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Study protocol for a double blinded, randomised controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease

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TITLE PAGE

Title

Study protocol for a double blinded, randomised controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease.

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Abstract

Introduction. Outcomes of surgery for Meniere'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. The present protocol describes a prospective, double blinded, randomized controlled trial that will be carried out to assess effectiveness of this surgical intervention.

Methods. Eighty-four patients with intractable Meniere's disease will be recruited from 13 hospitals in the Netherlands. Intraoperatively, randomization will determine whether endolymphatic duct blockage (EDB) or endolymphatic sac decompression (ESD) will be performed. Randomization 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 one 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 post-operatively. 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 chi-square test will be performed. Secondary outcomes will be analyzed using a linear mixed model (EDB vs 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.

Strengths and limitations of this study

- In this study, both patient and clinician will remain blinded throughout the follow up period to minimalize 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 centers 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. Between the attacks of vertigo intervals of days, weeks or even months may occur [1, 2]. The natural course of MD has been studied and it has been found that the attacks of vertigo become less severe and disappear after two years in 60% and after eight 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 and 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]. Visualization 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]. Perilymphatic signal intensity is a surrogate marker for impaired blood-labyrinth permeability. Signal intensity (without) hydrops is markedly increased in the acute phase of labyrinthitis and is 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 variations 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 dexamethasone injections [19], or methylprednisolone [20]), or destroy the labyrinth function (intratympanic gentamicin, labyrinthectomy, 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/betahistine. 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. Endolymphatic sac

decompression (ESD) consists of a mastoidectomy and, after identification of the endolymphatic sac, 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.

Endolymphatic sac surgery

Although surgery on the endolymphatic sac is briefly discussed in the guidelines, it may be worth further investigation. The advantage of procedures targeting the endolymphatic sac 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 [24-26]. Bretlau and Thomsen compared ESS to a sham operation (either mastoidectomy or placement of ventilation tubes); no differences between the groups was observed. Brinson compared shunting to decompression performed on 88 and 108 patients, respectively. He concluded that both procedures are effective.

Multiple histological studies refute the rationale of endolymphatic sac surgery. Firstly, Chung et al, performed a histopathological study 15 patients who had undergone ESS [27]. If the endolymphatic sac 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 Ménière's disease.

In addition, if the ES was responsible for endolymph resorption, an increase of hydrops can be expected after amputation of the ES. However, Linthicum et al. 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 these surgical interventions vary between 30-95% [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 MD patients 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 [25].

A new technique

Recently, a new surgical intervention has been studied by Saliba et al. [32]. A paradigm shift for the pathofysiological 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 endolymphatic sac [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 endolymphatic sac.

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 endolymphatic sac in guinea pigs by Takumida et al., the presence of dark cells in the endolymphatic sac was shown [35]. These cells have a secretory role. Moreover, a study performed by Friis on Lewis rats showed hyperactivity of the cells of the endolymphatic sac, leading to an increase of endolymph secretion [36]. In conclusion, histological evidence that the ES is –at least in part- responsible for the endolymph surplus.

Based on these findings, Saliba's hypothesis is that in Ménière's disease, there is imbalance in the fluid homeostasis of the endolymph at the level of the endolymphatic sac, where the increased secretion outweighs the decreased absorption in the ES. Thus, by blocking the endolymphatic duct, Saliba aims to decrease the volume of endolymph in the inner ear, thereby alleviating the symptoms of Ménière's disease. This operation, referred to as the Endolymphatic Duct Blockage (EDB), involves placing a clip on the endolymphatic duct to separate the endolymphatic sac 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 has performed a randomized 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's trial [32]. In earlier studies by Bretlau and later Thomsen, 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 study, causing patients to experience the 'nocebo-effect', caused by feeling like they have not been treated because they did not have the 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 Ménière disease. 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 (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 MD patients suffer, as on the quality of life. It should be noted that this study 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. In this group of 34 patients, a significant (p=.001) improvement of quality of life seen (unpublished data). Three of these 34 patients suffered drop attacks post-operatively, but these symptoms were all resolved within 8 weeks. In three patients, a postsurgical cerebrospinal fluid (CSF) 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 (unpublished data).

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 to endolymphatic sac decompression.

Methods and analysis

Participants

Patients will be recruited in the participating centers in the Netherlands. Thirteen hospitals take part in this study, five of which are academic centers. In order to include only active Meniere's disease, to avoid interference with follow up and to minimalize risk for the patients, eligibility criteria apply. These can be found in **Table I**. All participants will be informed about this trial by their own ENT-surgeon. Informed consent can be signed after a two week reflection period. Each surgeon collects the number of patients that was screened for this study in order to assess generalizability of the results. This will be done in the patient records of each hospital. After enrollment, all data will be collected in Castor EDC. All data will be treated confidentially.

Inclusion criteria
Definite unilateral MD according to diagnostic criteria of the Bárány Society (Lopez-Escamez, 2016)
More than 3 patient reported attacks in the 6 months prior to inclusion and at least 1 attack in the 2 months prior to inclusion
Non responding to a sufficient extent to conservative medical treatment including at least two sessions of at least one intra-tympanic injection (IT) each with corticosteroids (dexamethasone, methylprednisolone, triamcinolonacetonide)
Dutch health care insurance
Age ≥ 18 years at the start of the trial
Exclusion criteria
Severe disability (e.g. neurological, orthopedic, cardiovascular) according to the investigator, pregnancy or serious concurrent illness that might interfere with surgery or follow-up.
Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM), recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma, congenital disorders, enlarged vestibular aquaduct (EVA)-like or genetic disorders (like DFNA9), cervicogenic dizziness), based on the complete clinical record.
Unable to undergo MRI (such as gadolinium allergy, claustrophobia, implanted non-MRI compatible device of material, BMI)
Previous ear surgery for MD (IT 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

Table I. Inclusion and exclusion criteria

Interventions

All participants will undergo surgery. Participants will be allocated in the EDB group or endolymphatic sac decompression group using an automated telephone randomised service (Castor). Participants will be stratified according to gender and duration of MD (recent-onset versus mature MD participants). A "recent-onset MD participant" is defined as having their first MD vertigo attack in the two years prior to inclusion. "Mature MD participants" have had their first MD vertigo attack more than two 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 who attends all surgeries, we aim to minimize outcome heterogeneity due to surgeon specific factors.

The two ear surgeons will be present up to wherein the sac is completely skeletonized. Then one of the surgeons will leave the OR. The randomization for clip or decompression operation will be performed using the automated telephone randomized 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 [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 semi-circular canal (PSCC) and the dura mater of the posterior fossa are identified. Using the prominence of the horizontal semi-circular canal, Donaldson's line is identified to approximate the position of the endolymphatic sac. The bone over the sac and the dura are thinned with diamond burrs. The sac is completely skeletonized. 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 endolymphatic sac, 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 traumatize 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). 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 bone paste, ofloxacine (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, and the ES will be decompressed. No clips will be placed. The cortex is restored in the same procedure as described above.

Use of escape medication

Use of any co-intervention, such as intratympanic injection of steroid or use of anti-emetics, are 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 an app-based diary (the DizzyQuest App [38] in which they fill out a daily questionnaire. Attacks are also reported in this app. All participants receive an individual tailored vestibular rehabilitation program after surgery. Follow up visits will take place at 1 week, 3 months, 6 months and 12 months after surgery. What outcomes will be measured at what moment can be found in **Table II**. All data will be stored in Castor EDC.

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 Dynamic visual acuity Gait (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 Dynamic visual acuity Gait (DGI)
3 months after surgery	**ENT-surgeon**	(video-)HIT
	Physiotherapy	Balance test Dynamic visual acuity Gait (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 Dynamic visual acuity Gait (DGI)

	Questionnaires	DHI THI FLS E Q 5D VAS SF36 iMCQ iPCQ
	Imaging	-
	Other	PTA
12 months after surgery	**ENT-surgeon**	(video-)HIT
	Physiotherapy	Balance test Dynamic visual acuity Gait (DGI)
	Questionnaires	DHI THI FLS EQ 5D VAS SF36 iMCQ iPCQ VADL VAP
	Imaging	MRI
	Other	PTA Calorigram

We hypothesize that the number of patients without vertigo spells at 12 months 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 hypothesize that the outcomes of these measures will be better in participants undergoing EDB compared to participants who have had a decompression operation.

