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STUDY PROTOCOL

Effect of day-case cochlear implantation on general and disease-specific quality of life, postoperative complications and hearing results, tinnitus, vertigo and cost-effectiveness: protocol for a randomized controlled trial.

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Abstract

Introduction: cochlear implantation is an increasingly common procedure in the treatment of severe to profound sensorineural hearing loss in children and adults. The cochlear implantation is often performed as a day-case procedure. The major drive toward day-case surgery has been from a logistical, economical and societal perspective, but also most likely positively influences the patient's quality of life as a result of rapid discharge and rehabilitation. Even though cochlear implantation seems well suited to a day-case approach and this even seems to be common practice in some countries, evidence is scarce and of low quality to guide us towards the preferred treatment option.

Methods and Analysis: A single-center unblinded randomized controlled trial was designed to (primarily) investigate the effect on general quality of life of day-case cochlear implantation compared to inpatient cochlear implantation and (secondarily) the effect of both methods on (subjective) hearing improvement, disease-specific quality of life, tinnitus, vertigo and cost-effectiveness. Thirty adult patients with severe to profound bilateral post-lingual sensorineural hearing loss who are eligible for unilateral cochlear implantation will be randomly assigned to either the day-case or inpatient treatment group. The outcome measures will be assessed using auditory evaluations, questionnaires (preoperatively, at one-week, three-weeks, three-months and one-year follow-up) and costs diaries (weekly during the first month postoperatively, after which once a month until one year follow-up). Pre- and postoperative outcomes will be compared. The difference in costs and benefit will be represented using the Incremental Cost Utility/Effectiveness Ratio. The analyses will be carried out on an intention-to-treat basis

Ethics and Dissemination: This research protocol was approved by the Institutional Review Board of the UMC Utrecht (NL45590.041.13; version 5, November 2015). The trial results will

be disseminated through peer-reviewed medical journals and presented at scientific conferences.

Registration details: Netherlands Trial Register (www.trialregister.nl): NTR4464, registration date 13th March 2014.

Keyword: (3-10 keywords) sensorineural hearing loss, cochlear implantation, day-case, inpatient, hearing loss, hearing results, tinnitus, vertigo, quality of life, complications

Strengths and limitations of this study

- This study allows for a comparison between day-case and inpatient cochlear implantation to investigate the hypothesis that day-case cochlear implantation is associated with a higher QoL and higher cost-effectiveness, while maintaining an equal hearing outcome and complication rate, compared to inpatient cochlear implantation.
- This study is the first trial of high epidemiological quality evaluating and quantifying the benefits of day-case cochlear implantation for patients with severe to profound bilateral post-lingual sensorineural hearing loss.
- The findings of this trial will give evidence based proof of the feasibility of cochlear implantation in day-case setting, with great consequences for the postoperative management strategies of cochlear implantation.
- A limitation of this trial is that inclusion was only possible for patients with good understanding of the Dutch language and had quick access to communication and transportation in case of any complications.
- Another disadvantage is that due to logistic reasons some of the patients will be admitted one day before the surgery and others the day of surgery.

Background

Cochlear implantation is an increasingly common procedure in the treatment of severe to profound sensorineural hearing loss (SNHL) in children and adults [1–4]. For patients in whom amplification with hearing aids does not suffice, cochlear implantation can be considered. Several studies have shown that cochlear implantation significantly improves quality of life (QoL) [1, 2]. Cochlear implantation is associated with low complication rates: 1-9% for (transient) vertigo, 1-3% for tinnitus, 1-3% for postoperative bleeding or hematoma, 1-9% for wound infection, <1% for facial nerve injury and 4% for explantation [5–8].

Currently, in our university medical center cochlear implantation involves overnight hospital stay. Many other otologic procedures that involved overnight hospital stay in the past are presently being performed, with good result, on an outpatient basis [9–11]. Ear, nose and throat (ENT) surgery is well suited to a day-case approach as many of the disease entities are benign and procedures are associated with low complication rates [10]. Even though one of the major drives towards day-case surgery has been financial from a societal perspective, other non-financial benefits are of major importance. Day-case surgery is associated with shorter waiting time for surgery and reduced risk of infection [12]. Moreover, as a result of a more rapid social and emotional rehabilitation compared to overnight stay, patients might prefer day-case surgery.

Cochlear implantation is increasingly being performed as a day-case procedure in several Western countries. However, reports on day-case cochlear implantation are scarce and mostly describe pediatric day-cases [13, 14]. None of these studies compare the effects of day-case surgery to inpatient surgery. Liu et al. were the only ones to send out a patient satisfaction survey addressing parental and child satisfaction following outpatient cochlear implantation [13]. Overall satisfaction with day-case surgery was 91%. Preoperative anxiety was diminished in 47% of families by planning the operation as day surgery, whereas preoperative anxiety was increased in 34%. Of the latter group, 44% would schedule the surgery as day surgery if they had to undergo the operation again. A total of 19% of parents would have preferred to let their

children spend the night in the hospital. In the same study, two children (4%) had to be admitted for 23-hour observation as a result of postoperative nausea with vomiting and fever. In both studies, none of the subjects had to be readmitted as a result of adverse events arising in the home situation.

The lack of (high-quality) studies precludes firm evidence-based recommendations and demonstrates the need for high-quality studies quantifying the benefits of day-case surgery, both clinical and financial. In order to accommodate this need, in the proposed study we shall compare day-case cochlear implantation to inpatient cochlear implantation. The study will be conducted as a randomized controlled trial.

Methods and design

This protocol is reported according to the SPIRIT Statement, an international guideline on reporting protocols [15].

Study objectives

The primary objective of this study is to evaluate the effect on general QoL of day-case cochlear implantation compared to inpatient cochlear implantation. In addition, subjective participants' perception on hearing improvement, auditory evaluations, disease-specific QoL, tinnitus, vertigo and cost-effectiveness will be assessed.

Study design

The study design will be a single-center, unblinded, randomized controlled trial. Subjects will be assigned to one of two groups: day-case cochlear implantation under general anesthesia or inpatient cochlear implantation under general anesthesia followed by one- to two-day hospital admittance (Figure 1).

Study population

The study population consists of adults with severe to profound bilateral post-lingual sensorineural hearing loss, eligible for unilateral cochlear implantation. Subjects will be recruited from the outpatient clinic of the ENT department at the University Medical Center Utrecht (UMC Utrecht), the Netherlands. In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Inclusion criteria

- Age ≥ 18;
- Severe to profound bilateral post-lingual sensorineural hearing loss defined as ≥ 70 dB above normal adult hearing level on pure-tone audiometry in the range of 500, 1000 and 2000 Hz;
- Willingness and ability to participate in all scheduled procedures outlined in the research protocol;
- General health allowing general anesthesia in an outpatient setting as assessed by an anesthesiologist;
- Quick access to communication and transportation in case of any complications;
- Good understanding of the Dutch language.

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

Exclusion criteria

- Severe to profound pre-lingual or unilateral SNHL;
- Previous cochlear implantation;
- Aberrant (cochlear) anatomy on CT-scan or chronic ear infection;

- Disability that could interfere with questionnaire fulfillment;
- Other medical considerations (e.g. comorbidity) requiring inpatient care.

Sample size calculation and recruitment

To establish equivalence in general QoL of 0.15 points (standard deviation 0.15) on the Health Utilities Index – Mark 3 between the day-case and the inpatient group with an alpha of 0.05 and a power of 80%, 14 participants per group are needed. To anticipate withdrawal of 10% of participants, one more participant than needed will be recruited per group. At the ENT department at the UMC Utrecht, we perform an average of 25 unilateral cochlear implantations per year in patients with bilateral, post-lingual sensorineural hearing loss. Assuming a participation rate of 80%, we will be able to include the necessary number of 30 patients in 1.5 years. If participants wish to leave the study or the investigators decide to withdraw a participant from the study for urgent medical reasons, these participants will not be replaced unless these account for more than 10%.

Patients will be recruited from the outpatient ENT department at the UMC Utrecht. If a patient meets the criteria for cochlear implantation and the inclusion criteria for this study, one of the researchers will explain the content of the study and provide the patient with written patient information and an informed consent form. Patients consent to the use of their data for the research purposes outlined in this protocol, which includes publication of the results once the trial has been completed. Further details can be found in Appendix 1 (informed consent form; translated to English, original in Dutch). Patients that do not want to be included in the study because they want to undergo cochlear implantation in a clinical setting will be asked whether they would like to fulfill the study procedures anyway and whether their data can be used for analysis. Furthermore, these patients will be asked to motivate their preference for inpatient surgery.

Randomization, blinding and treatment allocation

A web-based randomization program (Julius Center, UMC Utrecht, Utrecht, The Netherlands) shall be used to allocate subjects randomly into two groups with stratification for age. Block randomization will be used with an allocation ratio of 1:1. The randomization chart, including block size, is established before the start of the study by an independent data manager and will not be available to any of the people involved with enrolment or treatment of participants. Consequently, treatment allocation sequence is concealed for participants, care providers and researchers. Blinding of participants and care providers is not possible, since both participants and care providers will be aware of the surgical setting and hospital stay.

Intervention

The surgical procedures, as well as hospitalization in the inpatient group, will take place at the UMC Utrecht. Patients in both groups will undergo unilateral cochlear implantation under general anesthesia.

Patients allocated to the conventional group will be admitted one day before or the day of surgery and will be discharged one to two days after surgery. Patients allocated to the day-case group will be admitted into the outpatient unit one day before or the day of surgery and will be discharged the day of surgery. Patients are not allowed to drive for 24 hours following day-case surgery and will be recommended 24 hours of relative bed rest. After a period of 24 hours, patients can return to their daily routine. Participants will be asked to contact the hospital in case of severe postoperative vertigo or pain. An ear compression bandage is applied to all patients during surgery. Patients allocated to the day-case group will either have to return to the hospital two days postoperatively to have the head dressings removed by the surgeon or will remove the head dressings themselves at home after being given proper instructions.

It is to be expected that patients who had surgery in day-case will sometimes stay overnight, for example due to postoperative nausea or dizziness. If patients are not physically capable of same-day discharge or if surgeons do not support same-day discharge, patients will stay overnight regardless of the group that they were allocated to. These patients will be asked to complete their follow-up and analyses will be carried out on an intention-to-treat basis. Reasons for the overnight stay will be recorded and we will differentiate between anesthesiological and otologic related reasons for cross-over.

Outcome measures

Evaluation will take place preoperatively and at one week, approximately three weeks, three months and one year postoperatively by means of questionnaires and auditory evaluation of hearing results. Vertigo and tinnitus will be evaluated directly postoperatively as well . In addition, participants will be asked to keep a costs diary for the duration of one year. Questionnaires and costs diaries can be fulfilled digitally or on paper and will be sent via email or mail respectively.

Primary outcome measure

Our primary outcome is the general QoL measured by the Health Utilities Index – Mark 3 at three weeks and one year postoperatively.

Secondary outcome measures

Our secondary outcome measures include (subjective) hearing improvement, patient satisfaction with regard to day-case surgery, disease-specific QoL, tinnitus, vertigo, cost-effectiveness and postoperative complications.

