Mindfulness meditation originates from Buddhist philosophy and psychology and is defined as 'the process of openly attending, with awareness, to one's present moment experience'<sup>14</sup> (p493). It aims to achieve a non-judgemental approach to thought, emotions and sounds.<sup>14</sup> Dr Kabat-Zinn first introduced elements of mindfulness meditation to western medicine in a systematically delivered group intervention called mindfulness-based stress reduction to treat chronic pain.<sup>15</sup> Over time, different types of psychological interventions that use elements of mindfulness meditation have been developed; these are often referred to as a mindfulness-based intervention (MBI).<sup>14</sup> A common structured group-based intervention is mindfulness-based cognitive therapy (MBCT). MBCT was originally developed for relapsing depression.<sup>15-17</sup> In MBCT, elements of CBT techniques are combined with mindfulness meditation.<sup>14 16</sup> MBIs are known to have beneficial effects in treating relapsing depression, anxiety, stress and chronic pain.<sup>18-21</sup>

The question why CBT, including 'third wave' methods, may reduce tinnitus distress can be explained by several, partly overlapping theories that explain mechanisms of tinnitus tolerance. It is thought that habituation and cognitive approaches interfere with defective behavioural and emotional reactions that are thought to maintain tinnitus distress.<sup>22-24</sup> Avoidance, considered a fear condition reaction, is correlated with tinnitus severity and distress.<sup>23 25</sup> Mindfulness meditation is believed to have a beneficial effect on tinnitus distress due to its focus on acceptance, the opposite of avoidance.<sup>23 26</sup> Also, cognitive and metacognitive awareness are thought to be enhanced by mindfulness meditation. This helps to diminish the emotional damages of negative cognitions that are associated with tinnitus severity.<sup>22 27-29</sup>

Several research groups have investigated the effectiveness of MBIs, in either randomised controlled trials, cohort studies or a comparative controlled trial.<sup>27 28 30-35</sup> The majority of observational studies show a decrease in tinnitus distress after MBI.<sup>27 28 30-34 36</sup> Two out of three published randomised controlled trials show a statistically superior decrease of tinnitus distress compared with a control group of relaxation therapy directly



**Figure 1** Study flowchart. CBT, cognitive behavioural therapy; MBCT; mindfulness-based cognitive therapy; TFI, Tinnitus Functional Index.

after treatment.<sup>28 30 31</sup> One study demonstrated results at 6 months after therapy in which this positive result remained significant.<sup>28</sup> In a letter to the editor, Gans *et al* additionally described a sustained positive effect of their MBI in terms of tinnitus distress relief 1 year after treatment in seven patients.<sup>37</sup>

Based on the short-term outcomes, mindfulness is effective in reducing tinnitus distress, in this study the longer term outcomes will be investigated (12 months). In this randomised study, the effect on tinnitus distress by MBCT versus CBT in patients with chronic tinnitus will be compared. We hypothesise a non-inferiority of tinnitus distress in MBCT compared with CBT.

## METHODS AND ANALYSIS

### Study objectives

The primary objective of this study is to compare the effect of MBCT and CBT on tinnitus distress, measured with the Tinnitus Functional Index (TFI) at 12 months after end of therapy.<sup>38</sup> Secondary objectives are to compare the effect of MBCT and CBT on tinnitus severity, quality of life, anxiety, depression, other symptoms of psychopathology, mindfulness awareness, the subjective effect of therapy and coping style.

### Study design and setting

In this non-inferiority RCT, patients will be randomised into two groups (figure 1). This is a monocentre study

performed in a tertiary referral clinic (university hospital) in the Netherlands (University Medical Center Utrecht). The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement.<sup>39</sup>

We will declare non-inferiority if the mean decrease in TFI score for MBCT is no worse than the mean decrease in TFI score in CBT, with statistical variability, with a margin of 13 points. Almost all secondary objectives (tinnitus severity (severity of problem and intrusiveness), quality of life, anxiety and depression, symptoms of psychopathology, perceived tinnitus complaints, coping style (all validated questionnaires)) are expected to show non-inferiority of MBCT compared with CBT. We expect a significant difference between MBCT and CBT for mindfulness awareness.

### Study population

The study population consists of patients who are referred to, diagnosed and/or counselled by the Tinnitus Care group of the outpatient department of Otorhinolaryngology of the University Medical Center Utrecht as a secondary and tertiary referral centre for tinnitus. Patients will be asked for permission to be contacted by the research team. The following criteria must be met to be eligible for inclusion. All elements of eligibility, except for the TFI score, will be judged by taking medical history.