The sample size for this RCT was computed using software package PASS 11. The sample size calculation is based on the study performed by Saliba [32], in which complete control of vertigo was reached in 96,5% of the patients who underwent EDB. According to literature, endolymphatic sac decompression is effective is ± 70% of the patients [26, 30, 31].

We compare MD participants undergoing an operation with clip (EDB group: A group) independently with MD participants undergoing operation without clip (decompression group: B group). 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% percent 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 group A and B (allocation ratio = 1). The total number of participants will be 84.

Endolymphatic hydrops on MRI

We hypothesize that EDB results in a decrease in hydrops and perilymph signal intensity. These two parameters will be measured pre-operatively, as well as 3-months and 12-months post-operatively 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 months follow-up. All statistical tests will be performed two-sided at a significance (α) level of 5%. When using confidence limits, the confidence interval will be 95%. The primary analysis will be performed following the intention-to-treat principle. A chi-square test (or Fisher's exact test) will be performed on the primary outcome variable data (number of patients free of vertigo attacks at 12 months post-operatively, in EDB vs endolymphatic sac decompression group). Although randomization 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. All other 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-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 (PROMs) 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 analyzed using a linear mixed model (EDB versus decompression group) at the different time measurement point.

Economic evaluation

A one-year trial-based cost-effectiveness analysis (costs per prevented vertigo-attack, from a healthcare perspective), a cost-utility analysis (costs per 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 3,6 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, 3, 6 ,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, the

frequency of questionnaires (mainly the app based diary) will be evaluated with the participants.

The SPIRIT reporting guidelines were used for publication of this protocol [39].

Ethics and dissemination

Ethics.

The protocol was reviewed and approved by the Medical Research Ethics Committee Leiden The Hague Delft. 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 Harmonization Good Clinical Practice (ICH GCP, November 2016).

This trial is registered in the Netherlands Trial Register (https://www.trialregister.nl/trial/9095) and in the ISRCTN registry (https://www.isrctn.com/ISRCTN12074571).

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 3 months after surgery 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.

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 health care system is also foreseen.

Publication of 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 centers included in this multicenter trial will not report or publish data from this center 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 of 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 centers involved.

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

List of abbreviations

BMI	Body mass index
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
DGI	Dynamic gait index
DHI	Dizziness handicap index
DSMB	Data Safety Monitoring Board
EDB	Endolymphatic duct blockage
ENT	Ear, nose, throat
EQ 5D	EuroQol 5D
ES	Endolymphatic sac
ESD	Endolymphatic sac decompression
ESS	Endolymphatic sac surgery
EVA	Enlarged vestibular aqueduct
FLS	Functional level scale
HIT	Head impulse test
IQR	Interquartile range
iMCQ	IMTA Medical Cost Questionnaire
iPCQ	IMTA Productivity Cost Questionnaire
IT	Intratympanic
MD	Meniere's disease
MRI	Magnetic resonance imaging
NPQ	Niigata PPPD Questionnaire
OR	Operating room
PROM	Patient reported outcome measure
PSCC	Posterior semi-circular canal
PTA	Pure-tone average
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
SF36	Short Form Health Survery 36
THI	Tinnitus handicap index

TIA	Transient ischemic attack
VADL	Vestibular Disorders Activities of Daily Living Scale
VAP	Vestibular activities and participation questionnaire
VAS	Visual analogue score
VM	Vestibular migraine

Authors' contributions: state how each author was involved in writing the protocol.

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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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Roles and responsibilities

The authors of this protocol form the trial steering committee. All were engaged in study design and will be involved in analysis, interpretation of data, writing of the report and the decision to submit the outcomes for publication. AS is the coordinating investigator and HB is the principal investigator and are responsible for data collection and management.

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Competing interests statement

None to declare.

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Reporting checklist for protocol of a clinical trial.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	12
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	15

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	12

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study protocol for a double blinded, randomised controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease

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TITLE PAGE

Title

Study protocol for a double blinded, randomised controlled trial to assess the effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière's disease.

Protocol version 6, June 16th, 2021

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Abstract

Introduction. Outcomes of surgery for Meniere'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. The present protocol describes a prospective, double blinded, randomized controlled trial that will be carried out to assess effectiveness of this surgical intervention.

Methods. Eighty-four patients with intractable Meniere's disease will be recruited from 13 hospitals in the Netherlands. Intraoperatively, randomization will determine whether endolymphatic duct blockage (EDB) or endolymphatic sac decompression (ESD) will be performed. Randomization 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 one 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 post-operatively. 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 chi-square test will be performed. Secondary outcomes will be analysed using a linear mixed model (EDB vs 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.

Strengths and limitations of this study

- In this study, both patient and clinician will remain blinded throughout the follow up period to minimize 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

Registration details

This trial is registered in the Netherlands Trial Register (trial NL9095, https://www.trialregister.nl/trial/9095) and in the ISRCTN registry (trial ISRCTN12074571, https://www.isrctn.com/ISRCTN12074571).

Introduction

Ménière's disease (MD) is an incapacitating disease of recurrent vertigo attacks, accompanied by hearing loss, tinnitus and/or aural fullness. Between the attacks of vertigo intervals of days, weeks or even months may occur [1, 2]. The natural course of MD has been studied and it has been found that the attacks of vertigo become less severe and disappear after two years in 60% and after eight 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 and 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]. Visualization 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]. Perilymphatic signal intensity is a surrogate marker for impaired blood-labyrinth permeability. Signal intensity (without) hydrops is markedly increased in the acute phase of labyrinthitis and is 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 variations 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 dexamethasone injections [19], or methylprednisolone [20]), or destroy the labyrinth function (intratympanic gentamicin, labyrinthectomy, 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/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. Endolymphatic sac

decompression (ESD) consists of a mastoidectomy and, after identification of the endolymphatic sac, 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.

Endolymphatic sac surgery

Although surgery on the endolymphatic sac is briefly discussed in the guidelines, it may be worth further investigation. The advantage of procedures targeting the endolymphatic sac 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 [24-26]. Bretlau and Thomsen compared ESS to a sham operation (either mastoidectomy or placement of ventilation tubes); no differences between the groups was observed. Brinson compared shunting to decompression performed on 88 and 108 patients, respectively. He concluded that both procedures are effective.

Multiple histological studies refute the rationale of endolymphatic sac surgery. Firstly, Chung et al, performed a histopathological study 15 patients who had undergone ESS [27]. If the endolymphatic sac 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 Ménière's disease.

In addition, if the ES was responsible for endolymph resorption, an increase of hydrops can be expected after amputation of the ES. However, Linthicum et al. 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 these surgical interventions vary between 30-95% [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 MD patients 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 [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 endolymphatic sac [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 endolymphatic sac.

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 endolymphatic sac in guinea pigs by Takumida et al., the presence of dark cells in the endolymphatic sac was shown [35]. These cells have a secretory role. Moreover, a study performed by Friis on Lewis rats showed hyperactivity of the cells of the endolymphatic sac, leading to an increase of endolymph secretion [36]. In conclusion, histological evidence that the ES is –at least in part- responsible for the endolymph surplus.

Based on these findings, Saliba's hypothesis is that in Ménière's disease, there is imbalance in the fluid homeostasis of the endolymph at the level of the endolymphatic sac, where the increased secretion outweighs the decreased absorption in the ES. Thus, by blocking the endolymphatic duct, Saliba aims to decrease the volume of endolymph in the inner ear, thereby alleviating the symptoms of Ménière's disease. This operation, referred to as the Endolymphatic Duct Blockage (EDB), involves placing a clip on the endolymphatic duct to separate the endolymphatic sac 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 has performed a randomized 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's trial [32]. In earlier studies by Bretlau and later Thomsen, 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 study, causing patients to experience the 'nocebo-effect', caused by feeling like they have not been treated because they did not have the 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 Ménière disease. 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 (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 MD patients suffer, as on the quality of life. It should be noted that this study 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=.001) improvement of quality of life seen [38]. Three of these patients suffered drop attacks post-operatively, but these symptoms were all resolved within 8 weeks. In three patients, a postsurgical cerebrospinal fluid (CSF) 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 to endolymphatic sac decompression.