Auditory evaluation of hearing results

Auditory evaluation will be performed at three weeks, three months and twelve months postoperatively. Speech perception tests will be performed in sound-treated booths at 65 dB sound pressure level. During the test recordings of a set of Dutch words with a consonant-vowel-consonant structure will be played in a free field setting and patients wearing the cochlear implant will be asked to repeat these. Besides this, patients will be asked to repeat Dutch sentences. The percentage of correctly repeated complete sentences, words and phonemes will be scored.

Patient satisfaction

Patient satisfaction will be evaluated at one week postoperatively using the Utrecht patient satisfaction survey (Appendix 2; translated to English, original in Dutch). This seven-item questionnaire was developed in our center and contains questions regarding hospital stay and whether patients were satisfied with the intervention group that they were allocated to.

Quality of life

QoL and hearing benefit will be assessed preoperatively and at three weeks and one year postoperatively using the following four questionnaires:

- The Glasgow Health Status Inventory Questionnaire: an 18-item questionnaire, which measures the effect of an otologic problem on QoL at the time the questionnaire is completed. Three domains (general, social support and physical health) are measured based on a 5-point Likert scale ranging from high health status to low health status. The total score ranges from 0 to +100.
- Glasgow Benefit Inventory: an 18-item questionnaire, which measures the change in health status as a result of a surgical intervention. A specific version of the Glasgow Benefit Inventory will be used that has been validated to measure changes in health status as a result of otorhinolaryngological procedures [16]. The same three domains as the Glasgow

Health Status Inventory questionnaire are measured according to the 5-point Likert scale. The total score ranges from -100 (maximal negative benefit), through 0 (no benefit), to +100 (maximum benefit);

- EuroQoL-5D: a five-item questionnaire on mobility, self-care, daily activities, pain and complaints and anxiety or depression that assesses general health status [17, 18]. In addition, the general health status is rated on a visual analogue scale than runs from 0 to 10. A score of 0 equals worst imaginable health state and a score of 10 equals best imaginable health state.
- Health Utilities Index 3: a fifteen-item questionnaire that measures general health status by evaluating eight domains: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain [19].

Tinnitus and vertigo

Tinnitus and vertigo will be assessed preoperatively and at three weeks and one year postoperatively, if present, using the following four questionnaires. The Utrecht Burden Questionnaire for tinnitus and vertigo will also be administered directly postoperatively in case of direct postoperative tinnitus and/or vertigo:

- Tinnitus Handicap Inventory: a 25-item questionnaire evaluating three domains: a functional, emotional and catastrophic domain [20, 21];
- Tinnitus Questionnaire: a 52-item questionnaire evaluating five domains: tinnitus-related emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints. The response categories are ‘true’ (0/2 points), ‘partly true’ (1 point) and ‘not true’ (0/2 points), depending on the question. A validated Dutch version will be used [22, 23];
- Dizziness Handicap Inventory: a 25-item questionnaire evaluating three domains: functional, emotional, and physical aspects of dizziness and unsteadiness. The response

categories are ‘yes’ (4 points), ‘sometimes’ (2 points), and ‘no’ (0 points). The total score discriminates between a mild (16–34 points), moderate (36–52 points), and severe (54+ points) handicap. A validated Dutch version will be used [24, 25];

- Utrecht Burden Questionnaire for tinnitus and vertigo measures severity and character of tinnitus and vertigo by using visual analogue scales and numerical rating scales (Appendix 3).

Cost-effectiveness/utility analysis

The difference in costs and benefit will be represented using the Incremental Cost Utility/Effectiveness Ratio (ICUR/ICER). The ICUR/ICER is calculated by dividing the difference in costs by the difference in utility or effectiveness. Utility reflects the amounts of money that people are willing to pay to achieve a certain health status. Utility scores derived from questionnaires such as the EuroQoL-5D and the Health Utilities Index 3 are used to calculate the ICUR.

Participants will be asked to keep a costs diary (Appendix 4). Participants will fulfill this diary preoperatively and at regular intervals postoperatively. The first month the diary will be fulfilled weekly followed by monthly fulfillment for the duration of one year. Costs will be measured from a societal and health care perspective. Both direct and indirect costs will be collected. Direct costs include hospitalization, surgery, doctor’s visits and diagnostic tests. Indirect costs include travel expenses and sick leave. The Dutch guidelines for costing research in health economic evaluations, issued by the National Healthcare Institute [26], will be used to calculate unit prices of resources that were used.

Statistical analysis

Baseline characteristics per group will be described as means and standard deviations. Differences in the baseline will be analyzed using the independent samples Student's *t*-test or non-parametric tests for continuous variables and the Fisher's exact test for categorical variables.

The primary and secondary outcome data are quantitative and will be presented both continuous and categorical. Between-group mean differences, rate differences and rate ratios with 95% confidence intervals will be calculated. For further analysis of between-group differences in both primary and secondary outcomes the independent samples Student's *t*–test or non-parametric tests will be used for continuous outcomes and the Fisher's exact test for categorical outcomes. Within-subject comparisons will entail differences in mean values and percentages before and after cochlear implantation. These will be analyzed using paired *t*-tests for continuous measures and using the McNemar test for categorical outcomes.

Missing values will be handled using multiple imputation and all analyses will be performed on an intention-to-treat basis. A sensitivity analysis will be performed using all of the data acquired from patients that opted not to be included in the study, but did fill out the questionnaires.

The data will be reported according to the CONSORT Statement [27, 28].

Ethics and dissemination

The study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This research protocol was approved by the Institutional Review Board of the UMC Utrecht (NL45590.041.13; version 5, November 2015).

All cases of serious adverse events will be reported to the local Institutional Review Board and adequately followed up. An independent monitor is appointed to check trial quality (completeness of informed consent forms, validity of data, etc.) once a year. All data will be handled confidentially. The data will be coded by using a unique PIN and two of the investigators will safeguard the key to this code. The primary source of the data will be paper files, which will be stored in a locked room. The data will be stored on the investigators' computers as well, which are secured by a password and located in a locked room.

The trial results will be disseminated through peer-reviewed medical journals and presented at scientific conferences.

Trial status

The trial is currently in recruitment phase.

Conclusion

Cochlear implantation seems to be a surgical procedure that is well suited for day-case treatment as it has proven to be a safe treatment with low complication rates. However, current literature lacks evidence-based recommendations supporting day-case cochlear implantation. This randomized controlled trial allows for a comparison between day-case and inpatient cochlear implantation to investigate the hypothesis that day-case cochlear implantation is associated with a higher QoL and higher cost-effectiveness, while maintaining an equal hearing outcome and complication rate, compared to inpatient cochlear implantation. This is the first trial of highest epidemiological quality evaluating and quantifying the benefits of day-case cochlear implantation for patients with severe to profound bilateral post-lingual sensorineural hearing loss.

Abbreviations

ENT: ear, nose and throat; QoL: quality of life; SNHL: Sensorineural hearing loss; TBQ: Tinnitus Burden Questionnaire; UMC Utrecht: University Medical Center Utrecht; VBQ: Vertigo Burden Questionnaire, WMO: Medical Research Involving Human Subjects Act.

Funding statement and competing interest

Wilko Grolman received an unrestrictive research grants from Cochlear Ltd., MED-EL GmbH and Advanced Bionics. No competing interests declared by the other authors.

Author's contributions

I.W. and L.S.M.D.: executive investigator, developing protocol, drafting manuscript, revising manuscript, approval of final version. A.L.S., V.T, and H.G.X.T.: surgeons, developing protocol, revising manuscript, approval of final version. W.G.: initial idea, principal investigator, developing protocol, revising manuscript, approval of final version.

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Figures

Figure 1: Flow diagram of Day-case cochlear implantation study. Abbreviations: RCT = Randomized Controlled Trial, TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

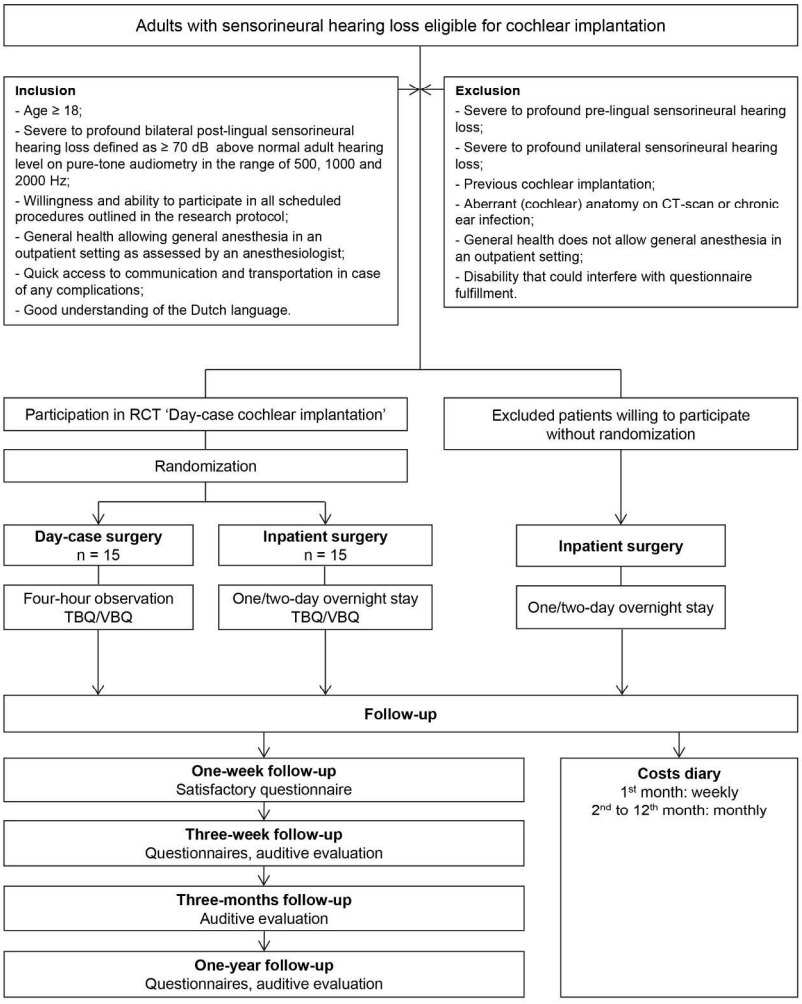

Fig.1 Flow diagram of Day-case cochlear implantation study. Abbreviations: TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

Flow diagram of Day-case cochlear implantation study. Abbreviations: TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

233x337mm (300 x 300 DPI)

Informed consent form

Day-case versus inpatient cochlear implantation: a randomized controlled trial.

- I have received and read the information brochure (version number 4, 11-03-2015) for participants. I understand the information that is written in the brochure. I had the opportunity to ask additional questions. These questions were answered adequately. I have had plenty of time to consider participation in this study;
- I am aware that participation is completely voluntary. I am aware that I have the possibility to withdraw participation at any moment, without any explanation;
- I am aware that my data are visible for some of the people involved in this study. These people include the researchers, monitors, auditors, etcetera;
- I give permission to use my data for the research purposes as described in the information brochure;
- I am aware that my data will be stored for 15 years following this study and will be destroyed after these 15 years;
- I give the researchers permission to inform my general practitioner about my participation in this study;
- I **will / will not*** give permission to contact me in the future (after this study) and ask me for participation in additional or new research projects;
- I **do / do not*** want to be informed about the results of this study;
- I agree to participate in this research project.

