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Effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease: study protocol for a double-blinded, randomised controlled trial

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ABSTRACT

Introduction Outcomes of surgery for Ménière's disease (MD) remain discordant. Recently, a new surgical procedure in which the endolymphatic duct is clipped was proposed. To date, only one prospective trial assessing this technique was published, yielding promising results. This protocol describes a prospective, double-blinded, randomised controlled trial that will be carried out to assess the effectiveness of this surgical intervention.

Methods Eighty-four patients with intractable MD will be recruited from 13 hospitals in the Netherlands. Intraoperatively, randomisation will determine whether endolymphatic duct blockage (EDB) or endolymphatic sac decompression (ESD) will be performed. Randomisation will be 1:1 stratified for gender and duration of MD (recent-onset versus mature MD). All participants receive vestibular rehabilitation after surgery. Patients are followed up during 1 year after surgery. Follow-up visits will take place at 1 week, 3 months, 6 months and 12 months after surgery. The main study endpoint is proportion of patients who are free of vertigo spells at 12 months postoperatively. Secondary parameters include cumulative number of vertigo bouts, co-intervention, tinnitus, hearing, quality of life, cost effectiveness and a budget impact analysis. Total duration of the study is 4 years.

Analysis The primary analysis will follow the intention-to-treat principle. For the primary outcome, a χ^2 test will be performed. Secondary outcomes will be analysed using a linear mixed model (EDB versus decompression group) at the different time measurement point.

Ethics and dissemination This study was reviewed and approved by a board of specialists before funding was obtained, as well as by the Medical Research Ethics Committee Leiden-The Hague-Delft and the boards of all participating centres. Results of this study will be published in international peer-reviewed scientific journals and will be presented on (inter)national scientific conferences and meetings.

Trial registration numbers NL9095 and ISRCTN12074571; Pre-Results.

Strengths and limitations of this study

- In this study, both patient and clinician will remain blinded throughout the follow-up period to minimise bias.
- The prospective design diminishes the risk of missing data and enables measurements of many parameters that are relevant for this disease.
- The number of participating centres ensures a quick dissemination of the results.
- The absence of comparison to a placebo intervention and a study arm with patients who do not undergo any intervention is a limitation of this trial.

INTRODUCTION

Ménière's disease (MD) is an incapacitating disease of recurrent vertigo attacks, accompanied by hearing loss, tinnitus and/or aural fullness. Intervals of days, weeks or even months may occur between the attacks of vertigo.[1 2] Studies on the natural course of MD have shown that the attacks of vertigo often become less severe, and disappear after 2 years in 60% and after 8 years in 80% of patients.[3–6] In the end phase of the disease, patients without vertigo attacks may still suffer from lasting hearing loss, tinnitus and chronic instability caused by hypofunction of the labyrinth.

The disease is of idiopathic origin, but is associated with endolymphatic hydrops in the inner ear.[7] Visualisation of the hydrops became possible with the introduction of delayed post-contrast high resolution MR imaging.[8–11] Hydrops is associated with duration of MD and saccular hydrops is associated with sensorineural hearing loss.[12] Moreover,

perilymphatic signal intensity is a surrogate marker for impaired blood–labyrinth permeability. Signal intensity (without hydrops) is markedly increased in patients with MD.[13]

Few articles have been published on the epidemiology of MD. Great variation exists in the published reports of the prevalence of MD, ranging from 34.5 to 218 cases per 100 000.[14–17] The difference in prevalence might be due to the wide variation in definitions of MD. There seems to be a slight female preponderance, with up to 1.3 times more women affected than men. The disease is more common in adults in their fourth and fifth decade of life.[5 6 17]

Treatment options

The treatment of MD both in primary and secondary care setting is focused on the reduction of the frequency and intensity of vertigo attacks. Current treatments have either proven to be ineffective (betahistin[18]), only have a temporary effect (intratympanic injections of dexamethasone[19] or methylprednisolone[20]), or destroy the labyrinth function (intratympanic gentamicin, labyrinthectomy and selective neurectomy[2 21 22]). Surgical destruction of the labyrinth reduces the episodes of attacks but causes loss of balance as well, due to one dysfunctional labyrinth. Moreover, permanent sensorineural hearing loss is reported after this treatment.