Methods and analysis

Participants

Patients will be recruited in 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 Meniere's disease, to avoid interference with follow up and to minimize risk for the patients, eligibility criteria apply. These can be found in **Table I**. All participants will be informed about this trial by their own ENT-surgeon. Informed consent can be signed after a two week reflection period. A model informed consent form can be found in Appendix 1.

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

Inclusion criteria
Definite unilateral MD according to diagnostic criteria of the Bárány Society (Lopez-Escamez, 2016)
More than 3 patient reported attacks in the 6 months prior to inclusion and at least 1 attack in the 2 months prior to inclusion
Non responding to a sufficient extent to conservative medical treatment including at least two sessions of at least one intra-tympanic injection (IT) each with corticosteroids (dexamethasone, methylprednisolone, triamcinolonacetonide)
Dutch health care insurance
Age ≥ 18 years at the start of the trial
Exclusion criteria
Severe disability (e.g. neurological, orthopaedic, 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 (e.g. vestibular migraine (VM), recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma, congenital disorders, enlarged vestibular aqueduct (EVA)-like or genetic disorders (like DFNA9), cervicogenic dizziness), based on the complete clinical record.
Unable to undergo MRI (such as gadolinium allergy, claustrophobia, implanted non-MRI compatible device of material, BMI)
Previous ear surgery for MD (IT 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

Table I. Inclusion and exclusion criteria

Interventions

All participants will undergo surgery. Participants will be allocated in the EDB group or endolymphatic sac decompression group using an automated telephone randomised service (Castor). Participants will be stratified according to gender and duration of MD (recent-onset versus mature MD participants). A “recent-onset MD participant” is defined as having their first MD vertigo attack in the two years prior to inclusion. “Mature MD participants” have had their first MD vertigo attack more than two 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 who attends all surgeries, we aim to minimize outcome heterogeneity due to surgeon specific factors.

The two ear surgeons will be present up to wherein the sac is completely skeletonized. Then one of the surgeons will leave the OR. The randomization for clip or decompression operation will be performed using the automated telephone randomized 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 [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 semi-circular canal (PSCC) and the dura mater of the posterior fossa are identified. Using the prominence of the horizontal semi-circular canal, Donaldson’s line is identified to approximate the position of the endolymphatic sac. The bone over the sac and the dura are thinned with diamond burrs. The sac is completely skeletonized. 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 endolymphatic sac, 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 traumatize 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 bone paste, ofloxacine (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, and 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 (BPPV) 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 literature nor in the patients operated in our centre).

To anticipate anatomic variation, a pre-operative CT-scan of the petrous part of the temporal bone will be mad. Moreover, a intraoperative CT-scan will be made (if available at the operating room) just before applying of the clip in the EDB group, to assess if the clip is placed correctly.

Use of escape medication

Use of any co-intervention, such as intratympanic injection of steroid or use of anti-emetics, are 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 an app-based diary (the DizzyQuest App [39] in which they fill out a daily questionnaire. Attacks are also reported in this app. All participants receive an individual tailored vestibular rehabilitation program 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 II**. All data will be stored in Castor EDC.

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 Dynamic visual acuity Gait (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 Dynamic visual acuity Gait (DGI)
3 months after surgery	**ENT-surgeon**	(video-)HIT
	Physiotherapy	Balance test Dynamic visual acuity Gait (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 Dynamic visual acuity Gait (DGI)
	Questionnaires	DHI THI FLS E Q 5D VAS SF36 iMCQ iPCQ
	Imaging	-
	Other	PTA
12 months after surgery	**ENT-surgeon**	(video-)HIT
	Physiotherapy	Balance test Dynamic visual acuity Gait (DGI)
	Questionnaires	DHI THI FLS EQ 5D VAS SF36 iMCQ iPCQ

		VADL VAP
	Imaging	MRI
	Other	PTA Calorigram

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 health care system is also foreseen.

We hypothesize that the number of patients without vertigo spells at 12 months 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 hypothesize that the outcomes of these measures will be better in participants undergoing EDB compared to participants who have had a decompression operation.

The sample size for this RCT was computed using software package PASS 11. The sample size calculation is based on the study performed by Saliba [32], in which complete control of vertigo was reached in 96,5% of the patients who underwent EDB. According to literature, endolymphatic sac decompression is effective is ± 70% of the patients [26, 30, 31].

We compare MD participants undergoing an operation with clip (EDB group: A group) independently with MD participants undergoing operation without clip (decompression group: B group). 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% percent 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 group A and B (allocation ratio = 1). The total number of participants will be 84.

Endolymphatic hydrops on MRI

We hypothesize that EDB results in a decrease in hydrops and perilymph signal intensity. These two parameters will be measured pre-operatively, as well as 3-months and 12-months post-operatively 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 months follow-up. All statistical tests will be performed two-sided at a significance (α) level of 5%. When using confidence limits, the confidence interval will be 95%. The primary analysis will be performed following the intention-to-treat principle. A chi-square test (or Fisher's exact test) will be performed on the primary outcome variable data (number of patients free of vertigo attacks at 12 months post-operatively, in EDB vs endolymphatic sac decompression group). Although randomization 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. All other 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-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 (PROMs) 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 versus decompression group) at the different time measurement point.

All the participating centres will be issued standard operating procedures (SOPs) 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 one-year trial-based cost-effectiveness analysis (costs per prevented vertigo-attack, from a healthcare perspective), a cost-utility analysis (costs per 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, 6 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, 3, 6 ,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, the frequency of questionnaires (mainly the app based diary) will be evaluated with the participants.

The SPIRIT reporting guidelines were used for publication of this protocol [40].

Ethics and dissemination

Ethics.

The protocol was extensively reviewed by the Dutch National Health Care 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 (METC-LDD, number P20.118). 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 Harmonization 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 3 months after surgery 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 of 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 for 15 years after termination of the trial.

List of abbreviations

BMI	Body mass index
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
DGI	Dynamic gait index
DHI	Dizziness handicap index
DSMB	Data Safety Monitoring Board
EDB	Endolymphatic duct blockage
ENT	Ear, nose, throat
EQ 5D	EuroQol 5D
ES	Endolymphatic sac
ESD	Endolymphatic sac decompression
ESS	Endolymphatic sac surgery
EVA	Enlarged vestibular aqueduct
FLS	Functional level scale
HIT	Head impulse test
IQR	Interquartile range
iMCQ	IMTA Medical Cost Questionnaire
iPCQ	IMTA Productivity Cost Questionnaire
IT	Intratympanic
MD	Meniere's disease
MRI	Magnetic resonance imaging
NPQ	Niigata PPPD Questionnaire
OR	Operating room
PROM	Patient reported outcome measure
PSCC	Posterior semi-circular canal
PTA	Pure-tone average
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
SF36	Short Form Health Survery 36
THI	Tinnitus handicap index

TIA	Transient ischemic attack
VADL	Vestibular Disorders Activities of Daily Living Scale
VAP	Vestibular activities and participation questionnaire
VAS	Visual analogue score
VM	Vestibular migraine

Authors' contributions

All authors were involved in conception of the trial: HB, JK, PvB and AS for the clinical aspects, SC provided epidemiological expertise, WvdH designed the economic evaluation, SB is the trial statistician, SHa is involved for the radiological aspects and SHo is responsible for the physiotherapeutical part of the study. Therefore, all authors contributed to writing of the protocol. This article was drafted by AS and critically revised by all authors, who provided feedback regarding their field of expertise and revised it for important intellectual content. During the trial, AS is responsible for data collection, management, analysis and interpretation. During the trial, the funder has an advisory role. Start-up of the trial will take 6 months, recruitment of participants 2 years, follow up 1 year and 6 months are provided for analysis and interpretation of the data. Outcomes will be reported to the funder after this total period of 4 years. Submitting of data to an international paper is the responsibility of HB and AS. All authors read and approved of the final version of this article.