Name participant:

Signature: Date: __ / __ / __

I hereby declare that I have fully informed the participant about this research project. I will inform the participant in case of new insight information that could affect the participant's consent. I will inform the participant in a timely manner.

Name researcher:

Signature: Date: __ / __ / __

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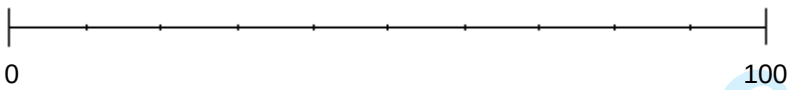
* Delete as applicable

Utrecht patient satisfaction survey

Day-case cochlear implantation

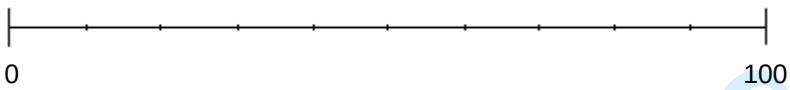
Day-case surgery means that you have been admitted one day before or the day of surgery and have been discharged the day of the surgery.

1.	Did you feel more anxious because the surgery was planned in a day-case setting?	Yes	No
2.	Did you feel less anxious because the surgery was planned in a day-case setting?	Yes	No
4.	Did you find it pleasant that you did not have to spend the night in the hospital after the surgery?	Yes	No
3.	If you would have the choice: would you undergo the surgery in day-case setting again next time?	Yes	No
4.	Would you have preferred to have spend the night in the hospital after the surgery?	Yes	No
5.	Would you have preferred to have been admitted the night prior to the surgery?	Yes	No
6.	Were you content with the hospital admittance in general?	Yes	No
7.	How easy or difficult was the first night after the operation on a scale from 0 to 10 (0 is very easy and 10 is as difficult as possible)?  0 100		

Utrecht patient satisfaction survey

Inpatient cochlear implantation

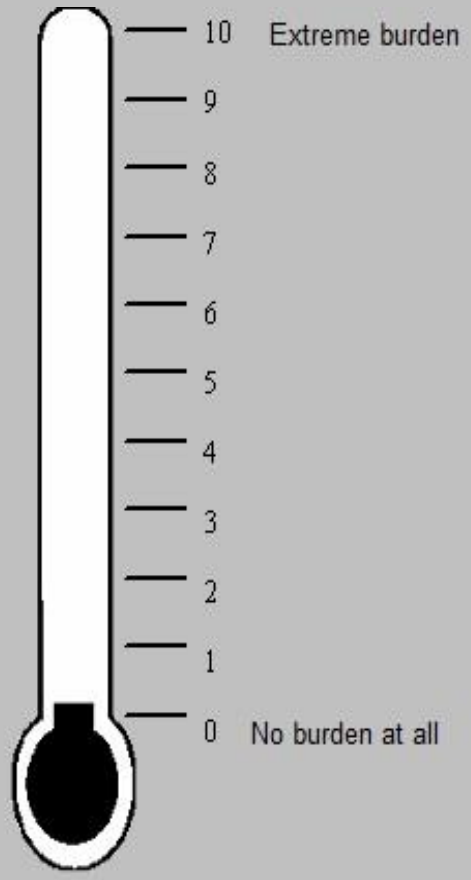
Inpatient surgery means that you have been admitted one day before or the day of surgery followed by one-day hospital admittance.

1.	Did you feel more anxious because the surgery was planned in an inpatient setting?	Yes	No
2.	Did you feel less anxious because the surgery was planned in an inpatient setting?	Yes	No
4.	Did you find it pleasant that you had to spend the night in the hospital after the surgery?	Yes	No
3.	If you would have the choice: would you undergo the surgery in an inpatient setting again next time?	Yes	No
4.	Would you have preferred to have spend the night at home after the surgery?	Yes	No
5.	Would you have preferred to have spend the night prior to the operation at home?	Yes	No
6.	Were you content with the hospital admittance in general?	Yes	No
7.	How easy or difficult was the first night after the operation on a scale from 0 to 10 (0 is very easy and 10 is as difficult as possible)?  0 100		

Utrecht Burden Questionnaire for tinnitus

First of all

Encircle the number on the thermometer below that summarizes best how much of a burden your tinnitus was in the past week (including today).



Secondarily

How many sounds does your tinnitus consist of at the moment? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Thirdly

Give an indication of how your tinnitus sounds on the scales below. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. The end of the scale indicates the extreme values. For instance, if you score a loudness of 10', this means that the tinnitus cannot be louder. If you hear multiple sounds, you can draw multiple lines on the scale. Please indicate whether the line belongs to the right ear, left ear or within the head, and add numbers if you hear multiple sounds on one side.

Example:

How loud is your tinnitus at this moment?

Inaudible 0 — 10 Extremely loud

How high does your tinnitus sound at this moment?

Extremely low 0 — 10 Extremely high

At what rate was your tinnitus present in the past 24 hours?

Constantly absent 0 — 10 Constantly present

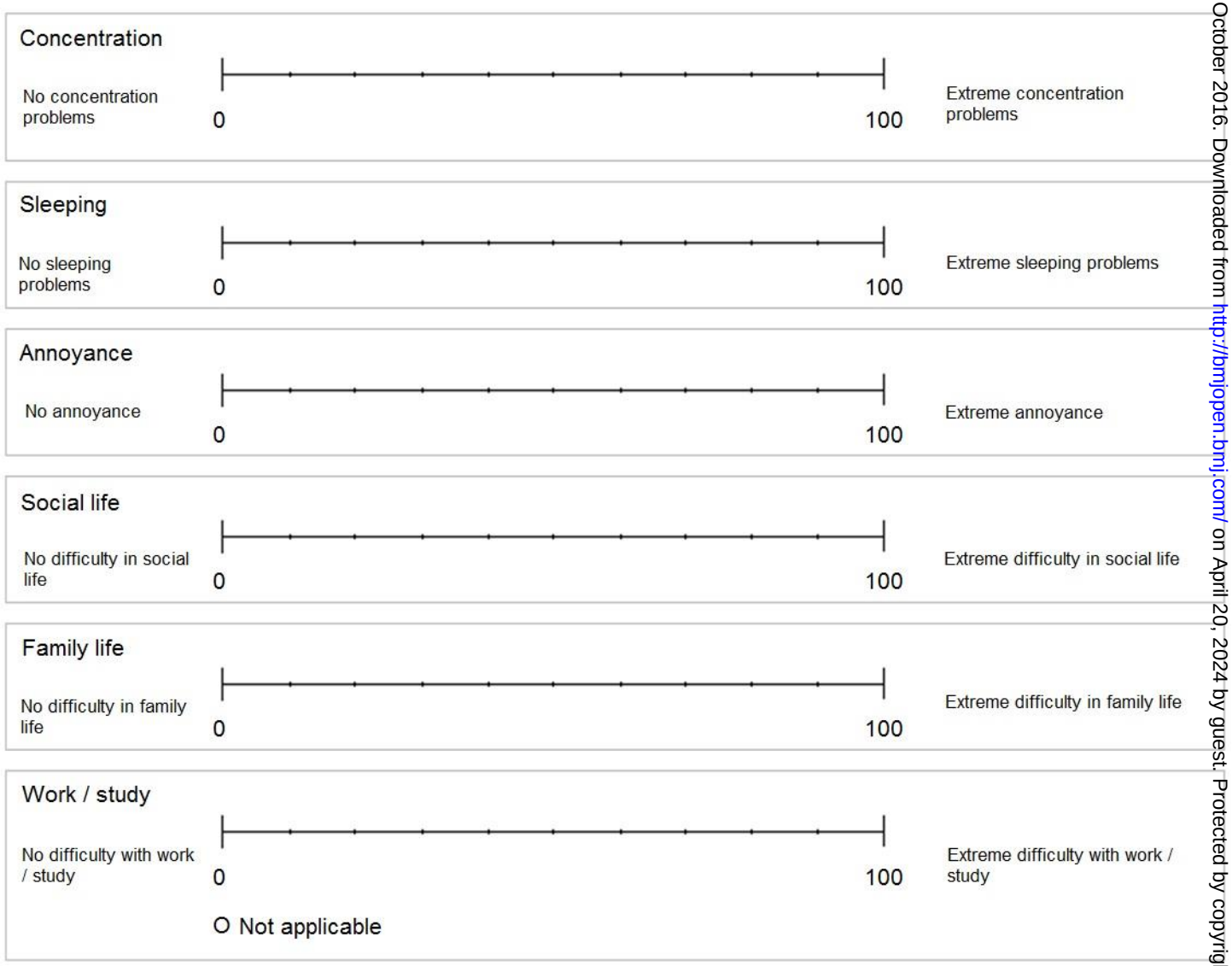
How variable (loudness and/or pitch) has your tinnitus been in the past 24 hours?

Not variable 0 — 10 Extremely variable

Utrecht Burden Questionnaire for tinnitus

Finally

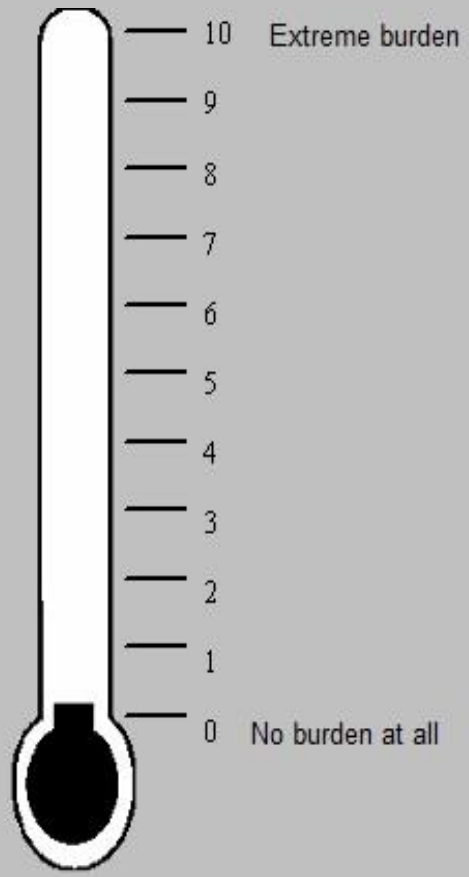
Give an indication on the scales below on whether you have had difficulties or trouble with the following activities in the past week (including today), due to the tinnitus. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. Take into account that the end of the scale indicates that this could not have been more difficult or given more trouble.



Utrecht Burden Questionnaire for vertigo

First of all

Encircle the number on the thermometer below that summarizes best how much of a burden your vertigo was in the past week (including today).



Secondarily

Answer the questions below about how the dizziness is best described (multiple answers are possible).

- How severe is your dizziness at this moment?

Absent 0 ——————————— 100 Extremely severe

- Type of dizziness?

□ Vertigo □ Lightheadedness □ Feeling of fainting

□ Other:.....

- Provoking factors?