Recently, an international guideline for the diagnostic work-up and treatment of MD was published.[23] It recommends step-up treatment, starting with education of patients and discussing diuretics and betahistin. Intratympanic administration of corticosteroids is considered optional if patients do not respond to more conservative therapy. The last non-ablative option that can be considered is endolymphatic sac decompression (ESD). ESD consists of a mastoidectomy and, after identification of the ES, wide decompression of this structure.[22] ESD has few surgical complications in comparison with the ablative surgery mentioned above. However, results from this type of surgery are inconclusive.[23]

If there is no response to non-ablative treatments, treatment with intratympanic gentamicin is recommended, and if the disease remains unmanageable and the patient has non-usable hearing, labyrinthectomy is advised. Patients should also be referred for vestibular rehabilitation therapy in case of chronic balance problems, and clinicians should counsel patients with hearing problems about hearing aids.

ES surgery

Although surgery on the endolymphatic sac (ES) is briefly discussed in the guidelines, it may be worth further investigation. The advantage of procedures targeting the ES is that they are non-destructive and do, therefore, not affect the cochlear and vestibular function. Apart from decompression of the sac, as is discussed in the guideline,[23] shunting or drainage of the ES has also been proposed. These techniques involve identification of the ES, followed by incision of the sac. A shunt is then placed, enabling drainage of the endolymph.

Several studies were directed to investigate surgery on the endolymphatic sac.[24–26] Bretlau *et al* and Thomsen *et al* compared endolymphatic sac surgery (ESS) to a sham operation (either mastoidectomy or placement of ventilation tubes); no differences between the groups were observed. Brinson *et al* compared shunting to decompression performed on 88 patients and 108 patients, respectively. They concluded that both procedures are effective.

Multiple histological studies refute the rationale of ESS. First, Chung *et al* performed a histopathological study on 15 patients who had undergone ESS.[27] If the ES does, indeed, have a function in resorption of the endolymph but does so inadequately, ESS and especially ESD would allow expansion of these structures and would therefore diminish hydrops. However, diffuse hydrops on temporal bone was seen in the cochlea, the saccule, the utricle and the ampulla after ESD. The authors conclude that ESD does not relieve hydrops in patients with MD.

In addition, if the ES was responsible for endolymph resorption, an increase of hydrops can be expected after amputation of the ES. However, Linthicum and Santos reported a case in which removal of the ES did not lead to an increase of hydrops, as seen on temporal bone histopathology.[28] In the assessed samples, Reissner's membrane was attached to the spiral ligament in a normal way, without any evidence of hydrops in the cochlea. In conclusion, the role of the ES is not merely absorption of the endolymph and, therefore, providing more space to allow dilatation is not the solution for the observed hydrops.

The success rates of the mentioned surgical interventions vary between 30% and 95%.[2 4 22 29–31] It should be noted that the natural course of MD is also favourable, and it cannot be determined to what extent the outcome of procedures are due to the surgical intervention. Moreover, the placebo effect may play a major role in the relief of complaints, as 70% of patients with MD in all groups (all surgical interventions as well as the control groups) experienced some relief of complaints. This either implicates a beneficial effect of any surgical intervention or of any intervention, be it surgical or non-surgical. This was earlier suggested by Thomsen *et al*.[25]

A new technique

Recently, a new surgical intervention has been studied by Saliba *et al*.[32] A paradigm shift for the pathophysiological model of MD underlies this new treatment. Until now, it is believed that the disease is caused by a surplus of endolymph originating in the inner ear, caused by a disequilibrium in the production of endolymph in the inner ear and its resorption in the ES.[7 33 34] However, Saliba *et al* state that the organic substrate of the disease—the surplus of endolymph causing the hydrops—also originates in the ES.