Roles and responsibilities

The authors of this protocol form the trial steering committee. All were engaged in study design and will be involved in analysis, interpretation of data, writing of the report and the decision to submit the outcomes for publication. AS is the coordinating investigator and HB is the principal investigator and are responsible for data collection and management.

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Competing interests statement

None to declare.

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Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

EDB-operatie bij de ziekte van Ménière

Officiële titel: "De effectiviteit van endolymfatische ductusblokkade versus endolymfatische saccusdecompressie bij patiënten met oncontroleerbare ziekte van Ménière."

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u de ziekte van Ménière heeft.
U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage E.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:
- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. Van der Schroeff
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Het HagaZiekenhuis, het Haaglanden Medisch Centrum en het Leids Universitair Medisch Centrum hebben dit onderzoek opgezet. Hieronder noemen we het HagaZiekenhuis steeds de 'opdrachtgever'. Onderzoekers (dit kunnen artsen, onderzoeksverpleegkundigen en fysiotherapeuten zijn) voeren het onderzoek uit in verschillende ziekenhuizen.

In deze informatiefolder wordt gesproken over 'de onderzoeker'. Dat is de KNO-arts die uw deelname aan deze studie regelt. Hij of zij is ook degene die bij de operatie aanwezig is en bij wie u terugkomt na de operatie. Hierover leest u meer in paragraaf 4.
Omdat niet alle KNO-artsen in Nederland meedoen met deze studie, is dit soms een andere arts dan uw eigen.

Voor dit onderzoek zijn in totaal 84 proefpersonen nodig.

De medisch-ethische toetsingscommissie van Leiden Den Haag Delft (METC LDD) heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

Er is een nieuwe operatietechniek bedacht als behandeling voor de ziekte van Ménière. Die operatie heet '**E**ndolymfatische **D**uctus**B**lokkade', afgekort EDB. In dit onderzoek bekijken we of proefpersonen na deze operatie minder duizeligheidsaanvallen hebben. We vergelijken hen met patiënten die een soortgelijke operatie krijgen, waarbij de ductus niet geblokkeerd wordt. Deze operatie heet 'endolymfatisch saccusdecompressie'. Behalve het clipje, lijken de operaties heel erg op elkaar.
In dit onderzoek zoeken we uit of EDB na 1 jaar betere resultaten geeft, dan de operatie waarbij de ductus niet geblokkeerd wordt.

3. Achtergrond van het onderzoek

In 2015 is deze nieuwe operatie voor de ziekte van Ménière bedacht. In Canada is de eerste groep patiënten geopereerd. Daar was 2 jaar na de operatie 95% van de deelnemers aanvalsvrij. Dat waren er meer dan in de controlegroep, die een andere operatie kregen. Dit onderzoek is echter niet helemaal goed uitgevoerd. Daardoor is niet zeker of de operatie echt zo goed is.
Omdat er geen zekerheid is over het effect van EDB, wordt de operatie in Nederland nog niet door de zorgverzekeraars vergoed.

Twee Nederlandse KNO-artsen hebben de operatie ook al een aantal keer uitgevoerd. Dit gebeurde in het buitenland. Ook bij deze groep waren de resultaten goed.

4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?
Doet u mee met het onderzoek? Dan duurt dat in totaal ongeveer 1.5 jaar.

Stap 1: bent u geschikt om mee te doen?
We willen eerst weten of u geschikt bent om mee te doen. Daarom doet de onderzoeker een aantal onderzoeken:

- De onderzoeker bespreekt uw klachten met u.
- Lichamelijk onderzoek. De onderzoeker doet een aantal simpele testjes om het evenwichtsorgaan en het gehoor te testen.
- Evenwichtsonderzoek. Hierbij wordt wat warm en koud water in uw oren gespoten.
- Een MRI-scan. Bij deze MRI-scan wordt contrastmiddel (gadolinium) gebruikt. U krijgt dit via een infuus. De scan wordt 4 uur na het infuus gemaakt. In de tussentijd mag u doen wat u wilt.

- Een CT-scan.
- Een hoortest.

Als u dat eerder nog niet gehad heeft, krijgt u als behandeling tegen de duizeligheidsaanvallen eerst een injectie met medicatie in het oor. Deze prikjes door het trommelvlies helpen bij sommige patiënten met de ziekte van Ménière goed. Omdat dit een minder zware behandeling is dan een operatie, wordt dit altijd eerst geprobeerd. Dit is allemaal nog 'reguliere zorg' en valt niet binnen het onderzoek.

Stap 2: voorafgaand aan de operatie

Als u mee doet aan de operatie, vinden de volgende onderzoeken vóór de operatie plaats:

- Vragenlijsten. Via de email ontvangt u verschillende vragenlijsten. Het is van groot belang dat u deze allemaal voor de operatie invult.
- Fysiotherapie. U gaat langs bij de fysiotherapeut, die een aantal metingen en oefeningen met u doet.
- Bezoek aan de anesthesioloog. U krijgt een afspraak bij de anesthesioloog, die bekijkt of u fit genoeg bent voor een operatie. Dit is een standaardbezoek.
- U installeert de 'DizzyQuest App' op uw telefoon. Hier vult u dagelijks een vragenlijst in.
- Er wordt een CT-scan gemaakt.

Stap 3: de operatie

Alle patiënten die meedoen aan dit onderzoek worden geopereerd.

Voor dit onderzoek maken we 2 groepen:

- Groep 1. De mensen in deze groep krijgen een nieuwe operatietechniek, EDB. Hierbij wordt een clip geplaatst over de ductus endolymfaticus (*zie bijlage D*). Dit is een nieuwe operatietechniek. Er is nog onvoldoende bewijs dat deze operatie goed werkt.
- Groep 2. Bij deelnemers in deze groep wordt dezelfde procedure gevolgd, maar hierbij wordt géén clip geplaatst. Verder is de operatie hetzelfde. Deze techniek heet 'decompressie' omdat er bot wordt weggenomen. Hierdoor staat er minder druk op bijvoorbeeld de saccus endolymfaticus. In veel landen wordt deze operatie uitgevoerd als behandeling van de ziekte van Ménière.

In Nederland worden beide operaties op dit moment niet uitgevoerd omdat er niet voldoende bewijs is dat ze effectief zijn.

Loting bepaalt welke operatie u krijgt. U en de onderzoeker weten niet in welke groep u zit. Als het op enig moment voor uw gezondheid belangrijk is, kan dit wel worden opgezocht.

Bij de operatie zijn twee artsen aanwezig. Eén arts is uw eigen KNO-arts. De andere arts heeft ervaring met deze operaties en werkt samen met uw arts. Op het moment van loting, verlaat uw arts de operatiekamer. Zo weet hij of zij niet in welke groep u zit.

Stap 4: onderzoeken en metingen na de operatie
Voor het onderzoek is het nodig dat u 4 keer in 12 maanden naar het ziekenhuis komt. Dit is 1 week na de operatie, en 3, 6 en 12 maanden na de operatie. Een bezoek duurt een half uur tot een uur.
We doen dan de volgende onderzoeken:

- We doen een lichamelijk onderzoek – bij alle bezoeken.
- Er wordt een MRI-scan gemaakt – 3 en 12 maanden na de operatie. Bij deze MRI-scans wordt contrastmiddel (gadolinium) gebruikt. U krijgt dit via een infuus. De scan wordt 4 uur na het infuus gemaakt. In de tussentijd mag u doen wat u wilt.
- Er wordt een hoortest gedaan – 3, 6 en 12 maanden na de operatie.
- Er wordt een evenwichtsonderzoek gedaan – 12 maanden na de operatie.
- Na elk bezoek krijgt u via de mail vragenlijsten. Deze vragenlijsten gaan over algemeen functioneren, duizeligheid en oorsuizen. Het invullen kost in totaal ongeveer een uur.