□ Head movements □ Change of body position □ Loud noises

□ When standing up □ During excercise □ Unknown

□ Other:.....

- Additional complaints?

□ Nausea □ Vomiting □ Hearing complaints □ Tinnitus

□ None □ Other:.....

- Aspect of the dizziness?

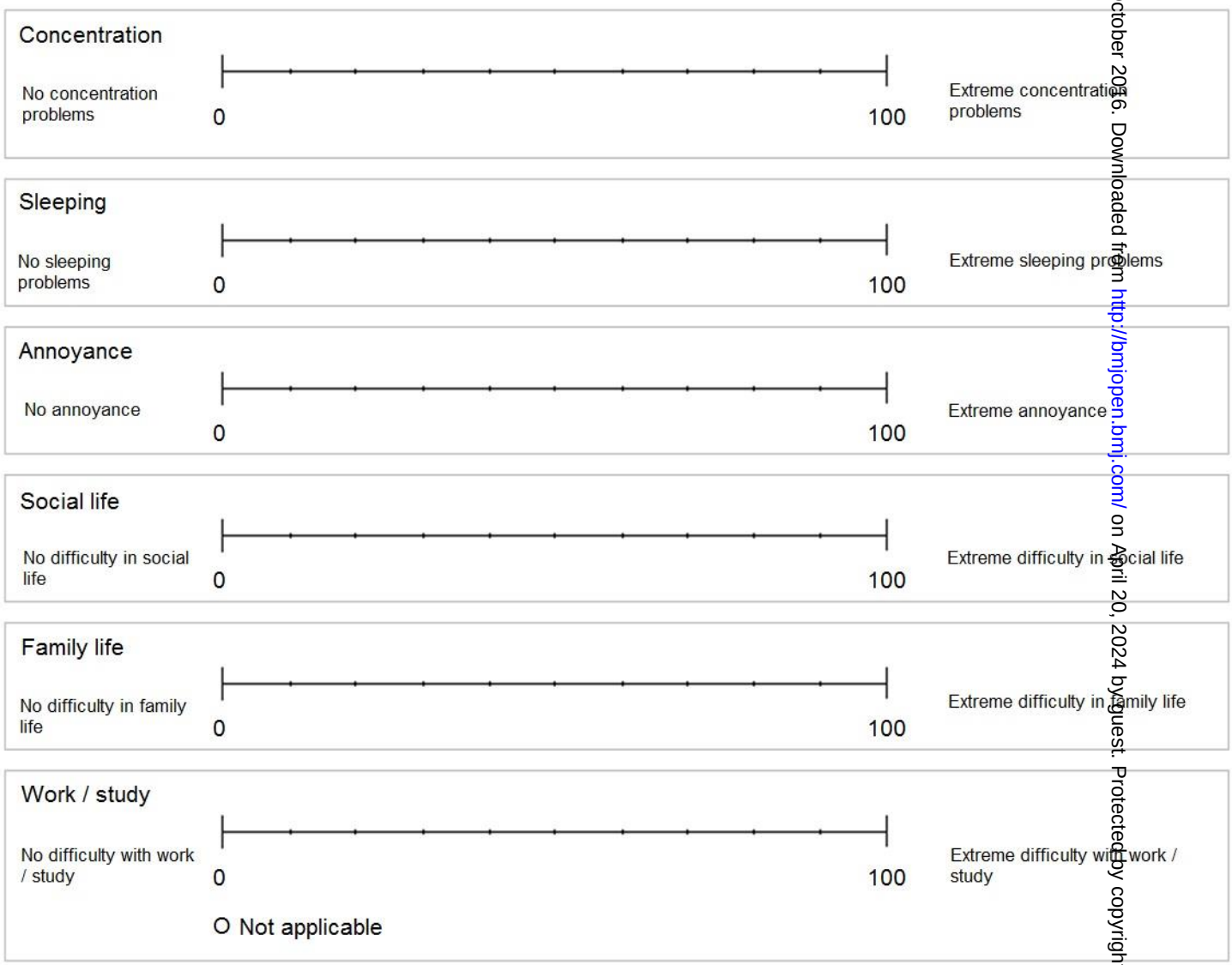
□ Constantly present □ Attack → give an indication of the duration:.....

□ Other:.....

Utrecht Burden Questionnaire for vertigo

Finally

Give an indication on the scales below on whether you have had difficulties or trouble with the following activities in the past week (including today), due to the tinnitus. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. Take into account that the end of the scale indicates that this could not have been more difficult or given more trouble.



UMC Utrecht

Costs diary

This costs diary regards **week / month *** _____ of the year _____

Date: ____ / ____ / _____

Unique participation number: _____

Treatment group: **day-case surgery / inpatient surgery ***

*** Delete as applicable**

Question 1 and 2 will be filled in once, only preoperatively:

1. What is your highest completed educational training?

0 No school or training completed

0 Primary school

0 Preparatory vocational education / lower vocational education

0 Intermediate secondary education

0 Intermediate vocational education

0 Higher vocational education / pre-university education

0 University of Professional Education (UPE)

0 College

0 Other: _____

2. What do you do in everyday life?

0 I am in school/college

0 I work in paid employment

0 I am self-employed

0 I am housewife, -husband

0 I am unemployed

0 I am unfit for work

0 I am retired

0 Other: _____

Part A. Questions regarding work

3. Do you have paid employment?

0 No. *Proceed to question 13.*

0 Yes, I have paid employment. *Proceed to question 4.*

4. What is your profession? _____

5. How many hours a week do you work?

Only count the hours you are being paid for.

_____ hours

6. How many days a week do you work?

_____ days

7. Were you absent from work in the past 4 weeks due to illness?

0 No

0 Yes, I have been absent for _____ *workdays*

8. Were you absent from work longer that the duration of 4 weeks due to illness?

This concerns a continuous period of absence.

0 No

0 Yes

9. What date did you call in sick? Date: ___ / ___ / _____

10. Were there days in the past 4 weeks on which you did attend work, but during which you suffered from psychiatric or physical distress during work?

0 No

0 Yes

11. On how many workdays did you suffer from psychiatric or physical distress during work?

Only count the workdays in the past 4 weeks _____ workdays

12. On the days that you suffered from these problems, it is possible that you performed your work less effectively than usual? Can you give an indication of this on the scale below?

Look at the numbers below. Number 10 indicates that on these days you were able to perform work as effectively as usual. Number 0 indicates that you could not perform your work at all on these days. Encircle the applicable number.

I could not perform work on these days				I could perform approximately half of work						I could perform work as effective as usual
0	1	2	3	4	5	6	7	8	9	10

.

Also in unpaid work (for example: voluntary work, the housework, work in the garden, doing groceries) it is possible to suffer from psychiatric or physical distress

13. Were there days in the past 4 weeks on which you could perform less unpaid work due to psychiatric or physical distress?

0 No

0 Yes

14. How many days was this the case? _____ days

15. Suppose that someone, for example your partner, relative or an acquaintance, would have helped you on these days and would have performed the unpaid work that you were not able to do for you. How many hours would that person have had to work on average on these days?

_____ hours

Part B. Questions regarding care

16. What medication have you used in the past 4 weeks?

0 No medication

0 Medicine 1: name: _____

0 Medicine 2: name: _____

0 Medicine 3: name: _____

0 Medicine 4: name: _____

0 Medicine 5: name: _____

0 Medicine 6: name: _____

0 Medicine 7: name: _____

0 Medicine 8: name: _____

17. How many appointments have you had with your family doctor in the past 4 weeks?

0 No appointments

0 _____ appointments *during regular working hours on workdays*

0 _____ appointments *on workdays outside working hours or in the weekend*

18. Did you have an appointment at the outpatient clinic of the hospital in the past 4 weeks?

This concerns appointments with a doctor for yourself, not for a family member or friend. For example: cardiologist, rheumatologist, ENT specialist, neurologist.

0 No

0 Yes

19. Which doctors have you visited in the past 4 weeks? And how often?

	Doctor:	Number of times:
For example:	*Cardiologist*	*2* *times*
1	_____	_____ times
2	_____	_____ times
3	_____	_____ times
4	_____	_____ times
5	_____	_____ times
6	_____	_____ times

20. Did you have an appointment with one or more of the caregivers mentioned below in the past 4 weeks? If so, how often?

	Caregiver:	Number of times:
0	Physiotherapist	_____ times
0	Occupational therapist	_____ times
0	Speech therapist	_____ times
0	Dietician	_____ times
0	Social worker	_____ times
0	Company doctor	_____ times
0	Audiologist	_____ times
0	Psychologist / psychotherapist	_____ times
0	Other, _____	_____ times

21. How many times have you visited the Emergency Room (ER) in the hospital in the past 4 weeks?

0 I have not visited the ER.

0 I have visited the ER _____ times.

22. Have you been admitted to the hospital in the past period?

During a hospital admission you sleep over in the hospital, for example if you are not allowed to leave the hospital after an operation.

A day-case admission is an admission whereby you do not sleep over in the hospital, for example when receiving chemotherapy treatment, dialysis or blood transfusions. This also includes a day of rehabilitation in a rehabilitation centre.

If you were admitted more than once for either hospital or day-case admission, sum up the total number of days.

0 No

0 Yes, for hospital admission _____ days

0 Yes, for day-case admission _____ days

23. Have you made costs this week for required extra help?

0 No

0 Yes:

0 Childcare, approximately € _____

0 Household, approximately € _____

0 Other costs, namely:

0 (reason) _____, approximately € _____

0 (reason) _____, approximately € _____

0 (reason) _____, approximately € _____

Thank you for completing this questionnaire!

You will receive notification when your next questionnaire is available.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	____2-3, 13__
Protocol version	3	Date and version identifier	____2, 13____
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1, 15____
	5b	Name and contact information for the trial sponsor	____n/a_____
	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	____ n/a _____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____ n/a _____

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	____4-5_____
	6b	Explanation for choice of comparators	_____4_____
Objectives	7	Specific objectives or hypotheses	____5_____
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, noninferiority, exploratory)	____5,7_____
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	____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)	____6-7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____8_____
	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)	____9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____n/a_____
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	____9-12__
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)	_8, figure 1__

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	7
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	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
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	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	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	9-12
	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	9

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	14
Statistical methods	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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	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)	13
Methods: Monitoring			
Data monitoring	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 details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	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	n/a
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
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
	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	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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	n/a
Dissemination policy	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	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	7, appendix 1
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of day-case unilateral cochlear implantation in adults on general and disease-specific quality of life, postoperative complications and hearing results, tinnitus, vertigo and cost-effectiveness: protocol for a randomized controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012219.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2016
Complete List of Authors:	Derks, Laura; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Wegner, Inge; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Smit, Adriana; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Thomeer, Hans; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Topsakal, Vedat; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Grolman, Wilko; Universitair Medisch Centrum Utrecht
Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Surgery
Keywords:	sensorineural hearing loss, cochlear implantation, day-case, inpatient, hearing results, quality of life

STUDY PROTOCOL

Effect of day-case unilateral cochlear implantation in adults on general and disease-specific quality of life, postoperative complications and hearing results, tinnitus, vertigo and cost-effectiveness: protocol for a randomized controlled trial.