The idea that the surplus of endolymph originates in the ES is supported by two studies that suggest that the

ES has secretory functions as well, rather than merely a function in absorption. In a study of the subcellular structure of the ES in guinea pigs by Takumida *et al*, the presence of dark cells in the ES was shown.[35] These cells have a secretory role. Moreover, a study performed by Friis *et al* on Lewis rats showed hyperactivity of the cells of the ES, leading to an increase of endolymph secretion.[36] In conclusion, histological evidence is that the ES is—at least in part—responsible for the endolymph surplus.

Based on these findings, Saliba *et al*'s hypothesis is that in MD, there is imbalance in the fluid homeostasis of the endolymph at the level of the ES, where the increased secretion outweighs the decreased absorption in the ES. Thus, by blocking the endolymphatic duct, Saliba *et al* aims to decrease the volume of endolymph in the inner ear, thereby alleviating the symptoms of MD. This operation, referred to as the endolymphatic duct blockage (EDB), involves placing a clip on the endolymphatic duct to separate the ES from the rest of the inner ear. Benefits of this technique are its permanent nature and the fact that it does not destroy the labyrinth or inner ear function.

Saliba *et al* have performed a randomised trial to study the effect of EDB.[32] The trial compared EDB to ESD and was conducted prospectively and non-blinded. There was no comparison to a group of patients receiving placebo treatment, for instance, a sham operation. The results have been published in 2015[32] and show that 34 of 35 treated patients were free of vertigo attacks after EDB surgery. It is interesting to note that the efficacy for the absence of vertigo attacks following ESD was only reported to be about 40% in Saliba *et al*'s trial.[32] In earlier studies by Bretlau *et al* and later Thomsen *et al*, percentages for both ESD and sham operations were reported to be as high as 70%. Possibly, this can be explained by the open character of the Saliba *et al*'s study, causing patients to experience the 'nocebo effect', caused by feeling like they have not been treated because they did not have the newly developed EDB surgery (but the ESD instead). The fact that Saliba *et al* did not assess outcomes in a double-blinded way is a flaw in methodology, given the high placebo effect of interventions in MD. Moreover, randomisation was not stratified and there is a risk of recall bias, as it is not described how vertigo bouts are recorded. Lastly, all participants were asked to follow the CATS (caffeine, alcohol, theophylline and salt) restricted diet. The role of this diet is not clear.

In a more recent publication by the group of Saliba, it is reported that 43 patients (79%) of a group of 54 patients treated with EDB had an improved quality of life (QoL).[37] The results of these studies indicate that EDB may have a favourable effect on both the bouts of vertigo that patients with MD suffer, as on the QoL. It should be noted that this study too was at risk for recall bias, as patients had to fill out questionnaire in retrospect.

EDB pilot

In the Netherlands, a pilot group of 34 patients underwent EDB. Quality of life was assessed in 26 of these patients; in this group, a significant (p=0.001) improvement of QoL was seen.[38] Three of these patients suffered drop attacks postoperatively, but these symptoms were all resolved within 8 weeks. In three patients, a postsurgical cerebrospinal fluid leakage occurred; successful surgical reintervention was performed the next day. In addition, EDB surgery was performed on another group of 60 patients. No adverse events occurred in this group of patients and most of the patients remained free of vertigo attacks.

According to the results discussed above, EDB is a promising surgical technique for treating MD that preserves hearing and equilibrium functions. The current trial further investigates the effectiveness of the EDB in treating MD, as compared with ESD.

METHODS AND ANALYSIS

Participants

Patients will be recruited from the participating centres in the Netherlands. Thirteen hospitals take part in this study, five of which are academic centres. In order to include only active MD cases, to avoid interference with follow-up and to minimise risk for the patients, eligibility criteria apply. These can be found in box 1. All participants will be informed about this trial by their own ear, nose and throat (ENT) specialist. Informed consent can be signed after a 2-week reflection period. A model informed consent form can be found in online supplemental appendix 1.