### Inclusion criteria

- ▶ Willingness and ability to participate in group therapy.
- ▶ Dutch language proficiency.
- ▶ 18 years or older.
- ▶ Suffering from chronic tinnitus for at least 6 months.
- ▶ A score of  $\geq 32$  on the TFI.

### Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study.

- ▶ Mentally incapable patients.
- ▶ Patients who have already been treated for tinnitus with CBT or MBCT.
- ▶ Presence of any instable psychiatric condition within 1 year before start of the study.

If eligibility is judged and approved for inclusion by the research team, patients will be sent the patient information letter and an informed consent (IC) form (online supplementary material 1). Patients will be given 2 weeks to consider participation. If participants decide not to take part, they will continue within the regular care of the tinnitus line of care in the UMC Utrecht. The IC form will be signed by the patient and a member of the research team.

### Randomisation and interventions

After inclusion and baseline assessment, patients will be randomly allocated into one of two intervention groups (MBCT or CBT). Block randomisation will be electronically performed by the study management system Castor Electronic Data Capture (EDC).<sup>40</sup> Both groups carry the

same weight (1:1). Block groups will be 2, 4. Investigators will be blinded to the randomisation sequence. Blinding of participant and care providers is not possible due to the nature of the intervention.

Intervention group A will receive 8 weekly sessions of MBCT; each session will last for two and a half hours (total 20 hours). All trainings will be supervised by a certified, experienced mindfulness trainer (experienced with psychological and psychiatric diseases). The MBCT is standard care in the psychiatry department of the UMC Utrecht. The study participants will join this group. The MBCT has not been adapted for tinnitus patients. Treatment group B will receive 5 weekly CBT sessions (solely tinnitus patients) and one refreshment session 2 to 3 months later, as a standard of care treatment. The CBT was specifically designed for tinnitus patients. The therapy will be supervised by a social worker and a psychologist, who both have several years of experience in CBT training for tinnitus patients. The CBT sessions will last approximately 2 hours (total 12 hours). The exact content of the intervention and control group can be found in [table 1](#).

Due to potentially limited capacity in both treatment groups, participants might have to wait a maximum of 6 months before the start of both treatments. A waiting list control group will be applicable for both treatment groups. The waiting list can last up to 6 months. Participants who have to wait for more than 4 weeks for therapy from the moment of randomisation will be on the waiting list.

Participants are not allowed to start another tinnitus treatment during the course of the study.

### Sample size

To achieve a power of 80%, with an alpha of 5%, a non-inferiority test of two means (T-test) was performed. This resulted in a sample size of 25 patients per group. To correct for possible drop outs, we will include 54 patients, with about 27 patients per arm. The low dropout rate was based on the motivated patient group. For this non-inferiority test, we used the primary end point of the TFI outcome at 12 months. We determined the equivalence margin to be 13 points. This is based on the minimally clinically important difference (MCID) of the TFI.<sup>38</sup> The acceptable SD was set at 18 points, based on the results of a previous RCT on mindfulness in tinnitus patients.<sup>28</sup>

### Outcomes

At intake baseline data will be collected. If necessary, patients will undergo audiometric tests. This will only happen when the audiometric tests were older than 6 months at the date of inclusion. Audiometric tests will consist of pure tone and speech audiometry, tinnitus loudness match, tinnitus pitch match and tinnitus maskability.

At inclusion, demographic data will be extracted from the electronic patient database: gender, age, highest level of education, marital status, working situation, number of