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Abstract

Introduction: cochlear implantation is an increasingly common procedure in the treatment of severe to profound sensorineural hearing loss in children and adults. The cochlear implantation is often performed as a day-case procedure. The major drive toward day-case surgery has been from a logistical, economical and societal perspective, but we also speculate that the patient's quality of life is at least equal to inpatient surgery if not increased as a result of rapid discharge and rehabilitation. Even though cochlear implantation seems well suited to a day-case approach and this even seems to be common practice in some countries, evidence is scarce and of low quality to guide us towards the preferred treatment option.

Methods and Analysis: A single-center unblinded randomized controlled trial was designed to (primarily) investigate the effect on general quality of life of day-case cochlear implantation compared to inpatient cochlear implantation and (secondarily) the effect of both methods on (subjective) hearing improvement, disease-specific quality of life, tinnitus, vertigo and cost-effectiveness. Thirty adult patients with severe to profound bilateral post-lingual sensorineural hearing loss who are eligible for unilateral cochlear implantation will be randomly assigned to either the day-case or inpatient treatment group. The outcome measures will be assessed using auditory evaluations, questionnaires (preoperatively, at one-week, three-weeks, three-months and one-year follow-up) and costs diaries (weekly during the first month postoperatively, after which once a month until one year follow-up). Pre- and postoperative outcomes will be compared. The difference in costs and benefit will be represented using the Incremental Cost Utility/Effectiveness Ratio. The analyses will be carried out on an intention-to-treat basis

Ethics and Dissemination: This research protocol was approved by the Institutional Review Board of the UMC Utrecht (NL45590.041.13; version 5, November 2015). The trial results will

be disseminated through peer-reviewed medical journals and presented at scientific conferences.

Registration details: Netherlands Trial Register (www.trialregister.nl): NTR4464, registration date 13th March 2014.

Keyword: (3-10 keywords) sensorineural hearing loss, cochlear implantation, day-case, inpatient, hearing loss, hearing results, tinnitus, vertigo, quality of life, complications

Strengths and limitations of this study

- This study allows for a comparison between day-case and inpatient cochlear implantation to investigate the hypothesis that day-case cochlear implantation is associated with a higher QoL and higher cost-effectiveness, while maintaining an equal hearing outcome and complication rate, compared to inpatient cochlear implantation.
- This study is the first trial of high epidemiological quality evaluating and quantifying the benefits of day-case cochlear implantation for patients with severe to profound bilateral post-lingual sensorineural hearing loss.
- The findings of this trial will give evidence based proof of the feasibility of cochlear implantation in day-case setting, with great consequences for the postoperative management strategies of cochlear implantation.
- A limitation of this trial is that inclusion was only possible for patients with good understanding of the Dutch language and had quick access to communication and transportation in case of any complications.
- Another disadvantage is that due to logistic reasons some of the patients will be admitted one day before the surgery and others the day of surgery.

Background

Cochlear implantation is an increasingly common procedure in the treatment of severe to profound sensorineural hearing loss (SNHL) in children and adults [1–4]. For patients in whom amplification with hearing aids does not suffice, cochlear implantation can be considered. Several studies have shown that cochlear implantation significantly improves quality of life (QoL) [1, 2]. Cochlear implantation is associated with low complication rates: 1-9% for (transient) vertigo, 1-3% for tinnitus, 1-3% for postoperative bleeding or hematoma, 1-9% for wound infection, <1% for facial nerve injury and 4% for explantation [5–8].

Currently, in our university medical center cochlear implantation involves overnight hospital stay. Many other otologic procedures that involved overnight hospital stay in the past are presently being performed, with good result, on an outpatient basis [9–11]. Ear, nose and throat (ENT) surgery is well suited to a day-case approach as many of the disease entities are benign and procedures are associated with low complication rates [10]. Even though one of the major drives towards day-case surgery has been financial from a societal perspective, other non-financial benefits are of major importance. Day-case surgery is associated with shorter waiting time for surgery and reduced risk of infection [12]. Moreover, as a result of a more rapid social and emotional rehabilitation compared to overnight stay, patients might prefer day-case surgery.

Cochlear implantation is increasingly being performed as a day-case procedure in several Western countries. However, reports on day-case cochlear implantation are scarce and mostly describe pediatric day-cases [13, 14]. None of these studies compare the effects of day-case surgery to inpatient surgery. Liu et al. were the only ones to send out a patient satisfaction survey addressing parental and child satisfaction following outpatient cochlear implantation [13]. Overall satisfaction with day-case surgery was 91%. Preoperative anxiety was diminished in 47% of families by planning the operation as day surgery, whereas preoperative anxiety was increased in 34%. Of the latter group, 44% would schedule the surgery as day surgery if they had to undergo the operation again. A total of 19% of parents would have preferred to let their

children spend the night in the hospital. In the same study, two children (4%) had to be admitted for 23-hour observation as a result of postoperative nausea with vomiting and fever. In both studies, none of the subjects had to be readmitted as a result of adverse events arising in the home situation.

The lack of (high-quality) studies precludes firm evidence-based recommendations and demonstrates the need for high-quality studies quantifying the benefits of day-case surgery, both clinical and financial. In order to accommodate this need, in the proposed study we shall compare day-case cochlear implantation to inpatient cochlear implantation. The study will be conducted as a randomized controlled trial.

Methods and design

This protocol is reported according to the SPIRIT Statement, an international guideline on reporting protocols [15].

Study objectives

The primary objective of this study is to evaluate the effect on general QoL of day-case cochlear implantation compared to inpatient cochlear implantation. In addition, subjective participants' perception on hearing improvement, auditory evaluations, disease-specific QoL, tinnitus, vertigo and cost-effectiveness will be assessed.

Study design

The study design will be a single-center, unblinded, randomized controlled trial. Subjects will be assigned to one of two groups: day-case cochlear implantation under general anesthesia or inpatient cochlear implantation under general anesthesia followed by one- to two-day hospital admittance (Figure 1).

Study population

The study population consists of adults with severe to profound bilateral post-lingual sensorineural hearing loss, eligible for unilateral cochlear implantation. Subjects will be recruited from the outpatient clinic of the ENT department at the University Medical Center Utrecht (UMC Utrecht), the Netherlands. In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Inclusion criteria

- Age ≥ 18;
- Severe to profound bilateral post-lingual sensorineural hearing loss defined as ≥ 70 dB above normal adult hearing level on pure-tone audiometry in the range of 500, 1000 and 2000 Hz;
- Willingness and ability to participate in all scheduled procedures outlined in the research protocol;
- General health allowing general anesthesia in an outpatient setting as assessed by an anesthesiologist;
- Quick access to communication and transportation in case of any complications;
- Good understanding of the Dutch language.

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

Exclusion criteria

- Severe to profound pre-lingual or unilateral SNHL;
- Previous cochlear implantation;
- Aberrant (cochlear) anatomy on CT-scan or chronic ear infection;

- Disability that could interfere with questionnaire fulfillment;
- Other medical considerations (e.g. comorbidity) requiring inpatient care.

Sample size calculation and recruitment

To establish equivalence in general QoL of 0.15 points (standard deviation 0.15) on the Health Utilities Index – Mark 3 between the day-case and the inpatient group with an alpha of 0.05 and a power of 80%, 14 participants per group are needed [16, 17]. To anticipate withdrawal of 10% of participants, one more participant than needed will be recruited per group. At the ENT department at the UMC Utrecht, we perform an average of 25 unilateral cochlear implantations per year in patients with bilateral, post-lingual sensorineural hearing loss. Assuming a participation rate of 80%, we will be able to include the necessary number of 30 patients in 1.5 years. If participants wish to leave the study or the investigators decide to withdraw a participant from the study for urgent medical reasons, these participants will not be replaced unless these account for more than 10%.

Patients will be recruited from the outpatient ENT department at the UMC Utrecht. If a patient meets the criteria for cochlear implantation and the inclusion criteria for this study, one of the researchers will explain the content of the study and provide the patient with written patient information and an informed consent form. Patients consent to the use of their data for the research purposes outlined in this protocol, which includes publication of the results once the trial has been completed. Further details can be found in Appendix 1 (informed consent form; translated to English, original in Dutch). Patients that do not want to be included in the study because they want to undergo cochlear implantation in a clinical setting will be asked whether they would like to fulfill the study procedures anyway and whether their data can be used for analysis. Furthermore, these patients will be asked to motivate their preference for inpatient surgery.

Randomization, blinding and treatment allocation

A web-based randomization program (Julius Center, UMC Utrecht, Utrecht, The Netherlands) shall be used to allocate subjects randomly into two groups with stratification for age. Block randomization will be used with an allocation ratio of 1:1. The randomization chart, including block size, is established before the start of the study by an independent data manager and will not be available to any of the people involved with enrolment or treatment of participants. Consequently, treatment allocation sequence is concealed for participants, care providers and researchers. Blinding of participants and care providers is not possible, since both participants and care providers will be aware of the surgical setting and hospital stay.

Intervention

The surgical procedures, as well as hospitalization in the inpatient group, will take place at the UMC Utrecht. Patients in both groups will undergo unilateral cochlear implantation under general anesthesia.

Patients allocated to the conventional group will be admitted one day before or the day of surgery and will be discharged one to two days after surgery. Patients allocated to the day-case group will be admitted into the outpatient unit one day before or the day of surgery and will be discharged the day of surgery. Patients are not allowed to drive for 24 hours following day-case surgery and will be recommended 24 hours of relative bed rest. After a period of 24 hours, patients can return to their daily routine. Participants will be asked to contact the hospital in case of severe postoperative vertigo or pain. An ear compression bandage is applied to all patients during surgery. Patients allocated to the day-case group will either have to return to the hospital two days postoperatively to have the head dressings removed by the surgeon or will remove the head dressings themselves at home after being given proper instructions.

It is to be expected that patients who had surgery in day-case will sometimes stay overnight, for example due to postoperative nausea or dizziness. If patients are not physically capable of same-day discharge or if surgeons do not support same-day discharge, patients will stay overnight regardless of the group that they were allocated to. These patients will be asked to complete their follow-up and analyses will be carried out on an intention-to-treat basis. Reasons for the overnight stay will be recorded and we will differentiate between anesthesiological and otologic related reasons for cross-over.

Outcome measures

Evaluation will take place preoperatively and at one week, approximately three weeks, three months and one year postoperatively by means of questionnaires and auditory evaluation of hearing results. Vertigo and tinnitus will be evaluated directly postoperatively as well. In addition, participants will be asked to keep a costs diary for the duration of one year. Questionnaires and costs diaries can be fulfilled digitally or on paper and will be sent via email or mail respectively.

Primary outcome measure

Our primary outcome is the general QoL measured by the Health Utilities Index – Mark 3 at three weeks and one year postoperatively.

Secondary outcome measures

Our secondary outcome measures include (subjective) hearing improvement, disease-specific QoL, tinnitus and vertigo at three weeks and one year postoperatively, patient satisfaction with regard to day-case surgery at one week postoperatively and overall cost-effectiveness and occurrence of postoperative complications within one year postoperatively.