Each surgeon collects the number of patients that was screened for this study in order to assess generalisability of the results. This will be done in the patient records of each hospital. After enrolment, data will be collected in Castor EDC. All data will be treated confidentially.

Interventions

All participants will undergo surgery. Participants will be allocated in the EDB group or ESD group using an automated telephone randomised service (Castor EDC). Participants will be stratified according to gender and duration of MD (participants with recent-onset MD vs participants with mature MD). A 'participants with recent-onset MD' is defined as having their first MD vertigo attack in the 2 years prior to inclusion. 'Participants with mature MD' have had their first MD vertigo attack more than 2 years prior to inclusion. By stratification for the duration of the disease, the effect of the natural course of disease on the outcome is reduced.

The surgeries will be performed by two surgeons. One surgeon is experienced in this intervention and will act as proctor in all surgeries carried out for this trial. The second surgeon is the ENT surgeon who included the patients in this study. By working with only one proctor

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- Definite unilateral Ménière's disease (MD) according to diagnostic criteria of the Bárány Society.[1]
- More than three patients reported attacks in the 6 months prior to inclusion and at least one attack in 2 months prior to inclusion.
- Not responding to a sufficient extent to conservative medical treatment, including at least two sessions of at least one intratympanic (IT) injection each with corticosteroids (dexamethasone, methylprednisolone and triamcinolonacetonide).
- Dutch healthcare insurance.
- Age ≥18 years at the start of the trial.

Exclusion criteria

- Severe disability (eg, neurological, orthopaedic and cardiovascular) according to the investigator, pregnancy or serious concurrent illness that might interfere with surgery or follow-up.
- Active additional neuro-otological disorders that may mimic MD (eg, vestibular migraine, recurrent vestibulopathy, phobic postural vertigo, vertebrobasilar transient ischemic attacks (TIAs), acoustic neuroma, congenital disorders, enlarged vestibular aqueduct (EVA) or genetic disorders (like DFNA9) and cervicogenic dizziness), based on the complete clinical record.
- Unable to undergo MRI-scan (such as gadolinium allergy, claustrophobia, implanted non-MRI compatible device of material and body mass index).
- Previous ear surgery for MD (intratympanic injection is not an exclusion criterion).
- Deafness of the contralateral ear.
- Language difficulties.
- Active otitis media (with or without effusion).
- Unable or unwilling to use app-based diary.

who attends all surgeries, we aim to minimise outcome heterogeneity due to surgeon-specific factors.

The two ear surgeons will be present up to wherein the sac is completely skeletonised. Then, one of the surgeons will leave the operating room (OR). The randomisation for clip or decompression operation will be performed using the automated telephone randomised service. The surgeon who leaves the OR will take care of the follow-up of the patient and does not know whether the clip has been placed or not.

EDB surgery protocol

Surgery is performed as described by Saliba *et al*.[32] First, a canal wall-up mastoidectomy is performed: the mastoid tegmen, sigmoid sinus and sinodural angle are identified, and the posterior bony external ear canal wall is thinned. The posterior semicircular canal and the dura mater of the posterior fossa are identified. Using the prominence of the horizontal semicircular canal, Donaldson's line is identified to approximate the position of the ES. The bone over the sac and the dura are thinned with diamond burrs. The sac is completely skeletonised. The infralabyrinthine dura is exposed because the main body of the sac and its lumen often lie within this area. The bone of the vestibular aqueduct operculum is dissected. The posterior fossa dura from the retrolabyrinthine bone medial to the sac around the endolymphatic duct is exposed in order to identify the duct in its superior and inferior part in continuity from the ES, and to create a place to insert the tips of the instrument to clip the duct. At this level, care must be taken not to traumatise the dura, which is often thin.

Finally, the dissected endolymphatic duct is blocked with an adequate titanium clip (Weck Horizon, size 'micro' to 'wide, Teleflex). The size and numbers of clips used will be determined intraoperatively. The titanium clips are applied by using a clip applier (Weck Horizon). If available, a CT scan is then performed to assess clip position. In the case of tearing of the dura leading to liquor leakage, this will be treated with tisseel, fascie and novacol. Bone paste is collected during surgery and the cortex is restored with a mix of ofloxacin (3 mg/mL, Bausch & Lomb) and tisseel (4 mL, Baxter B.V.).