**Table 1** Detailed content of both intervention groups

Content of both intervention groups	
MBCT	CBT
<ul style="list-style-type: none"> <li>▶ 8 weekly courses</li> </ul>	<ul style="list-style-type: none"> <li>▶ 5 weekly course, 1 refreshment session after 2–3 months</li> </ul>
<ul style="list-style-type: none"> <li>▶ Certified, experienced mindfulness trainers</li> </ul>	<ul style="list-style-type: none"> <li>▶ Experienced psychologist and experienced social worker</li> </ul>
<b>Session 1</b>	
<b>Life on autopilot</b>	<b>Information and acquaintance</b>
<ul style="list-style-type: none"> <li>▶ Introduction</li> <li>▶ Acquaintance</li> <li>▶ Practical information</li> <li>▶ Eat meditation and evaluation</li> <li>▶ Theme</li> <li>▶ Pause</li> <li>▶ Bodyscan and evaluation</li> <li>▶ Explanation of course book and practice</li> </ul>	<ul style="list-style-type: none"> <li>▶ Introducing supervisors</li> <li>▶ Organisational and practical information</li> <li>▶ Group rules</li> <li>▶ Inventory and comparison</li> <li>▶ Objectives and design of the training</li> <li>▶ Exercise: distraction from tinnitus</li> </ul>
<b>Session 2</b>	
<b>Dealing with obstacles</b>	<b>Tinnitus and distraction</b>
<ul style="list-style-type: none"> <li>▶ Bodyscan and evaluation</li> <li>▶ Pause</li> <li>▶ Theme</li> <li>▶ Evaluation home exercise, discuss next week's home exercise</li> <li>▶ Closing</li> </ul>	<ul style="list-style-type: none"> <li>▶ Discuss content and exercise session</li> <li>▶ Tinnitus and distraction</li> <li>▶ Decreasing tinnitus' influence</li> <li>▶ Ways of distraction</li> <li>▶ Choosing a new distraction</li> <li>▶ Exercise: a new way of distraction</li> </ul>
<b>Session 3</b>	
<b>Exploring your boundaries</b>	<b>Tinnitus and attention</b>
<ul style="list-style-type: none"> <li>▶ Opening meditation</li> <li>▶ Explanation breathing space and evaluation</li> <li>▶ Theme</li> <li>▶ Evaluation home exercise, discuss next week's home exercise</li> <li>▶ Meditation lying down</li> <li>▶ Closing</li> </ul>	<ul style="list-style-type: none"> <li>▶ Discuss content and exercise session 2</li> <li>▶ Tinnitus and attention</li> <li>▶ Practice shifting of focus</li> <li>▶ Exercise breathing/relaxation</li> <li>▶ Techniques decreasing focus</li> <li>▶ Exercise: apply focus-technique</li> </ul>
<b>Session 4</b>	
<b>Stress</b>	<b>Tinnitus and meaning</b>
<ul style="list-style-type: none"> <li>▶ Auditory and visual meditative exercise</li> <li>▶ Standing meditation and evaluation</li> <li>▶ Theme</li> <li>▶ Evaluation home exercise, discuss next week's home exercise</li> <li>▶ Sedentary meditation and evaluation</li> </ul>	<ul style="list-style-type: none"> <li>▶ Exercise breathing/relaxation</li> <li>▶ Discuss content and exercise session 3</li> <li>▶ Exercise progressive muscle relaxation</li> <li>▶ Tinnitus and thoughts, formula: G+G = G+G</li> <li>▶ Possibilities of thought alteration</li> <li>▶ Exercise: administering though alteration</li> </ul>
<b>Session 5</b>	
<b>Conscious handling of challenges</b>	<b>Tinnitus and relaxation</b>

Continued

**Table 1** Continued

Content of both intervention groups	
<ul style="list-style-type: none"> <li>▶ Opening meditation</li> <li>▶ Sedentary meditation and evaluation</li> <li>▶ Evaluation home exercise</li> <li>▶ Theme</li> <li>▶ Discuss next week's home exercise</li> <li>▶ Walking meditation</li> <li>▶ Closing</li> </ul>	<ul style="list-style-type: none"> <li>▶ Exercise breathing/relaxation</li> <li>▶ Discuss content and exercise session 4</li> <li>▶ Summary course content</li> <li>▶ Expectations/goals/difficulties</li> </ul>
<b>Session 6</b>	
<b>Thought are not facts</b>	<b>Refreshment</b>
<ul style="list-style-type: none"> <li>▶ Meditation, extra focus on sedentary meditation and evaluation</li> <li>▶ Evaluation home exercise</li> <li>▶ Theme</li> <li>▶ Discuss next week's home exercise</li> <li>▶ Walking meditation and physical exercise</li> <li>▶ Closing</li> </ul>	<ul style="list-style-type: none"> <li>▶ Exchanging experiences</li> <li>▶ Refreshing course content</li> <li>▶ Evaluation and closing</li> </ul>
<b>Session 7</b>	
<b>Taking care of yourself</b>	
<ul style="list-style-type: none"> <li>▶ Opening meditation</li> <li>▶ Sedentary meditation and evaluation</li> <li>▶ Evaluation home exercise</li> <li>▶ Theme</li> <li>▶ Discuss next week's home exercise</li> <li>▶ Walking meditation and physical exercise</li> <li>▶ Closing</li> </ul>	
<b>Session 8</b>	
<ul style="list-style-type: none"> <li>▶ Opening meditation</li> <li>▶ Bodyscan</li> <li>▶ Evaluation bodyscan</li> <li>▶ Evaluation home exercise</li> <li>▶ Tips on integrating mindfulness in your life</li> <li>▶ Evaluation training</li> <li>▶ Closing</li> </ul>	

CBT, cognitive behavioural therapy; MBCT, mindfulness-based cognitive therapy.

people in the household, average income of household, native language and postal codes.