Daarnaast gaat de fysiotherapeut u behandelen. Na de operatie komt u 7 keer bij de fysiotherapeut. De fysiotherapeut doet metingen en oefeningen met u. Ook krijgt u oefeningen mee die u thuis moet doen.

Tot 1 jaar na de operatie vult u elke dag een vragenlijst in de DizzyQuest App in. Het invullen duurt 5 tot 10 minuten. De vragen gaan over uw functioneren op die dag.

Als ook de laatste proefpersoon 1 jaar lang gevolgd is, kunt u ervoor kiezen te horen in welke groep u zit. Als blijkt dat u in de EBD-groep zat, en u heeft nog aanvallen, dan kunt u een CT-scan krijgen om te zien of de clip goed zit.

In bijlage C staat uitgebreid beschreven welke handelingen, tests en onderzoeken er bij elk van die bezoeken plaatsvinden.

Wat is er anders dan bij gewone zorg?
Het eerste bezoek aan de polikliniek is ‘reguliere zorg’. Hiervoor moet u dus mogelijk eigen risico betalen.

Als u in aanmerking komt om mee te doen aan het onderzoek, worden alle bezoeken en onderzoeken betaald door het onderzoek. Hier hoeft u dus geen eigen risico voor te betalen.

Niet alle KNO-artsen in Nederland doen mee aan dit onderzoek. Het kan dus zijn dat u, vanwege deelname aan het onderzoek, zal worden behandeld door een andere KNO-arts dan uw vaste KNO-arts.

Ook kan zijn dat u voor sommige onderzoeken of behandelingen naar een ander ziekenhuis moet. Dit heeft te maken met de aanwezigheid van instrumenten en de opleiding van de zorgverleners.

5. Welke afspraken maken we met u?

Om het onderzoek goed te laten verlopen, is het belangrijk dat u zich aan de volgende afspraken houdt.

De afspraken zijn dat u:

- Indien u betahistine of cinnarizine gebruikt, deze vanaf 24 uur vóór de operatie niet meer neemt.
- Afspraken voor bezoeken nakomt.
- Niet aan een ander medisch-wetenschappelijk onderzoek meedoet.
- De vragenlijst in de DizzyQuest App dagelijks invult. Dit is van zeer groot belang. Of u de app invult, wordt gecontroleerd door de coördinerend onderzoeker. Indien blijkt dat u regelmatig vergeet de lijst in te vullen, neemt zij telefonisch contact met u op.
- De vragenlijsten via de email invult.
- De oefeningen van de fysiotherapie thuis volgens schema uitvoert.
- U krijgt een deelnamekaart, waarin staat dat u deelneemt aan dit onderzoek. Indien er een scan van uw hoofd gemaakt wordt (buiten het onderzoek om), is het van belang dat u aan de arts die de scan afspreekt, vertelt dat u meedoet met dit onderzoek en dit kaartje laat zien.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- Als u in een ziekenhuis wordt opgenomen of behandeld.
- Als u plotseling gezondheidsklachten krijgt.
- Als u niet meer wilt meedoen aan het onderzoek.
- Als uw contactgegevens wijzigen.

Zwangerschap

Vrouwen die zwanger zijn, kunnen niet meedoen aan dit onderzoek. Ook mogen vrouwen niet zwanger worden tijdens het onderzoek. Dit is omdat narcose niet veilig is voor een zwangerschap. Daarnaast wordt tijdens het onderzoek een CT-scan gemaakt. De straling is een risico voor het kind.

Wordt u tijdens het onderzoek toch zwanger? Laat dit dan direct weten aan de onderzoeker. U moet dan in overleg met de onderzoeker zo snel mogelijk stoppen met dit onderzoek.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

Er kunnen bijwerkingen en complicaties voorkomen bij beide operaties. De volgende bijwerkingen zijn bekend:

- Pijn achter het oor.
- Tijdelijke misselijkheid.
- Tijdelijke duizeligheid.
- Tijdelijk (bescheiden) gehoorverlies.

Complicaties van de operaties kunnen zijn:

- Schade aan de aangezichtszenuw. Tot nu tot gebeurt dit bij minder dan 1% van de patiënten.
- Schade aan het evenwichtsorgaan.
- Lekkage van hersenvocht.
- Ontsteking van de hersenen (meningitis).
- Tijdelijke positieduizeligheid (BPPD).
- Gehoorverlies. Dit komt voor bij minder dan 4% van de patiënten.

7. Wat zijn de voordelen en de nadelen als u meedoet aan het onderzoek?

Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op een rij. Denk hier goed over na, en praat erover met anderen.

De operaties kunnen het aantal Ménière-aanvallen verminderen, maar zeker is dat niet. Op elk moment tijdens dit onderzoek kunnen de aanvallen terugkomen of verergeren.

Meedoen aan het onderzoek kan deze nadelen hebben:

- Mogelijke bijwerkingen en complicaties van de operatie
- Mogelijke ongemakken van de metingen in het onderzoek. U kunt bijvoorbeeld duizelig worden tijdens het evenwichtsonderzoek

Deelname aan het onderzoek betekent ook:

- Dat u extra tijd kwijt bent;
- Extra testen en onderzoeken;
- Dat u afspraken heeft waaraan u zich moet houden;

Wat zijn de nadelen van onderzoeken die gebruik maken van straling?
Bij de CT-scan voor de operatie gebruiken we röntgenstraling. U krijgt 1 of 3 CT-scans. Dit hangt af van in welke groep u zit.
Een CT-scan geeft ongeveer 2 mSv stralingsbelasting. Ter vergelijking: de achtergrondstraling in Nederland is ~2,5 mSv per jaar.

Het kan geen kwaad als u voor een medische reden een onderzoek of behandeling met straling moet ondergaan.

- Krijgt u vaker een onderzoek met straling? Bespreek dan met de onderzoeker of het verstandig is dat u meedoet.
- De straling die we tijdens het onderzoek gebruiken kan leiden tot schade aan uw gezondheid. Maar dit is een klein risico. Wel adviseren we u de komende tijd niet nog een keer mee te doen aan een wetenschappelijk onderzoek met straling.

Het is mogelijk dat u voor een ander medisch probleem een scan van het hoofd moet krijgen. Dat is geen probleem voor het onderzoek. Het clipje dat gebruikt wordt in dit onderzoek, kan zonder problemen in de MRI- of CT-scan.
Wel is het belangrijk dat u aan de arts die de scan met u afspreekt, vertelt dat u meedoet aan dit onderzoek. U kunt dan het zakkaartje laten zien.Daarop staat dat er geen bezwaar is om een scan te ondergaan, maar vragen wij de radioloog niks te zeggen over een eventuele clip. Dit is om te zorgen dat u niet weet in welke groep u zit. De radioloog schrijft in het verslag van de scan op dat er gekeken is of er een clip gezien is, maar dat daar vanwege het onderzoek niks over in het verslag opgeschreven wordt.

Het is mogelijk dat er op de CT-scan of MRI-scan toevallig iets wordt ontdekt dat niet direct van belang is voor het onderzoek maar wel voor uw gezondheid of die van uw familieleden. In dit geval zal uw eigen huisarts of specialist met u bespreken wat er verder moet gebeuren. De kosten hiervan vallen onder uw eigen zorgverzekering.

Wilt u niet meedoen?
U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan krijgt u de gewone behandeling voor de ziekte van Ménière. Uw arts kan u meer vertellen over de behandelingsmogelijkheden die er zijn. En over de voor- en nadelen daarvan.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Alle onderzoeken volgens het schema zijn voorbij.
- Het einde van het hele onderzoek is bereikt, dus als er 84 mensen zijn geopereerd en zij allemaal een jaar lang gevolgd zijn.
- U bent zwanger geworden.
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling voor de ziekte van Ménière. De onderzoeker kan voor uw veiligheid nog een of meer controles afspreken.