Decompression surgery protocol

The same surgical procedure is carried out in the decompression group. However, after identification of the posterior canal, the ES will be decompressed. No clips will be placed. The cortex is restored in the same procedure as described above.

Expected risks of surgery

Usual risk for surgery, such as infection and bleeding, apply. The main perioperative risk is liquor leakage. In most cases, this can be solved during surgery. If the leakage occurs after surgery, the patients will need to be operated again to repair the leak. Moreover, shortly after surgery, benign paroxysmal positional vertigo may occur as a result of burring during surgery. Other surgery-related risks are meningitis, hearing loss, facial nerve palsy and labyrinth function loss. Meningitis and facial nerve palsy have not been reported (nor in the literature nor in the patients operated in our centre).

Use of escape medication

Use of any co-intervention, such as intratympanic injection of steroid or use of antiemetics, is allowed and will be based on the participants' experience of vertigo attack frequency and patient–doctor preference (shared decision making). Shared decision making ensures wide applicability of study results and reflects daily medical practice.

Follow-up and outcome measures

From the moment of inclusion, all participants will use the DizzyQuest App,[39] an app based diary in which they fill out a daily questionnaire. Attacks are also reported in this app. All participants receive an individual tailored vestibular rehabilitation programme after surgery. Follow-up visits will take place at 1 week, 3 months, 6 months and 12 months after surgery. Which outcomes will be measured at what moment can be found in table 1. All data will be stored in Castor EDC.

Table 1 Overview of all moments and measures of follow up.

Moment in trial	Type of follow-up	Outcomes
From moment of inclusion until 1 year after surgery		Daily questionnaire in app
>4 weeks before surgery	ENT surgeon	(Video-)HIT
	Physiotherapy	Balance test DVA DGI
	Questionnaires	Baseline characteristics HADS DHI THI FLS EQ 5D VAS SF36 NPQ Assessment of expectations patient VADL VAP
	Imaging	MRI CT
	Other	PTA Calorigram
1 week after surgery	ENT surgeon	Standard postoperative care (Video-)HIT
	Physiotherapy	Balance test DVA DGI
3 months after surgery	ENT surgeon	(video-)HIT
	Physiotherapy	Balance test DVA DGI
	Questionnaires	DHI THI FLS EQ 5D VAS SF36 iMCQ iPCQ
	Imaging	MRI
	Other	PTA
6 months after surgery	ENT surgeon	(Video-)HIT
	Physiotherapy	Balance test DVA DGI
	Questionnaires	DHI THI FLS EQ 5D VAS SF36 iMCQ iPCQ
	Imaging	–
	Other	PTA
12 months after surgery	ENT surgeon	(Video-)HIT
	Physiotherapy	Balance test DVA DGI
	Questionnaires	DHI THI FLS EQ 5D VAS SF36 iMCQ iPCQ VADL VAP
	Imaging	MRI
	Other	PTA Calorigram

CT, Computed Tomography; DGI, Dynamic Gait Index; DHI, Dizziness Handicap Index; DVA, Dynamic Visual Acuity; ENT, ear, nose, throat; EQ 5D, EuroQol 5D; FLS, Functional Level Scale; HADS, Hospital Anxiety and Depression Scale; HIT, Head Impulse Test; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire; MRI, Magnetic Resonance Imaging; NPQ, Niigata PPPD Questionnaire; PTA, Pure Tone Average; SF36, Short Form 36; THI, Tinnitus Handicap Index; VADL, Vestibular Disorders Activities of Daily Living Scale; VAP, Vestibular Activities and Participation Measure; VAS, Visual Analogue Scale.