Auditory evaluation of hearing results

Auditory evaluation will be performed at three weeks, three months and twelve months postoperatively. Speech perception tests will be performed in sound-treated booths at 65 dB sound pressure level. During the test recordings of a set of Dutch words with a consonant-vowel-consonant structure will be played in a free field setting and patients wearing the cochlear implant will be asked to repeat these. Besides this, patients will be asked to repeat Dutch sentences. The percentage of correctly repeated complete sentences, words and phonemes will be scored.

Patient satisfaction

Patient satisfaction will be evaluated at one week postoperatively using the Utrecht patient satisfaction survey (Appendix 2; translated to English, original in Dutch). This seven-item questionnaire was developed in our center and contains questions regarding hospital stay (day-case or overnight stay) and whether patients were satisfied with the intervention group that they were allocated to.

Quality of life

QoL and hearing benefit will be assessed preoperatively and at three weeks and one year postoperatively using the following four questionnaires:

- The Glasgow Health Status Inventory Questionnaire: an 18-item questionnaire, which measures the effect of an otologic problem on QoL at the time the questionnaire is completed. Three domains (general, social support and physical health) are measured based on a 5-point Likert scale ranging from high health status to low health status. The total score ranges from 0 to +100.
- Glasgow Benefit Inventory: an 18-item questionnaire, which measures the change in health status as a result of a surgical intervention. A specific version of the Glasgow Benefit

Inventory will be used that has been validated to measure changes in health status as a result of otorhinolaryngological procedures [18]. The same three domains as the Glasgow Health Status Inventory questionnaire are measured according to the 5-point Likert scale. The total score ranges from -100 (maximal negative benefit), through 0 (no benefit), to +100 (maximum benefit);

- EuroQoL-5D: a five-item questionnaire on mobility, self-care, daily activities, pain and complaints and anxiety or depression that assesses general health status [19, 20]. In addition, the general health status is rated on a visual analogue scale than runs from 0 to 10. A score of 0 equals worst imaginable health state and a score of 10 equals best imaginable health state.
- Health Utilities Index 3: a fifteen-item questionnaire that measures general health status by evaluating eight domains: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain [21].

Tinnitus and vertigo

Tinnitus and vertigo will be assessed preoperatively and at three weeks and one year postoperatively, if present, using the following four questionnaires. These questionnaires will assess tinnitus in the patients' daily life with the cochlear implant switched on. The Utrecht Burden Questionnaire for tinnitus and vertigo will also be administered directly postoperatively in case of direct postoperative tinnitus and/or vertigo:

- Tinnitus Handicap Inventory: a 25-item questionnaire evaluating three domains: a functional, emotional and catastrophic domain [22, 23];
- Tinnitus Questionnaire: a 52-item questionnaire evaluating five domains: tinnitus-related emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints. The response categories are 'true' (0/2 points),

'partly true' (1 point) and 'not true' (0/2 points), depending on the question. A validated Dutch version will be used [24, 25];

- Dizziness Handicap Inventory: a 25-item questionnaire evaluating three domains: functional, emotional, and physical aspects of dizziness and unsteadiness. The response categories are 'yes' (4 points), 'sometimes' (2 points), and 'no' (0 points). The total score discriminates between a mild (16–34 points), moderate (36–52 points), and severe (54+ points) handicap. A validated Dutch version will be used [26, 27];
- Utrecht Burden Questionnaire for tinnitus and vertigo measures severity and character of tinnitus and vertigo by using visual analogue scales and numerical rating scales (Appendix 3).

It needs to be noted that none of these questionnaires were validated for measuring treatment outcome [28, 29].

Postoperative complications

The severity of complications that can occur after cochlear implant surgery are classified according to Hoffman and Cohen's criteria [30]. Complications are considered major if hospitalization or additional or revision surgery are required and minor if it resolves spontaneously or if only medication is required. Complications are prospectively registered in the patients' charts.

Cost-effectiveness/utility analysis

The difference in costs and benefit will be represented using the Incremental Cost Utility/Effectiveness Ratio (ICUR/ICER). The ICUR/ICER is calculated by dividing the difference in costs by the difference in utility or effectiveness. Utility reflects the amounts of money that people are willing to pay to achieve a certain health status. Cost analysis will be performed from

a health insurance and patient perspective. Utility scores derived from questionnaires such as the EuroQoL-5D and the Health Utilities Index 3 are used to calculate the ICUR.

Participants will be asked to keep a costs diary (Appendix 4). Participants will fulfill this diary preoperatively and at regular intervals postoperatively. The first month the diary will be fulfilled weekly followed by monthly fulfillment for the duration of one year. Costs will be measured from a societal and health care perspective. Both direct and indirect costs will be collected. Direct costs include hospitalization, surgery, postoperative complications, doctor's visits and diagnostic tests. Indirect costs include travel expenses and sick leave. Published data of cumulative complications in large cohorts were used to determine weighted costs of complications [31]. Costs of medication such as antibiotics, outpatient clinic visits, hospitalization, surgery, second implants, etcetera will be accounted for. The Dutch guidelines for costing research in health economic evaluations, issued by the National Healthcare Institute [32], will be used to calculate unit prices of resources that were used.

Statistical analysis

Baseline characteristics per group will be described as means and standard deviations. Differences in the baseline will be analyzed using the independent samples Student's *t*-test or non-parametric tests for continuous variables and the Fisher's exact test for categorical variables.

The primary and secondary outcome data are quantitative and will be presented both continuous and categorical. Between-group mean differences, rate differences and rate ratios with 95% confidence intervals will be calculated. For further analysis of between-group differences in both primary and secondary outcomes the independent samples Student's *t*–test or non-parametric tests will be used for continuous outcomes and the Fisher's exact test for

categorical outcomes. Within-subject comparisons will entail differences in mean values and percentages before and after cochlear implantation. These will be analyzed using paired *t*-tests for continuous measures and using the McNemar test for categorical outcomes.

Missing values will be handled using multiple imputation and all analyses will be performed on an intention-to-treat basis. A sensitivity analysis will be performed using all of the data acquired from patients that opted not to be included in the study, but did fill out the questionnaires.

The data will be reported according to the CONSORT Statement [33, 34].

Ethics and dissemination

The study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This research protocol was approved by the Institutional Review Board of the UMC Utrecht (NL45590.041.13; version 5, November 2015). Protocol modifications will be presented to the Institutional Review Board of the UMC Utrecht for approval.

All cases of serious adverse events will be reported to the local Institutional Review Board and adequately followed up. An independent monitor is appointed to check trial quality (completeness of informed consent forms, validity of data, etc.) once a year. All data will be handled confidentially. The data will be coded by using a unique PIN and two of the investigators will safeguard the key to this code. The primary source of the data will be paper files, which will be stored in a locked room. The data will be stored on the investigators' computers as well, which are secured by a password and located in a locked room. The final trial dataset will only be available to the research team.

The trial results will be disseminated through peer-reviewed medical journals and presented at scientific conferences.

Trial status

The trial is currently in recruitment phase.

Conclusion

Cochlear implantation seems to be a surgical procedure that is well suited for day-case treatment as it has proven to be a safe treatment with low complication rates. However, current literature lacks evidence-based recommendations supporting day-case cochlear implantation. This randomized controlled trial allows for a comparison between day-case and inpatient cochlear implantation to investigate the hypothesis that day-case cochlear implantation is associated with a higher QoL and higher cost-effectiveness, while maintaining an equal hearing outcome and complication rate, compared to inpatient cochlear implantation. This is the first trial of highest epidemiological quality evaluating and quantifying the benefits of day-case cochlear implantation for patients with severe to profound bilateral post-lingual sensorineural hearing loss.

Abbreviations

ENT: ear, nose and throat; QoL: quality of life; SNHL: Sensorineural hearing loss; TBQ: Tinnitus Burden Questionnaire; UMC Utrecht: University Medical Center Utrecht; VBQ: Vertigo Burden Questionnaire, WMO: Medical Research Involving Human Subjects Act.

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Author's contributions

I.W. and L.S.M.D.: executive investigator, developing protocol, drafting manuscript, revising manuscript, approval of final version. A.L.S., V.T, and H.G.X.T.: surgeons, developing protocol, revising manuscript, approval of final version. W.G.: initial idea, principal investigator, developing protocol, revising manuscript, approval of final version.

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Acknowledgments

None.

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Figures

Figure 1: Flow diagram of Day-case cochlear implantation study. Abbreviations: RCT = Randomized Controlled Trial, TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

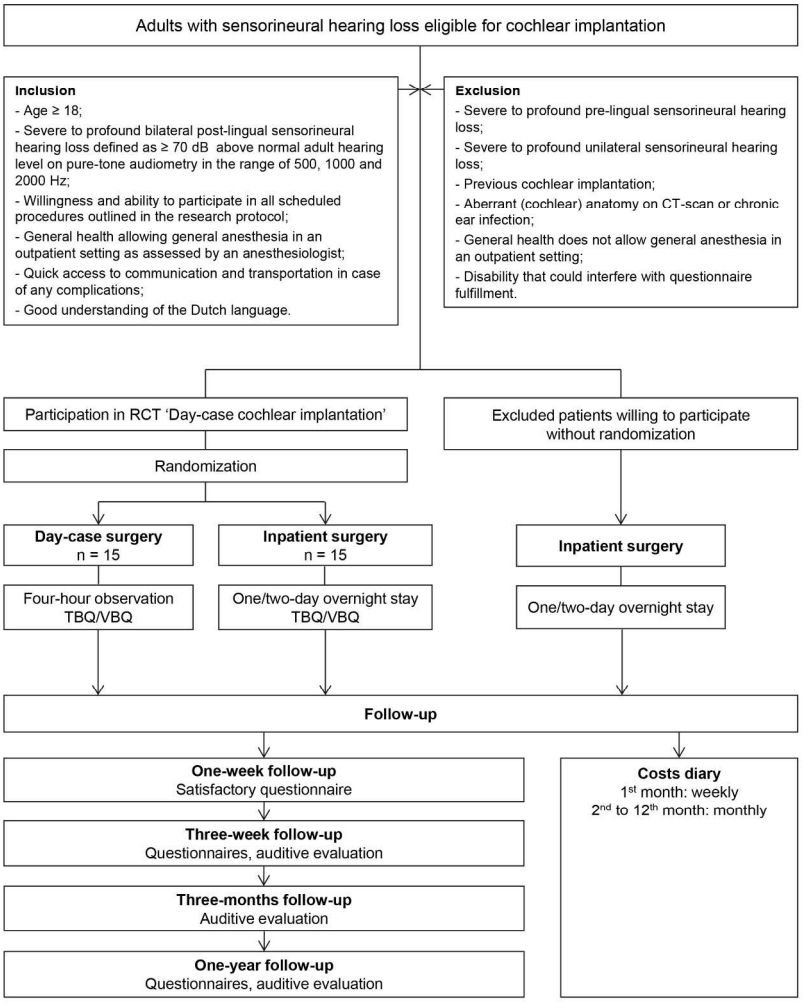

Fig.1 Flow diagram of Day-case cochlear implantation study. Abbreviations: TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

Flow diagram of Day-case cochlear implantation study. Abbreviations: TBQ = Tinnitus Burden Questionnaire, VBQ = Vertigo Burden Questionnaire

233x337mm (300 x 300 DPI)

Informed consent form

Day-case versus inpatient cochlear implantation: a randomized controlled trial.