- De onderzoeker vindt het beter voor u om te stoppen. De onderzoeker zal u nog wel uitnodigen voor een nacontrole.
- Een van de volgende instanties besluit dat het onderzoek moet stoppen:
    - Het HagaZiekenhuis, of
    - Het Zorginstituut Nederland, of
    - de overheid, of
    - de medisch-ethische commissie die het onderzoek beoordeelt.

Wat gebeurt er als u stopt met het onderzoek?
Als u niet meer mee wil doen met het onderzoek, mag u dat op elk moment aangeven. U hoeft niet uit te leggen waarom u niet meer mee wil doen. U kunt dit melden bij uw eigen KNO-arts; hij/zij zal contact opnemen met de coördinerend onderzoeker om dit te melden. De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn verzameld.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.

9. Wat gebeurt er na het onderzoek?

Krijgt u de resultaten van het onderzoek?
Ongeveer 1.5 jaar na uw deelname laat de onderzoeker u weten wat de belangrijkste uitkomsten zijn van het onderzoek. De onderzoeker kan u ook vertellen in welke groep u zat, dus welke operatie u gehad heeft. Wilt u dit niet weten? Zeg dat dan tegen de onderzoeker. Hij of zij zal het u dan niet vertellen.

Het kan zijn dat blijkt dat de EDB-operatie beter werkte. Als u niet in de EDB-groep zat, en nog wel aanvallen heeft, kunt u alsnog de EDB-operatie krijgen.

10. Wat doen we met uw gegevens?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?
We bewaren deze gegevens:
- uw naam
- uw geslacht
- uw adres
- uw geboortedatum
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Waarom verzamelen, gebruiken en bewaren we uw gegevens?

We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren. De gegevens worden verzameld in Castor, een online omgeving voor onderzoekers.

Hoe beschermen we uw privacy?
Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis waar u behandeld wordt. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.
De gegevens die in de DizzyQuest App worden verzameld, zijn ook niet gekoppeld aan uw naam. In de app staat alleen uw deelnemerscode. De personen die de ingevulde gegevens in de app kunnen zien, zijn:

- De coördinerend onderzoeker. Zij bekijkt of u de app invult.
- De maker van de app. Hij kan gegevens inzien voor kwaliteits- en veiligheidsdoeleinden. Hij kan geen gegevens zien die naar u zijn te herleiden.
- Een onafhankelijk arts heeft toegang tot de database. Deze arts zal niet inloggen, tenzij de coördinerend onderzoeker onverwachts niet meer in staat is het onderzoek uit te voeren. Deze arts kan dan de toegang en verantwoordelijkheden overdragen aan een nieuwe coördinerend onderzoeker.

Er wordt bijgehouden en gecontroleerd wie de gegevens van de app opent en inziet.

Wie kunnen uw gegevens zien?
Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Leden van de commissie die de veiligheid van het onderzoek in de gaten houdt.
- Een controleur die door het HagaZiekenhuis is ingehuurd of voor het HagaZiekenhuis werkt.
- Nationale toezichthoudende autoriteiten namelijk Inspectie Gezondheidszorg en Jeugd.

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens en lichaamsmateriaal?
We bewaren uw gegevens 15 jaar in Castor. Dit is de online omgeving waar alle gegevens worden opgeslagen.

Mogen we uw gegevens gebruiken voor ander onderzoek?
Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander wetenschappelijk onderzoek op het gebied van de ziekte van Ménière. Daarvoor zullen uw gegevens 15 jaar worden bewaard in Castor. In het toestemmingformulier geeft u aan of u dit

goed vindt. Geeft u geen toestemming? Dan kunt u nog steeds meedoen met dit onderzoek. U krijgt dezelfde zorg.

Wat gebeurt er bij onverwachte ontdekkingen?
Tijdens het onderzoek kunnen we toevallig iets vinden dat belangrijk is voor uw gezondheid. De onderzoeker neemt dan contact op met uw eigen KNO-arts. U bespreekt dan met uw specialist wat er moet gebeuren. U geeft met het formulier toestemming voor het informeren van uw specialist.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Dit geldt voor het gebruik in dit onderzoek en voor het gebruik in ander onderzoek. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Voor uw onderzoek is dat:
    - Het HagaZiekenhuis. Zie bijlage A voor contactgegevens, en website.
- Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het HagaZiekenhuis gaan. Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek.
https://www.hagaziekenhuis.nl/meniere
https://www.trialregister.nl/trial/9095 (Let op: deze website is in het Engels). Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De **extra** ziekenhuisbezoeken, onderzoeken en de operatie voor het onderzoek kosten u niets. U krijgt geen vergoeding als u meedoet aan dit onderzoek. Wel krijgt u een vergoeding voor uw (extra) reiskosten. De gemaakte reiskosten worden aan het eind van uw deelname aan u vergoed. U dient altijd kopieën te maken van de parkeerkaartjes en/of ov-bewijzen. Voor het berekenen van de reiskosten gebruiken wij de ANWB-routeplanner en rekenen wij €0,19 per kilometer. Voor het bereken van kosten van het openbaar vervoer gebruiken wij OV9292.

12. Bent u verzekerd tijdens het onderzoek?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade. In **bijlage B** vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

13. We informeren uw huisarts

De onderzoeker stuurt uw huisarts een brief om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid.

14. Heeft u vragen?

Bij vragen kunt u contact opnemen met arts-onderzoeker Jet Schenck via duizeligheid@hagaziekenhuis.nl. Wilt u advies van iemand die geen belang heeft bij het onderzoek? Neem dan contact op met professor dr. Bruintjes, KNO-arts. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.
Heeft u een klacht? Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenfunctionaris van uw eigen ziekenhuis. In bijlage A staat waar u die kunt vinden.

15. Ondertekening toestemmingsformulier

U kunt eerst rustig nadenken over dit onderzoek. Binnen twee weken vertelt u de onderzoeker of u de informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

[Lokale hoofdonderzoeker], [lokaal ziekenhuis]

Het onderzoeksteam:

- Drs. A.A. Schenck, arts-onderzoeker KNO-heelkunde, HagaZiekenhuis, Den Haag
- Dr. H. Blom, KNO-arts, HagaZiekenhuis, Den Haag
- Drs. J.M. Kruyt, KNO-arts, Haaglanden Medisch Centrum, Den Haag
- Prof. dr. P.P. van Benthem, afdelingshoofd KNO, LUMC, Leiden

16. Bijlagen bij deze informatie

Bijlage A.	Contactgegevens
Bijlage B.	Informatie over de verzekering
Bijlage C.	Schema bezoeken en metingen
Bijlage D.	Uitgebreide informatie over de operaties
Bijlage E.	Toestemmingsformulier(en)

Bijlage A: contactgegevens voor [naam deelnemend centrum]

[Onderzoeker]: [Naam, contactgegevens en bereikbaarheid]

Onafhankelijk arts: dr. Van der Schroeff, KNO-arts Erasmus Medisch Centrum Rotterdam
Telefoon: (010) 703 60 73

Klachten: [dienst of persoon met contactgegevens en bereikbaarheid]

Functionaris voor de Gegevensbescherming van de instelling:

Voor meer informatie over uw rechten: [Contactgegevens [inclusief website] van de verantwoordelijke(n) voor de verwerking van persoonsgegevens]:

Coördinerend onderzoeker
Drs. A.A. Schenck
Afdeling KNO-heelkunde, HagaZiekenhuis, Den Haag
Email: duizeligheid@hagaziekenhuis.nl
Telefoon: 070 210 2602

Bijlage B: informatie over de verzekering

Het HagaZiekenhuis heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Heeft u schade door het onderzoek? Meld dit dan telefonisch bij deze verzekeraar:

De verzekeraar van het onderzoek is:	
Naam:	CentraMed
Adres:	Postbus 7374, 2701 AJ Zoetermeer
Telefoonnummer:	070 301 70 70
E-mail:	info@centramed.nl
(Polisnummer:	624.100.025)

De verzekering betaalt maximaal € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek (en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever).