After follow-up

When the last patient has been followed up for a year, patients can choose to be deblinded if they wish. If the patient was allocated to the EDB group but still suffers vertigo bouts, a CT scan will be performed to assess if the clip is correctly in place. If the results of this trial are in favour of EDB, patients in the decompression group who still suffer vertigo attacks will be offered EDB. In case of a favourable outcome of EDB, a trajectory for implementation in the current Dutch healthcare system is also foreseen.

We hypothesise that the number of patients without vertigo spells at 12-month follow-up will be higher in the group that has undergone EDB than in the decompression group. Secondary outcomes include minimally clinically significant differences in cumulative incidence of vertigo bouts, hearing, use of escape medication, co-interventions, complications of surgery, questionnaire outcomes, cost-effectiveness analysis, budget impact analysis, endolymphatic hydrops on MRI and multiple physiotherapeutical outcomes. We hypothesise that the outcomes of these measures will be better in participants undergoing EDB compared with participants who have had a decompression operation.

The sample size for this randomized controlled trial was computed using software package PASS V.11. The sample size calculation is based on the study performed by Saliba *et al*,[32] in which complete control of vertigo was reached in 96.5% of the patients who underwent EDB.

According to the literature, ESD is effective in ±70% of the patients.[26 30 31]

We compare participants with MD undergoing an operation with clip (EDB group: group A) independently with participants with MD undergoing operation without clip (decompression group: group B). Null hypothesis is that the percentage points difference between groups percentages is nil (pA=pB), with two-sided alternative hypothesis (pA<>pB) and with anticipated 25% difference (pA=95% and pB=70%). Power is at least 80%. The chance of a false positive finding for either of the analyses is controlled at the 5% level (family wise error rate). To obtain a power of at least 80% for Fisher's exact test, the required sample size is 32 in groups A and B (allocation ratio=1). Loss to follow-up will likely occur in a small percentage of cases. No selective loss to follow-up is anticipated and a missing-at-random assumption is reasonable. Missing outcomes will, therefore, be imputed using multiple imputation in the main analysis. Two sensitivity analyses will be conducted as well, where missing outcomes will be treated as failures or success, respectively. In this case, the sample size would be 42 in groups A and B (allocation ratio=1). The total number of participants will be 84.

Endolymphatic hydrops on MRI

We hypothesise that EDB results in a decrease in hydrops and perilymph signal intensity. These two parameters will be measured preoperatively, as well as 3 months and 12 months postoperatively to assess if the hydrops diminishes after EDB and is clinically relevant.

Data analysis

All collected data will be accessible for the coordinating investigator, the principal investigator and for the investigators involved in carrying out analyses.

The primary outcome is defined as being attack free at 12-month follow-up. All statistical tests will be performed two-sided at a significance (α) level of 5%. When using confidence limits, the CI will be 95%. The primary analysis will be performed following the intention-to-treat principle. A χ^2 test (or Fisher's exact test) will be performed on the primary outcome variable data (the number of patients free of vertigo attacks at 12 months postoperatively, in EDB vs ESD group). Although randomisation is stratified, the impact of gender and duration of MD is deemed small. These variables will only be added as covariates to the analysis if they are independently associated with the outcome. In the case, a logistic regression will be performed.

The daily questionnaire taken via the DizzyQuest app is likely to contain missing data. Missing data will be labelled 'NAmissing' in SPSS. Multiple imputation will be used to create complete data sets. Depending on the missing data pattern, different strategies will be followed. Preferably, 'wide' data format will be used to account for time dependent effects. As an alternative for larger percentages of missingness, data will be imputed in long format, ignoring time-dependent effects.

The outcome will be determined from the imputed app's data. It is expected that attacks are reported reliably and missing data can be reliably imputed as being attack free. In principle, a patient can be sometimes imputed as having an attack on otherwise as being attack free. To account for these potential cases, a cut-off of 10% for the attack probability (as the imputed frequency for having an attack) will be used to determine presence/absence of attacks.

The patient-reported outcome measures used in this study are assumed to be continuous numerical and will be tested checked for near-Gaussian distribution normality before analysis. Results will be described as means (with 95% CI) in case of near-Gaussian distribution, or otherwise medians (with IQR) will be presented at each time point. Categorical outcomes will be presented in numbers of participants with accompanying percentages of group total.