- I have received and read the information brochure (version number 4, 11-03-2015) for participants. I understand the information that is written in the brochure. I had the opportunity to ask additional questions. These questions were answered adequately. I have had plenty of time to consider participation in this study;
- I am aware that participation is completely voluntary. I am aware that I have the possibility to withdraw participation at any moment, without any explanation;
- I am aware that my data are visible for some of the people involved in this study. These people include the researchers, monitors, auditors, etcetera;
- I give permission to use my data for the research purposes as described in the information brochure;
- I am aware that my data will be stored for 15 years following this study and will be destroyed after these 15 years;
- I give the researchers permission to inform my general practitioner about my participation in this study;
- I **will / will not*** give permission to contact me in the future (after this study) and ask me for participation in additional or new research projects;
- I **do / do not*** want to be informed about the results of this study;
- I agree to participate in this research project.

Name participant:

Signature: Date: __ / __ / __

I hereby declare that I have fully informed the participant about this research project. I will inform the participant in case of new insight information that could affect the participant's consent. I will inform the participant in a timely manner.

Name researcher:

Signature: Date: __ / __ / __

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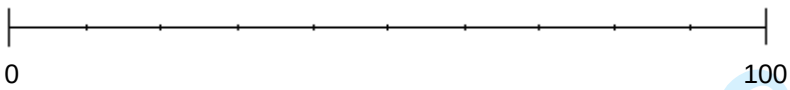
* Delete as applicable

Utrecht patient satisfaction survey

Day-case cochlear implantation

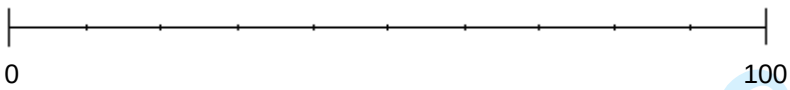
Day-case surgery means that you have been admitted one day before or the day of surgery and have been discharged the day of the surgery.

1.	Did you feel more anxious because the surgery was planned in a day-case setting?	Yes	No
2.	Did you feel less anxious because the surgery was planned in a day-case setting?	Yes	No
4.	Did you find it pleasant that you did not have to spend the night in the hospital after the surgery?	Yes	No
3.	If you would have the choice: would you undergo the surgery in day-case setting again next time?	Yes	No
4.	Would you have preferred to have spend the night in the hospital after the surgery?	Yes	No
5.	Would you have preferred to have been admitted the night prior to the surgery?	Yes	No
6.	Were you content with the hospital admittance in general?	Yes	No
7.	How easy or difficult was the first night after the operation on a scale from 0 to 10 (0 is very easy and 10 is as difficult as possible)?  0 100		

Utrecht patient satisfaction survey

Inpatient cochlear implantation

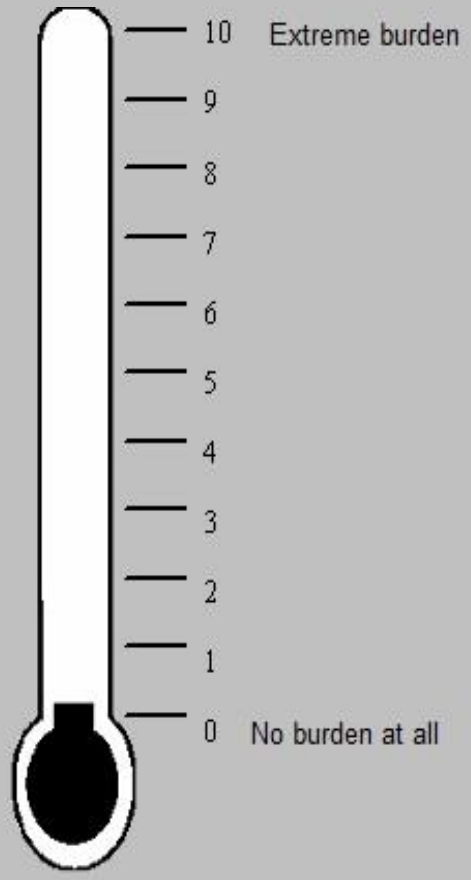
Inpatient surgery means that you have been admitted one day before or the day of surgery followed by one-day hospital admittance.

1.	Did you feel more anxious because the surgery was planned in an inpatient setting?	Yes	No
2.	Did you feel less anxious because the surgery was planned in an inpatient setting?	Yes	No
4.	Did you find it pleasant that you had to spend the night in the hospital after the surgery?	Yes	No
3.	If you would have the choice: would you undergo the surgery in an inpatient setting again next time?	Yes	No
4.	Would you have preferred to have spend the night at home after the surgery?	Yes	No
5.	Would you have preferred to have spend the night prior to the operation at home?	Yes	No
6.	Were you content with the hospital admittance in general?	Yes	No
7.	How easy or difficult was the first night after the operation on a scale from 0 to 10 (0 is very easy and 10 is as difficult as possible)?  0 100		

Utrecht Burden Questionnaire for tinnitus

First of all

Encircle the number on the thermometer below that summarizes best how much of a burden your tinnitus was in the past week (including today).



Secondarily

How many sounds does your tinnitus consist of at the moment? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Thirdly

Give an indication of how your tinnitus sounds on the scales below. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. The end of the scale indicates the extreme values. For instance, if you score a loudness of '10', this means that the tinnitus cannot be louder. If you hear multiple sounds, you can draw multiple lines on the scale. Please indicate whether the line belongs to the right ear, left ear or within the head, and add numbers if you hear multiple sounds on one side.

Example:

How loud is your tinnitus at this moment?

Inaudible 0 — 10 Extremely loud

How high does your tinnitus sound at this moment?

Extremely low 0 — 10 Extremely high

At what rate was your tinnitus present in the past 24 hours?

Constantly absent 0 — 10 Constantly present

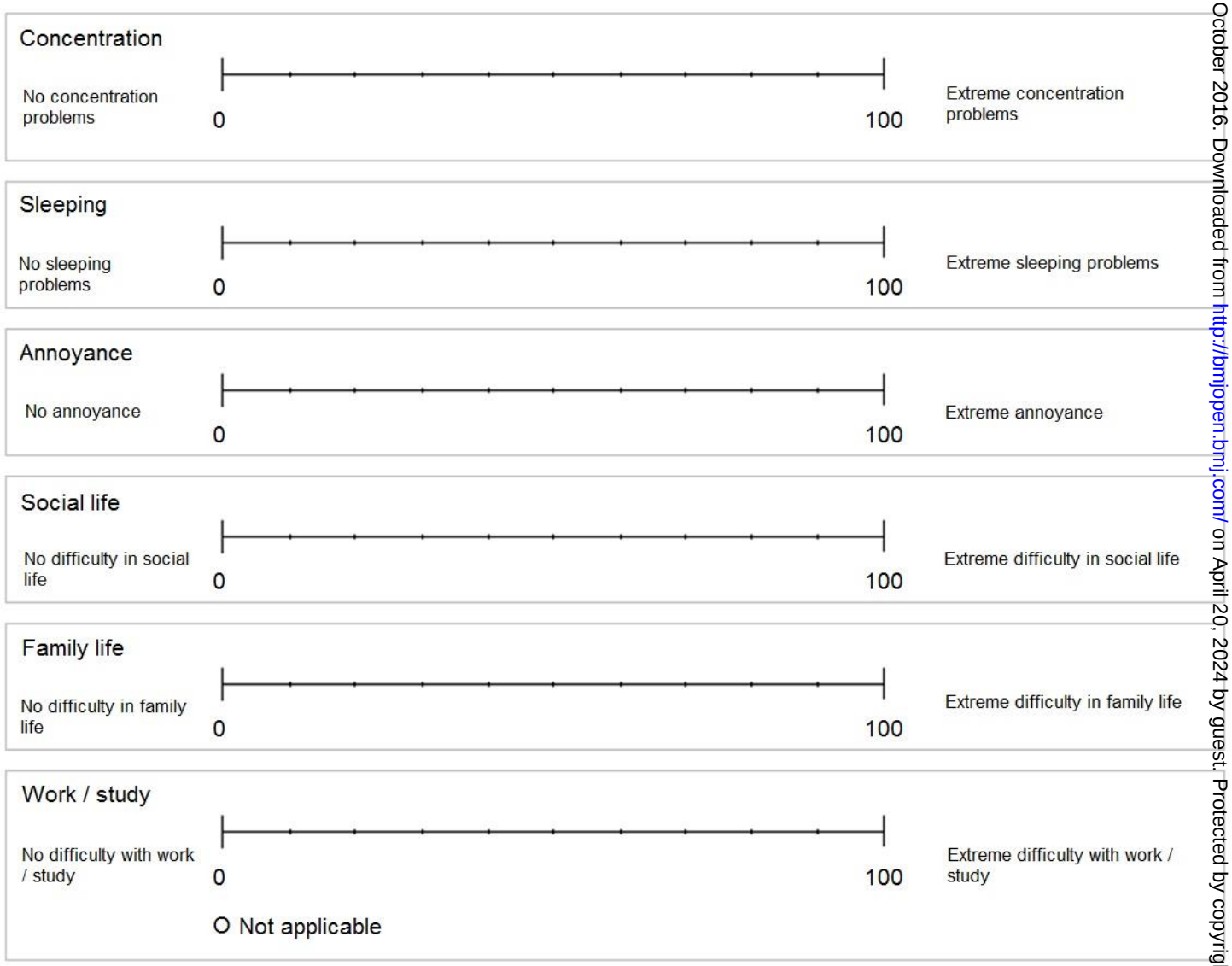
How variable (loudness and/or pitch) has your tinnitus been in the past 24 hours?

Not variable 0 — 10 Extremely variable

Utrecht Burden Questionnaire for tinnitus

Finally

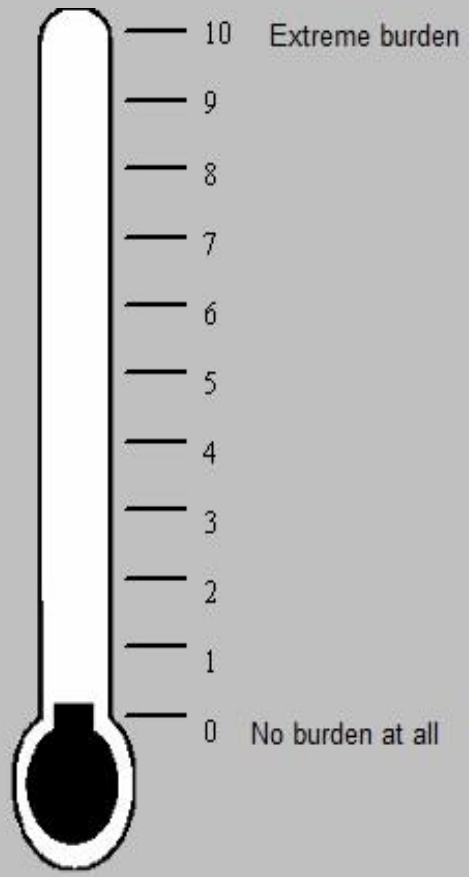
Give an indication on the scales below on whether you have had difficulties or trouble with the following activities in the past week (including today), due to the tinnitus. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. Take into account that the end of the scale indicates that this could not have been more difficult or given more trouble.