Outcome measures will be assessed by questionnaires. These questionnaires will be sent by e-mail to the study participants through the data management programme Castor EDC.<sup>40</sup> If participants do not want to receive the set of questionnaires electronically, they will receive them by postal services. Patients will receive the different questionnaires at five moments in time; at baseline, end of



**Table 2** Timing of different questionnaires

Questionnaire	Baseline/s.o.t.*	Waiting list (3 months)†	FU e.o.t.‡	FU 3 months	FU 6 months	FU 12 months
TSCHQ	X					
TFI	X	X	X	X	X	X
Tinnitus VAS scales	X	X	X	X	X	X
HADS	X			X		X
WHOQOL-BREF	X			X		X
CISS	X			X		X
CGI-CHANGE			X	X	X	X
MAAS	X			X		X
SCL-90-R	X					X
General Questions§	X	X	X	X	X	X

\*s.o.t.: start of treatment (applicable for participants if therapy starts more than 4 weeks after baseline measurement).

†Data on the waiting list questionnaire will be valid for 4 weeks. If participants start treatment within 4 weeks after this short questionnaire, they will not be asked to repeat these questionnaires (TFI, tinnitus VAS scales, questions about medication, comorbidities, etc) before the start of treatment.

‡e.o.t.: end of treatment.

§General questions include questions on medication, comorbidities, additional tinnitus therapies and adverse events.

CGI-CHANGE, Clinical Global Impression; CISS, Coping Inventory for Stressful Situation; FU, follow-up; HADS, Hospital Anxiety and Depression Scale; MAAS, Mindful Attention Awareness Scale; SCL, symptom checklist-90-R; TFI, Tinnitus Functional Index; TSCHQ, Tinnitus Sample Case History Questionnaire; VAS, visual analogue scale; WHOQOL-BREF, WHO Quality of Life (Questionnaire)-BREF.

treatment (MBCT after session eight, CBT after session six) and after 3, 6 and 12 months follow-up after end of treatment (table 2).

If participants are on the waiting list (>4 weeks before start therapy after study inclusion), they will be required to fill out a set of questionnaires (identical to the baseline set of questionnaires) before the start of treatment. If participants are on the waiting list for 3 months, they will be sent a short questionnaire during the waiting list period. This questionnaire will be valid for 4 weeks. If participants start treatment within 4 weeks after this short questionnaire, they will not be asked to repeat these questionnaires (TFI, tinnitus visual analogue scale (VAS) scales, questions about medication, comorbidities, etc) before the start of treatment (table 2).

### Explanation of different questionnaires

- ▶ TFI, consisting out of 25 questions to measure the impact of tinnitus on daily life on 11-point Likert scales. The TFI was translated to Dutch and validated in 2014, with a reported Cronbach  $\alpha=0.91$ . The TFI consists of eight subscales to assess intrusiveness, sense of control, cognition, sleep, hearing (auditory), relaxation, quality of life and emotions (emotional). The score of the TFI ranges from 0 to 100, with an MCID of 13. The scores can be stratified into five levels: 0–17=nota problem, 18–31=small problem, 32–53=moderate problem, 54–72=big problem, 73–100=very big problem.<sup>38 41</sup>
- ▶ Tinnitus Sample Case History Questionnaire; 35 questions assessing the tinnitus history.
- ▶ Tinnitus VAS scales; two questions regarding the severity of tinnitus patients might experience scored

on a VAS scale (severity of the tinnitus (one no problem to five very large problem) and intrusiveness (0 not intrusive at all–10 extremely intrusive).

