A Study Protocol for a Randomised Controlled Trial Evaluating the Benefits from Bimodal Solution with Cochlear Implant and Hearing Aid vs. Bilateral Hearing Aids in Patients with Asymmetric Speech Identification Scores.

Trial Registration Number: NCT04919928 (ClinicalTrials.gov)

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Statistical analysis plan (SAP) for randomised clinical studies.

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Title A Study Protocol for a Randomised Controlled Trial Evaluating the Benefits from Bimodal Solution with Cochlear Implant and Hearing Aids vs. Bilateral Hearing Aids in Patients with Asymmetric Speech Identification Scores.
Deadline 30.07.2024
Study design Randomised controlled trial
Samplesize 60 participants
Aim This randomised controlled trial is designed to improve clinical decision-making for CI candidacy for patients with asymmetric hearing. It is necessary to establish more evidence to support the effectiveness and the fitting optimization of bimodal CI+HA versus HAs in patients with asymmetric hearing.

The first objective of the study is to evaluate the subjective (SSQ12) and objective (Hearing In Noise Test (HINT) which is word and sentence based and DANTALE I, which is monosyllabic word-based) benefits of a bimodal solution (CI+HA) compared to (HA+HA).
The second objective is to compare and evaluate patient self-reported outcomes with NCIQ, THI and DHI in the intervention group (CI+HA) with the control group (HA+HA).
The third objective is to evaluate if listening effort, hypothesized to cause fatigue, can be measured objectively by HINT with pupillometry.
To minimize listening effort and optimize the fitting of bimodal solution the CI fitting and loudness balancing on individual level will be evaluated.

Hypothesis

Patients treated with a CI on the poorer hearing ear and a HA to the better hearing ear (CI+HA) in a bimodal solution have increased objective and subjective measured speech intelligibility compared to patients treated with new bilateral replacement hearing aids (HA+HA).

2) Data description

See Appendix A

3) The statistical analysis plan (SAP)

Definition of outcome

Primary Outcome

Primary outcomes are Speech intelligibility scores measured objectively with HINT (sentences and words) and DANTALE I and subjectively with Speech, Spatial and Qualities of Hearing scale (SSQ-12).

Secondary Outcome

Patient reported outcomes scores assessed with the Nijmegen Cochlear Implant Questionnaire (NCIQ), The Tinnitus Handicap Inventory (THI) and Dizziness Handicap Inventory (DHI).

Third Outcome

Listening effort assessed with pupil dilation with HINT.

Definition of treatment variables

Treatments are HAs and CI-surgery assigned by randomisation. The primary comparison will be between the CI+HA and HA+HA groups.

Covariates used in analyses

Stratified randomisation for thresholds of the ear to be implanted.

Definition of effect size/parameter of interest

Primary effect size:

Objective outcome: Mean difference in HINT in quiet and in noise between intervention group (HA+CI) and control group (HA+HA) at 3, 6 and 12 months follow-up post- bimodal CI+HA-fitting and 3 months post-HA-fitting respectively.

Subjective outcome: Mean difference in SSQ-12-scores at 3, 6 and 12 months follow-up post- bimodal CI+HA-fitting and 3 months post-HA-fitting respectively

Definition of Analysis Sets

Strategy for intention to treat analysis with incomplete observations.1)

1. Attempt to follow-up on all randomised participants, even if they withdraw from allocated treatment.
2. Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data.
3. Perform sensitivity analyses to explore the effect of deviations from the assumption made in the main analysis.
4. Account for all randomised participants, at least in the sensitivity analyses.

1)

White, Ian R., Nicholas J. Horton, James Carpenter, and Stuart J. Pocock. 2011. 'Strategy for Intention to Treat Analysis in Randomised Trials with Missing Outcome Data'. *BMJ* 342 (February): d40. https://doi.org/10.1136/bmj.d40.

Analysis specification

A constrained linear mixed model is used to analyse the outcome.

The model will include randomisation group (CI+HA / HA+HA) and time (baseline/follow-up) and their interaction as fixed effects along with the threshold strata that were used in stratifying the randomisation. The model is constrained so that the mean at baseline agrees

across the two treatment groups adjusted for threshold stratum, which is reasonable due to the randomisation of implant fitting. Patient ID will be included as a random effect to account for the repeated measurements.

Secondary outcomes will be analysed analogously in a constrained linear mixed model adjusting for randomisation strata. Model validation checks will be undertaken as described above, switching to bootstrapping the standard errors when model assumptions are rejected.

Covariates such as age and gender will be included in all models.

Sensitivity analysis

Inclusion is performed conditional on Pure Tone Average (PTA) (from 0.5 to 4 kHz) PTA > 40 dB HL and SIS <50% in the ear considered for CI implantation and <70% in the best-aided condition which may lead to a truncation effect in the distribution of baseline measurements. To address this, an analysis of covariance (ANCOVA) model conditioning on the baseline will be used to obtain a sensitivity analysis estimate for the main outcome. (2)

The statistical analysis plan is attached as "supplementary file" along with the Data Description listed in Appendix A.

2)

Liu, Guanghan F., Kaifeng Lu, Robin Mogg, Madhuja Mallick, and Devan V. Mehrotra. 'Should Baseline Be a Covariate or Dependent Variable in Analyses of Change from Baseline in Clinical Trials?: ANALYSES OF CHANGE FROM BASELINE IN CLINICAL TRIALS'. *Statistics in Medicine* 28, no. 20 (10 September 2009): 2509–30. https://doi.org/10.1002/sim.3639.

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