All secondary outcomes will be analysed using a linear mixed model (EDB vs decompression group) at the different time measurement point.

All the participating centres will be issued standard operating procedures for procedures such as inclusion of patients, a format for follow-up visits and reporting of (serious) adverse events. With these checklists, an effort is made to improve adherence to the protocol. The coordinating investigator will be in close contact with all the local investigators to discuss problems experienced during recruitment and follow-up.

Substantial protocol amendments will be reviewed by the medical ethics committee. If approved, the amendments will be directly communicated to the local investigator of the participating centres. Moreover, the funding party and the trial registries will be informed. This is the responsibility of the coordinating investigator.

Economic evaluation

A 1-year trial-based cost-effectiveness analysis (costs per prevented vertigo attack, from a healthcare perspective), a cost–utility analysis (costs per quality adjusted life year (QALY), from a societal perspective) and a budget-impact analysis will be performed. Societal costs will be assessed from the patients' medical records and from patient questionnaires at 3 months, 6 months and 12 months. QALYs will be calculated as the area under the utility curve, estimated using the Dutch tariff for the EQ-5D-5L at 0 month, 3 months, 6 months and 12 months (and the EuroQol visual analogue scale with power transformation as secondary analysis). Average costs and patient outcome will be compared according to intention to treat, using net benefit analysis, and multiple imputation to account for missing data.

Patient and public involvement

Several patients and the patient support group for hearing and equilibrium disorders were involved in the design of

this trial. Patients have provided feedback on feasibility of the number of questionnaires. The patient support group will also be involved in recruitment of patients, by spreading information about the trial. During the conduct of the trial, feasibility of questionnaire frequency will be evaluated with the participants, and adjusted if necessary.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines were used for publication of this protocol.[40]

ETHICS AND DISSEMINATION

Ethics

The protocol was extensively reviewed by the Dutch National Healthcare Institute and was approved by their board (decision number: 2020010440). Moreover, the protocol was reviewed and approved by the Medical Research Ethics Committee Leiden-The Hague-Delft (number: P20.118). The boards of all participating centres must approve the study before commencement of local recruitment. The study will be conducted according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO, 26 February 1998) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP, November 2016).

Patient safety

A Data Safety Monitoring Board (DSMB) was established to monitor the safety of the participants throughout the trial. The three members are not in any other way involved in the trial and have, therefore, no conflict of interest with the sponsor of the study. An interim analysis of the data for the first 21 participants will be performed, focusing on safety of the surgical procedures. The DSMB will assess the results and discuss the outcome, and give advice whether or not to continue the study. Termination of the trial will be considered if there are more (serious) adverse events than expected, that are related to the intervention. Moreover, monitoring of the conduct of the study will be performed, according to the monitor plan that was written.

All serious adverse events will be reported in the official tool of the Dutch Central Committee on Research Involving Human Subjects.

An emergency phone number will be provided to the participants, for when deblinding is necessary because of a medical emergency.

Dissemination

The protocol will be submitted for open access publication to make it publicly available. Data from the dataset will not be accessible, but can be requested. The same applies for the statistical code.

RESULTS

Results of this study will be published in international peer-reviewed scientific journals and will be presented on (inter)national scientific conferences and meetings. Individual centres included in this multicentre trial will not report or publish data from this centre alone. Transfer of ownership of the data will be reported to the appropriate authority/authorities, as required by the applicable regulatory requirement(s). All publications and presentations are to protect the research integrity of the participants and objectives of the study. No data will be presented or released that may break the masking of the study trial. The timing of presentation and/or publications of the primary and/or secondary outcomes will be secured by the supervising researchers and will be communicated first with all centres involved.

All data remains stored in Castor EDC for 15 years after termination of the trial.

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Contributors All authors were involved in the conception of the trial, writing of the protocol and critical revision for intellectual content. All authors read and approved of the final version.

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