Let op: de verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

Bijlage C – Overzicht bezoeken en metingen

Voorafgaand aan het onderzoek

Als u gaat deelnemen aan de studie, vult u met uw arts uw toestemmingsformulier in. Daarnaast worden de volgende metingen uitgevoerd:

- Head impulse test (vHIT). Hierbij houdt de onderzoeker met beide handen uw hoofd vast, en vraagt hij u om naar de neuspunt van de onderzoeker te kijken. Met een korte en snelle beweging wordt uw hoofd horizontaal naar rechts en vervolgens naar links gedraaid. De onderzoeker kijkt hierbij naar uw oogbewegingen.
- Hoortest
- CT-scan
- Een evenwichtsonderzoek waarbij koud en warm water in uw oor gespoten wordt

Ook ontvangt u de volgende vragenlijsten via de email:

- Hospital Anxiety and Depression Scale (HADS)
- Dizziness Handicap Inventaris (DHI): een algemene vragenlijst over duizeligheid
- Tinnitus Handicap Inventaris (THI): een algemene vragenlijst over oorsuizen
- Functional Level Scale (FLS): schaalverdeling waarin u kunt aangeven hoe u vindt dat u dagelijks functioneert
- EQ-5D: 5 vragen en een schaalverdeling waarmee u kunt aangeven hoe u uw gezondheidstoestand ervaart.
- SF-36: waarmee u uw mogelijkheden van functioneren in dagelijks activiteiten, vrijetijd en werk kan aangeven.
- NPQ: dit is een vragenlijst over duizeligheid
- VAP: dit is een vragenlijst over de last van duizeligheid in uw dagelijks functioneren
- VADL: ook deze vragenlijst gaat over last van duizeligheid in uw dagelijks functioneren
- Een vragenlijst over uw verwachtingen van het onderzoek

Tot slot komt u vlak voor de operatie langs bij de anesthesioloog voor standaard onderzoek. Hier beoordeelt de anesthesioloog of u fit genoeg bent voor een operatie.

1 week na de operatie

- Controleafspraak bij uw KNO-arts
- Lichamelijk onderzoek
- Bezoek fysiotherapeut voor metingen en oefeningen

In de daaropvolgende weken

- In totaal 3 afspraken bij de fysiotherapeut. Die doet steeds oefeningen met u en voert metingen uit.

3 maanden na de operatie

U komt weer terug bij de KNO-arts. Dan worden de volgende tests gedaan:

- Lichamelijk onderzoek
- MRI-scan. Bij deze MRI-scans wordt contrastmiddel (gadolinium) gebruikt. U krijgt dit via een infuus. De scan wordt 4 uur na het infuus gemaakt. In de tussentijd mag u doen wat u wilt.
- Hoortest

Ook krijgt u de volgende vragenlijsten via de email:

- DHI
- THI
- FLS
- EQ-5D
- VAS
- SF-36
- iMCQ: deze vraagt uit hoeveel zorg u gehad heeft (aantal polikliniekbezoeken, onverwachte opnames)
- iPCQ: deze vraagt uit hoe 'productief' u bent geweest, dus of/hoeveel u heeft kunnen werken.

- Bezoek fysiotherapie voor metingen en het afronden van de behandeling.

6 maanden na de operatie

U komt weer terug bij de KNO-arts. Dan worden de volgende tests gedaan:

- Lichamelijk onderzoek
- Hoortest

Ook krijgt u de volgende vragenlijsten via de email:

- DHI
- THI
- FLS
- EQ-5D
- VAS
- SF-36
- iMCQ
- iPCQ

- Bezoek fysiotherapie voor metingen

12 maanden na de operatie

U komt weer terug bij de KNO-arts. Dan worden de volgende tests gedaan:

- Lichamelijk onderzoek
- MRI-scan. Bij deze MRI-scans wordt contrastmiddel (gadolinium) gebruikt. U krijgt dit via een infuus. De scan wordt 4 uur na het infuus gemaakt. In de tussentijd mag u doen wat u wilt.
- Hoortest
- Een evenwichtsonderzoek

Ook krijgt u de volgende vragenlijsten via de email:

- DHI
- THI
- FLS
- EQ-5D
- VAS
- SF-36
- NPQ
- iMCQ
- iPCQ
- VAP
- VADL

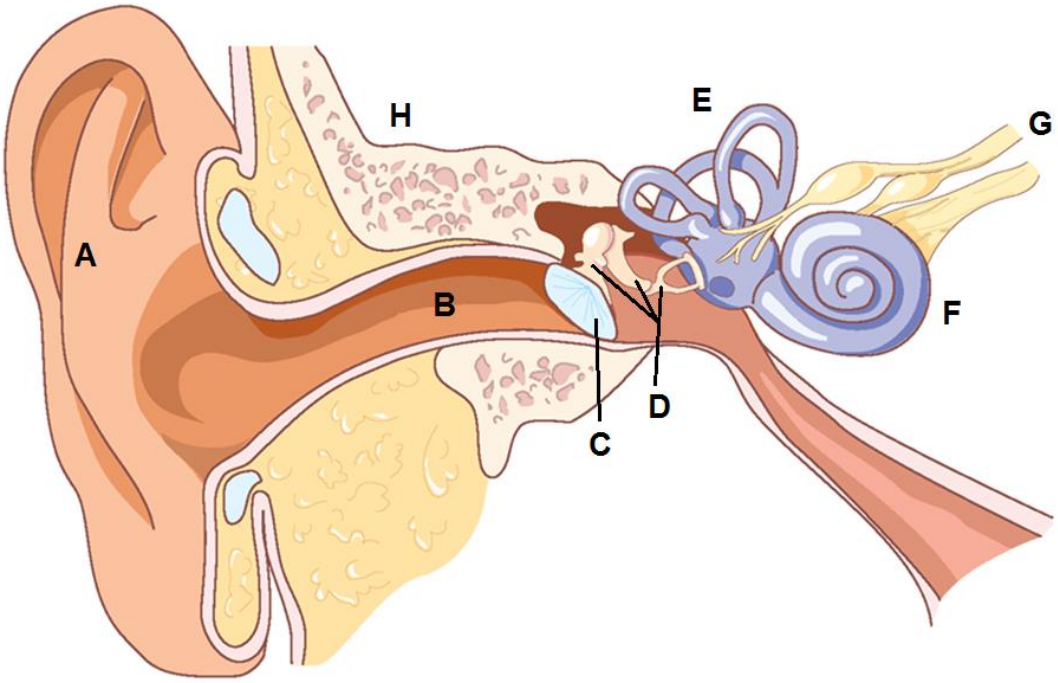
- Bezoek fysiotherapie voor metingen
- Als blijkt dat u in de EDB-groep zat, krijgt u ook een CT-scan om te controleren of het clipje goed zit.

Bijlage D – Uitgebreide informatie over de operaties

In dit onderzoek worden twee verschillende operaties uitgevoerd. Deze operaties lijken op elkaar, maar zijn niet exact hetzelfde. In deze bijlage kunt u meer informatie vinden over de operaties.

Anatomie van het oor

Ten eerste leggen wij u de anatomie van het oor uit. Hieronder ziet u een plaatje van het rechteroor, alsof u iemand van voren aankijkt.