- ▶ WHO Quality of Life (Questionnaire)-BREF (WHOQOL-BREF); 26 questions to measure participants' quality of life on a five-point Likert scale. The WHOQOL-BREF was translated to and validated in Dutch in 2005. The WHOQOL-BREF measures four subdomains: physical health (Cronbach  $\alpha=0.80$ ), psychological health (Cronbach  $\alpha=0.74$ ), social relationships (Cronbach  $\alpha=0.66$ ) and environment (Cronbach  $\alpha=0.73$ ).<sup>42</sup>
- ▶ Hospital Anxiety and Depression Scale (HADS); 14 questions to assess anxiety and depression on four point scales. It consists of two scales of seven items, one for anxiety and the other for depression. Cronbach  $\alpha$  ranges between 0.71 and 0.90 on both subscales and the total scale. Total scores range from 0 to 21 per scale. The HADS was translated to and validated in Dutch in 1997.<sup>43</sup>
- ▶ Mindful Attention Awareness Scale (MAAS); 15 questions to assess mindfulness awareness on a six-point Likert scale (1=almost always to 6=almost never). The MAAS was translated to and validated in Dutch in 2008, Cronbach  $\alpha$  ranging from 0.80 to 0.85. A mean of the sum of scores is calculated to score the MAAS.<sup>1–6</sup> Higher scores indicate more mindfulness.<sup>44</sup>
- ▶ Questions to assess whether participants started to use concomitant medication suffer from comorbidities, adverse events (AE) or started another treatment for their tinnitus during the course of the study.



- ▶ Coping Inventory for Stressful Situation; 48 questions to assess patient's coping style on a five-point Likert scale (1=not at all, 5=very much). There are three subscales: task-oriented, emotion-oriented and avoidance-oriented. Avoidance-oriented can be divided into two other subscales: distraction and social diversion. Cronbach  $\alpha$  is above 0.80 for task-oriented, emotion-oriented and avoidance-oriented coping, and higher than 0.70 for distraction and social diversion.<sup>45</sup>
- ▶ Clinical Global Impression scale; one question to assess subjective improvement of tinnitus after therapy, scored on a scale of 1 (very much improved) to 7 (very much worse).<sup>46</sup>
- ▶ SCL-90-R; 90 questions to assess symptoms of psychopathology on a five-point scale for not at all=0 to 4=extremely. Translated and validated in Dutch in 2004, Cronbach  $\alpha$  range between 0.76 and 0.97 over the subscales in the general population. There are nine subscales: somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism.<sup>47</sup>

### Statistical analysis

Baseline characteristics will be presented in means or medians, depending on the normality of the data. Categorical data will be presented quantitatively. For the longitudinal analysis, a mixed-model analysis will be performed. Non-inferiority will be established when both approaches support non-inferiority. A margin of 13 point on the TFI is defined as non-inferiority. We expect limited missing data, due to the motivated nature of the patient population. Potentially missing variables will be handled with multiple imputation, a complete case analysis will be performed as a sensitivity analysis. A p value of <0.05 is considered statistically significant. Intention to treat and per protocol analysis will be performed. No interim analyses will be performed.

Analyses of between-group differences of the secondary outcomes measures will be performed with a mixed-model analysis.

### ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the 'gedragscode gezondheidsonderzoek' and 'code goed gebruik'.

Protocol amendments will be notified to the local Medical Research Ethics Committee (MREC). The trial results will be made accessible to the public in a peer-review journal.

All data will be handled confidentially. The data will be analysed anonymously by using a unique patient identification number. Data will be collected through Castor EDC and data will be pseudonymised. The investigator will

safeguard the key to the code. Patient data will be stored on a password-protected computer in a lockable room. IC forms will be kept in a locked cabin. If a patient does not wish to fill out the questionnaires electronically, they will receive them by postal services. Data will be administered in Castor by an investigator to the correct patient. The final trial data set will be safeguarded and available to the principal investigator and approved members of the research team.

Trial quality will be independently monitored by a local monitor (UMC Utrecht) once a year. The local monitor will check 10% of signed ICs, inclusion and exclusion criteria, source data and serious adverse events (SAE). From the first three participants, the inclusion and exclusion criteria will also be checked. The speed of inclusion, drop-out rate and the presence and completeness of the monocentre study file will be monitored. AE will be recorded; SAE will be reported to the local Institutional Review Board.

### Trial status

The trial is currently in recruitment phase. The first patient was recruited on 29 October 2019. Nine of 54 patients were included in the study on 17 January 2020.

### Author affiliations

<sup>1</sup>Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>2</sup>Department of Otorhinolaryngology, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands

<sup>3</sup>Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands

**Contributors** MMR developed the protocol, drafted the manuscript, revised the manuscript and approved the final version. MS, RS, AL, IS and ALS developed the protocol, revised the manuscript and approved the final version.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL67838.041.18, V.4, April 2019).

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### ORCID iD

Maaïke Maartje Rademaker <http://orcid.org/0000-0002-4904-1394>

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