Utrecht Burden Questionnaire for vertigo

First of all

Encircle the number on the thermometer below that summarizes best how much of a burden your vertigo was in the past week (including today).



Secondarily

Answer the questions below about how the dizziness is best described (multiple answers are possible).

- How severe is your dizziness at this moment?

Absent 0 ——————— 100 Extremely severe

- Type of dizziness?

□ Vertigo □ Lightheadedness □ Feeling of fainting

□ Other:.....

- Provoking factors?

□ Head movements □ Change of body position □ Loud noises

□ When standing up □ During excercise □ Unknown

□ Other:.....

- Additional complaints?

□ Nausea □ Vomiting □ Hearing complaints □ Tinnitus

□ None □ Other:.....

- Aspect of the dizziness?

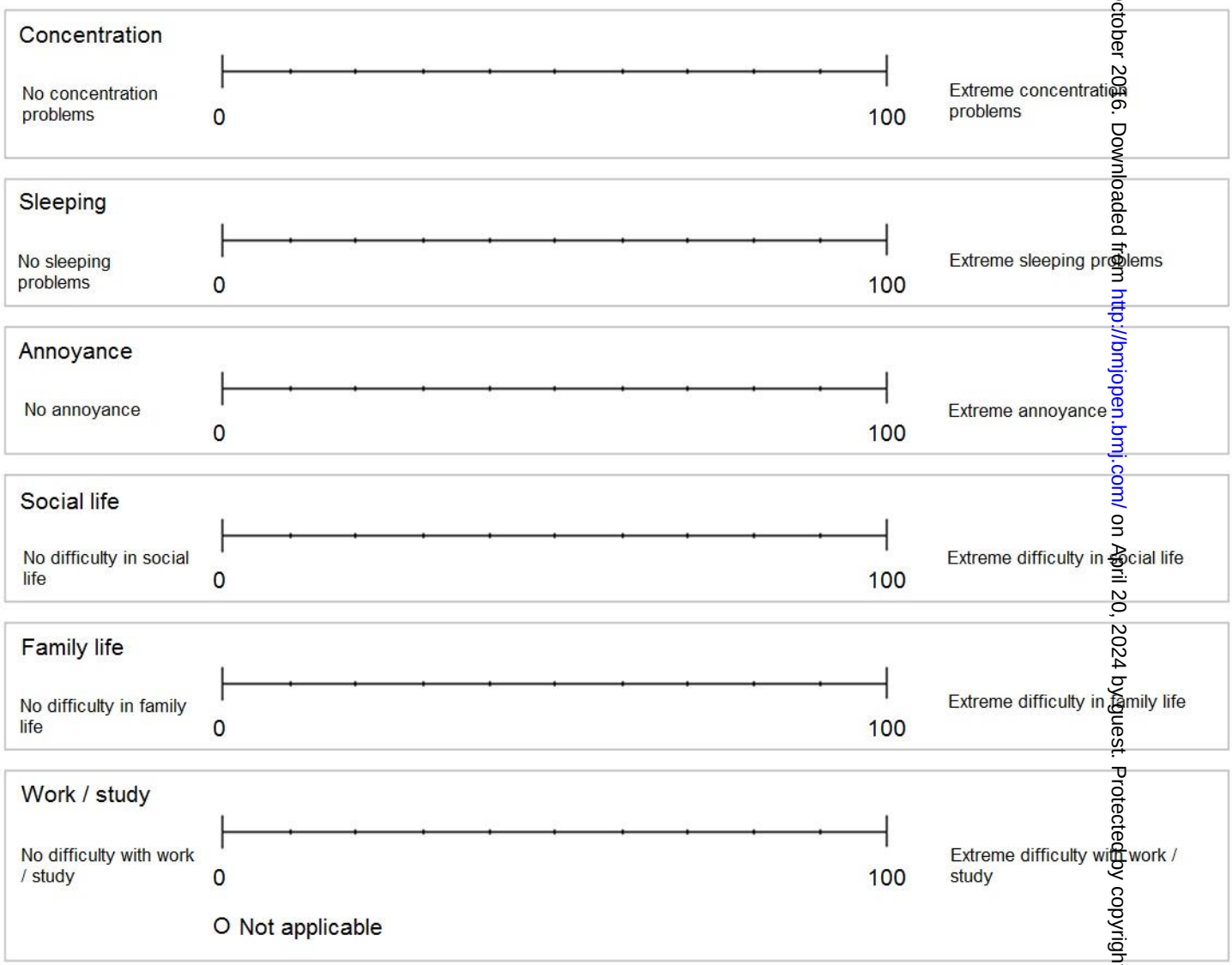
□ Constantly present □ Attack → give an indication of the duration:.....

□ Other:.....

Utrecht Burden Questionnaire for vertigo

Finally

Give an indication on the scales below on whether you have had difficulties or trouble with the following activities in the past week (including today), due to the tinnitus. Draw a vertical line through each of the scales. You are allowed to place the vertical line anywhere on the scale. Take into account that the end of the scale indicates that this could not have been more difficult or given more trouble.



UMC Utrecht

Costs diary

This costs diary regards **week / month *** _____ of the year _____

Date: ____ / ____ / _____

Unique participation number: _____

Treatment group: **day-case surgery / inpatient surgery ***

*** Delete as applicable**

Question 1 and 2 will be filled in once, only preoperatively:

1. What is your highest completed educational training?

0 No school or training completed

0 Primary school

0 Preparatory vocational education / lower vocational education

0 Intermediate secondary education

0 Intermediate vocational education

0 Higher vocational education / pre-university education

0 University of Professional Education (UPE)

0 College

0 Other: _____

2. What do you do in everyday life?

0 I am in school/college

0 I work in paid employment

0 I am self-employed

0 I am housewife, -husband

0 I am unemployed

0 I am unfit for work

0 I am retired

0 Other: _____

Part A. Questions regarding work

3. Do you have paid employment?

0 No. *Proceed to question 13.*

0 Yes, I have paid employment. *Proceed to question 4.*

4. What is your profession? _____

5. How many hours a week do you work?

Only count the hours you are being paid for.

_____ hours

6. How many days a week do you work?

_____ days

7. Were you absent from work in the past 4 weeks due to illness?

0 No

0 Yes, I have been absent for _____ *workdays*

8. Were you absent from work longer that the duration of 4 weeks due to illness?

This concerns a continuous period of absence.

0 No

0 Yes

9. What date did you call in sick? Date: ___ / ___ / _____

10. Were there days in the past 4 weeks on which you did attend work, but during which you suffered from psychiatric or physical distress during work?

0 No

0 Yes

11. On how many workdays did you suffer from psychiatric or physical distress during work?

Only count the workdays in the past 4 weeks _____ workdays

12. On the days that you suffered from these problems, it is possible that you performed your work less effectively than usual? Can you give an indication of this on the scale below?

Look at the numbers below. Number 10 indicates that on these days you were able to perform work as effectively as usual. Number 0 indicates that you could not perform your work at all on these days. Encircle the applicable number.

I could not perform work on these days				I could perform approximately half of work						I could perform work as effective as usual
0	1	2	3	4	5	6	7	8	9	10

.

Also in unpaid work (for example: voluntary work, the housework, work in the garden, doing groceries) it is possible to suffer from psychiatric or physical distress

13. Were there days in the past 4 weeks on which you could perform less unpaid work due to psychiatric or physical distress?

0 No

0 Yes

14. How many days was this the case? _____ days

15. Suppose that someone, for example your partner, relative or an acquaintance, would have helped you on these days and would have performed the unpaid work that you were not able to do for you. How many hours would that person have had to work on average on these days?

_____ hours

Part B. Questions regarding care

16. What medication have you used in the past 4 weeks?

0 No medication

0 Medicine 1: name: _____

0 Medicine 2: name: _____

0 Medicine 3: name: _____

0 Medicine 4: name: _____

0 Medicine 5: name: _____

0 Medicine 6: name: _____

0 Medicine 7: name: _____

0 Medicine 8: name: _____

17. How many appointments have you had with your family doctor in the past 4 weeks?

0 No appointments

0 _____ appointments *during regular working hours on workdays*

0 _____ appointments *on workdays outside working hours or in the weekend*

18. Did you have an appointment at the outpatient clinic of the hospital in the past 4 weeks?

This concerns appointments with a doctor for yourself, not for a family member or friend. For example: cardiologist, rheumatologist, ENT specialist, neurologist.

0 No

0 Yes

19. Which doctors have you visited in the past 4 weeks? And how often?

	Doctor:	Number of times:
For example:	*Cardiologist*	*2* *times*
1	_____	_____ times
2	_____	_____ times
3	_____	_____ times
4	_____	_____ times
5	_____	_____ times
6	_____	_____ times

20. Did you have an appointment with one or more of the caregivers mentioned below in the past 4 weeks? If so, how often?

	Caregiver:	Number of times:
0	Physiotherapist	_____ times
0	Occupational therapist	_____ times
0	Speech therapist	_____ times
0	Dietician	_____ times
0	Social worker	_____ times
0	Company doctor	_____ times
0	Audiologist	_____ times
0	Psychologist / psychotherapist	_____ times
0	Other, _____	_____ times

21. How many times have you visited the Emergency Room (ER) in the hospital in the past 4 weeks?

0 I have not visited the ER.

0 I have visited the ER _____ times.

22. Have you been admitted to the hospital in the past period?

During a hospital admission you sleep over in the hospital, for example if you are not allowed to leave the hospital after an operation.

A day-case admission is an admission whereby you do not sleep over in the hospital, for example when receiving chemotherapy treatment, dialysis or blood transfusions. This also includes a day of rehabilitation in a rehabilitation centre.

If you were admitted more than once for either hospital or day-case admission, sum up the total number of days.

0 No

0 Yes, for hospital admission _____ days

0 Yes, for day-case admission _____ days

23. Have you made costs this week for required extra help?

0 No

0 Yes:

0 Childcare, approximately € _____

0 Household, approximately € _____

0 Other costs, namely:

0 (reason) _____, approximately € _____

0 (reason) _____, approximately € _____

0 (reason) _____, approximately € _____

Thank you for completing this questionnaire!

You will receive notification when your next questionnaire is available.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	____2-3, 13__
Protocol version	3	Date and version identifier	____2, 13____
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1, 15____
	5b	Name and contact information for the trial sponsor	____n/a_____
	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	____ n/a _____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____ n/a _____

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	____4-5_____
	6b	Explanation for choice of comparators	_____4_____
Objectives	7	Specific objectives or hypotheses	____5_____
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, noninferiority, exploratory)	____5,7_____
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	____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)	____6-7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____8_____
	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)	____9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____n/a_____
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	____9-12__
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)	_8, figure 1__

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	7
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	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
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	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	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	9-12
	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	9

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	14
Statistical methods	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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	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)	13
Methods: Monitoring			
Data monitoring	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 details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	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	n/a
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
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
	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	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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	n/a
Dissemination policy	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	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	7, appendix 1
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.