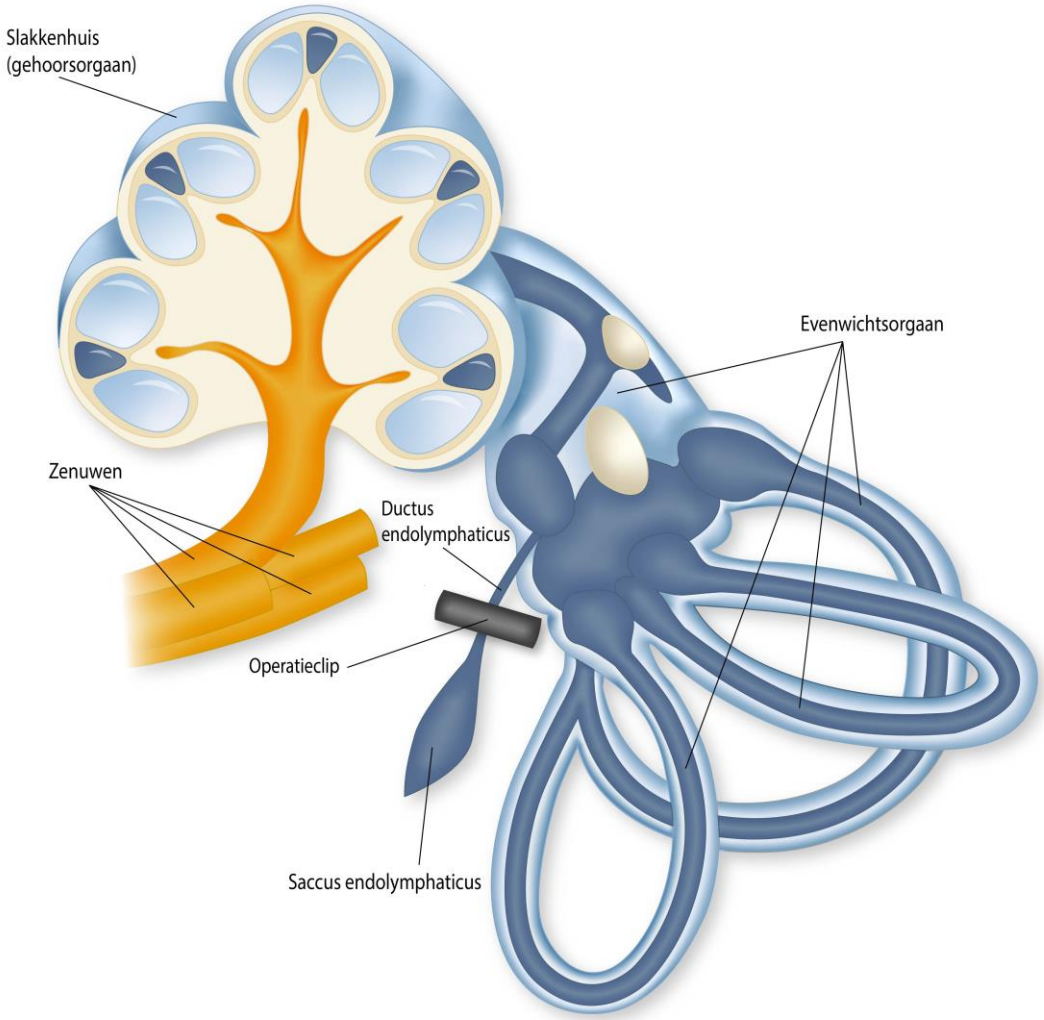
Figuur 1. Het oor. Bron: Leerschool audicien

A is de oorschelp en B de gehoorgang. De gehoorgang eindigt bij het trommelvlies (C). Geluid is een luchttrilling, het trommelvlies geeft die trillingen via de gehoorbeentjes (D) door naar het binnenoor.

Het binnenoor bestaat uit het evenwichtsorgaan (E) en het slakkenhuis (F).
Het evenwichtsorgaan (E) bestaat uit drie halfcirkelvormige kanalen die bewegingen meten. Die kanalen meten allemaal een nét andere beweging. Het ene halfcirkelvormige kanaal meten bijvoorbeeld hoofdbewegingen van boven naar beneden, zoals bij ja schudden. Een van de andere meet bijvoorbeeld nee schudden. De bewegingen worden omgezet in elektrisch signaal, dat via de zenuw (G) naar de hersenen wordt doorgegeven.
Het slakkenhuis (F) verwerkt geluiden. Trillingen die via het trommelvlies (C) en de gehoorbeentjes (D) in het binnenoor terechtkomen, worden in het slakkenhuis omgezet in elektrisch signaal. Ook dat signaal wordt via de zenuw (G) naar de hersenen gestuurd.
Al deze structuren liggen in de schedel (H).

Het binnenoor

We kijken nu beter naar het binnenoor, waar het evenwichtsorgaan (E) en het slakkenhuis (F) onderdeel van uitmaken.



Figuur 2. Het binnenoor. Bron en copyright: L. de Pont.

Op Figuur 2 kunt u de halfcirkelvormige kanalen weer herkennen. Het slakkenhuis is ook afgebeeld, maar dan door de helft.
Op deze afbeeldingen staat een aantal structuren dat van belang is voor de ziekte van Ménière. Ten eerste de ‘ductus endolymfaticus’. Dat is een uitloper van het evenwichtsorgaan, waar de halfcirkelvormige kanalen samenkomen. Aan het eind van de ductus endolymfaticus bevindt zich de ‘saccus endolymphaticus’. Tussen de saccus endolymfaticus, het slakkenhuis en de halfcirkelvormige kanalen stroomt vloeistof: ‘endolymfe’. Het endolymfe zorgt ervoor dat geluidsgolven goed worden voortgeleid en dat er signalen kunnen worden opgewekt in het evenwichtsorgaan en het gehoorsorgaan. Die signalen zorgen ervoor dat wij geluid horen en beweging kunnen voelen.

Bij de ziekte van Ménière is er te veel endolymfe, zowel in het slakkenhuis als in het evenwichtsorgaan. Hierdoor zijn er symptomen van zowel het gehoor (oorsuizen, gehoorverlies) als van het evenwicht (de draaiduizeligheidsaanvallen).

Na een aanval kan het binnenoor zich een beetje herstellen, maar omdat de druk eigenlijk de hele tijd te hoog is, wordt dat steeds moeilijker. Daarom worden de problemen met gehoor en evenwicht met de tijd steeds groter.

Het is dus van belang om te zorgen dat die druk niet te hoog wordt. Momenteel is er een operatie die zorgt dat de saccus endolymfaticus meer ruimte krijgt. Daarvoor wordt wat bot van de schedel rondom deze saccus, voorzichtig weggeboord. Dit wordt ook wel '*endolymphatic sac decompression*', ofwel drukvermindering van de saccus endolymfaticus, genoemd. Hierbij hebben de saccus en ductus endolymfaticus meer ruimte om uit te zetten, wanneer er teveel endolymfe (de vloeistof in het binnenoor) is.
Deze operatie wordt in een aantal landen uitgevoerd, waaronder in Canada en Amerika. In Nederland wordt deze operatie niet uitgevoerd, omdat er niet voldoende bewijs is dat hij goed werkt.

Naast deze techniek, is er nu een nieuwe operatie bedacht. Deze heet 'endolymphatic duct blockage', ofwel blokkade van de ductus endolymfaticus. Het wordt afgekort tot EDB. Ook hierbij wordt ruimte vrijgemaakt rondom de saccus en ductus endolymfaticus. Bij EDB wordt de ductus endolymfaticus daarna afgesloten met een clipje. Dit clipje is ook te zien op Figuur 2. Dat maakt deze nieuwe operatie anders de decompressie-techniek. Hierdoor is er geen vochtuitwisseling tussen de saccus endolymfaticus en het binnenoor mogelijk. Hierdoor ontstaat er geen vochtoverschot in het binnenoor, waardoor de Ménière-aanvallen waarschijnlijk wegblijven.

In deze studie wordt EDB vergeleken met de saccusdecompressie. Zoals hierboven beschreven staat, lijken deze operaties op elkaar. Bij EDB wordt echter na het 'decomprimeren' nog een clip geplaatst.

Bijlage E: toestemmingsformulier proefpersoon

Behorende bij

EDB bij de ziekte van Ménière

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden tijdens het onderzoek.
- De onderzoeker heeft met mij besproken hoe ik het beste voorkom dat ik zwanger word.

- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja ☐	Nee☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee☐
Ik geef de onderzoekers toestemming om na het onderzoek te laten weten welke behandeling ik heb gehad/ in welke groep ik zat.	Ja ☐	Nee☐

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….
Handtekening:…… Datum: __ / __ / __

<indien van toepassing>
Aanvullende informatie is gegeven door:
Naam:……..
Functie:……
Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	20

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-16

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	10

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	17

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15-16

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17-18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a