Study Protocol and Statistical Analysis Plan

Hearing aid performance study for different spatial configurations

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Hearing aid performance study for different spatial configurations

1 Background

Hearing aids are designed to amplify and transmit sound to compensate for impaired hearing.

The main objective of this medical device is to improve the perception of speech, which can

be defined among many attributes by intelligibility or listening effort. Evaluating the performance of the hearing aid or different features reasonably assumes that the talker location should be in front and close of the hearing aid user. However, listening situations in daily life might show much more variability regarding the spatial configuration of the talker, listener and noise sources.

This investigation is designed to extend the evaluation of hearing aid features to different spatial configuration and also to evaluate the benefit of the investigational device. The investigational device is CE marked and will be used within its defined use and on the intended population. The investigation is divided into three independent parts:

- Beamformer benefit: the first part of the study will evaluate the effect of a wider beamformer on intelligibility and listening effort for a speech-in-noise condition when the talker is not in front of the listener in comparison to a narrower beamformer (StereoZoom),
- Speech Enhancer benefit: the second part of the study will evaluate the effect of the Speech Enhancer algorithm on distant speech in quiet and when speech in quiet is coming from an adjacent room with different measures such as listening effort, objective and subjective speech intelligibility,
- Hearing aid benefit: the third part of the study will evaluate the benefit provided by amplification with a speech-in-noise test where the talker is in front and close to the hearing aid user.

This investigation should provide further knowledge about the perception of speech in different listening conditions with different spatial configurations. Results from the investigation should provide additional input to the development of further products.

2 Objectives

The primary objective for the beamformer benefit part is

(1) to evaluate whether I-BF provides better SRTs in noisy situation with speech from side and behind than with the R-BF with hearing impaired listeners (moderate to severe hearing loss) during a lab test session. Expected SRT improvement based on previous data is about 1 dB SNR with the I-BF and SRTs are measured with the OLSA test. Tested null hypothesis: there is no difference between the RBF and the I-BF.

Secondary objective for the beamformer benefit part is
(2) to evaluate whether I-BF provides less listening effort in noisy situation with speech from side and behind than with the R-BF with hearing impaired listeners (moderate to severe hearing loss) during a lab test session. Tested null hypothesis: there is no difference between the R-BF and the I-BF measured with the ACALES test with varying SNR.

Secondary objectives for the Speech Enhancer benefit part are:

(3) to evaluate whether the investigational device with Speech Enhancer activated provides

less listening effort than without speech enhancer for distant speech in a quiet listening situation for people with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not measured with the ACALES test with varying distance.

(4-a) to evaluate whether the investigational device with Speech enhancer activated provides better speech intelligibility than without speech enhancer for distant speech in a quiet situation for people

with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not measured with the WaKo Rhyme Test.

(4-b) to evaluate whether the investigational device with Speech enhancer activated provides better speech intelligibility than without speech enhancer for speech from an adjacent room in a quiet situation for people with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not measured with the WaKo Rhyme Test.

(5-a) to evaluate whether the investigational device with Speech enhancer activated provides better subjective speech intelligibility and less listening effort than without speech enhancer for distant speech in a quiet situation without access to visual cues for people with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not with the subjective assessment questionnaire.

(5-b) to evaluate whether the investigational device with Speech enhancer activated provides better subjective speech intelligibility and less listening effort than without speech enhancer for distant speech in a quiet situation with access to visual cues for people with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not with the subjective assessment questionnaire.

(5-c) to evaluate whether the investigational device with Speech enhancer activated provides better subjective speech intelligibility and less listening effort than without speech enhancer for speech from an adjacent room a quiet situation without access to visual cues for people with moderate to severe hearing loss. Tested null hypothesis: there is no difference between Speech Enhancer activated or not with the subjective assessment questionnaire. Secondary objectives for the Hearing aid benefit part are:

3 Identification and description of the investigational device

In this clinical investigation, the investigational device will be used according to its intended use. The intended use of the hearing aid is to amplify and transmit sound to the ear and thereby compensate for impaired hearing.

4 Design of the clinical investigation

This clinical investigation is an interventional study, executed at one investigation site, with a confirmatory design. The investigation model is single group, with a randomized test order where the test conditions are fully crossed-over. It is a single blinded study because all test conditions are implemented in the same hearing aid, so that the tested condition cannot be identified by the test participant.

The tested conditions for the primary and secondary objectives are programed in the investigational device, the CE marked Phonak Audeo P-90-R. The tested features can be activated via the MyPhonak APP by the subjects/investigator.

5 Risks and benefits of the investigational device and clinical Investigation

The product-related risks and the clinical investigation procedure-related risks are well controlled during the clinical investigation as the participant will always be under the supervision of the investigator. Even if the residual risk probabilities range from remote (1:100’000 – 1:1’000’000) to incredible (< 1:10.000.000), any adverse effect will be recorded, reported and monitored during the clinical investigation.

The clinical investigation shall provide data to confirm the superiority of the I-BF over the RBF in listening situations where the dominant talker is not located in the front of the hearing aid user. These data shall be used as input for further product improvement and more efficient use of existing feature.

The clinical investigation shall provide data to confirm the superiority of the Speech Enhancer in communication situations with a distant talker. These data shall be used as evidence for further marketing communications and more efficient use of existing feature.

Better perception in different situations has been identified as one of the key elements to provide satisfaction to the hearing aid users (Picou, 2020). Therefore, the overall risk/benefit ratio is considered to be acceptable for this clinical investigation.

6 Endpoints

1) Oldenburg Sentence Test: Speech reception threshold (SRT)

The measure of the speech reception threshold (SRT) is a procedure to evaluate the speech intelligibility in different listening conditions. The SRT in noise is defined as the signal-to-noise ratio (SNR) needed to understand 50% of the presented sentences. The SRT can be obtained with an adaptive procedure to overcome floor and ceiling effects, where the SNR is adapted based on the intelligibility score of the previous sentence. The adaptive procedure is defined so that the test conditions lead to a SNR with 50 % speech intelligibility: the SNR for the next sentence is decreased (more difficult situation) when the presented sentence is correctly understood or the SNR is increased (easier situation) when the presented sentence is not correctly understood. For the adaptive procedure, the noise is presented at fixed 65 dB level and the speech level is adapted according the reference procedure. The Oldenburg Sentence Test (OLSA) is a standard speech intelligibility test in German (Wagener et al., 1999 a-b-c) recommended for the evaluation of hearing aid performances (Kollmeier et al., 2011). The OLSA test uses nonsense sentences with equivalent difficulty. The OLSA test was already used for previous evaluations of the R-BF with the talker located in the front (Neher et al., 2017). The OLSA will be repeated in 8 times for the primary objective: 2 test conditions (R-BF and IBF) by two talker locations (speech from the side and speech from the back) by two test sessions (test at visit 1 and retest at visit 2); in 3 test conditions for the secondary objective with the speaker from the front: unaided, aided with Fixed Directional and aided with Stereo Zoom. The SRT (in dB SNR) is provided for each OLSA measure.

2) ACALES: Listening effort

To determine listening effort in different situations, speech stimuli are presented in different conditions. The listening effort is subjectively rated on a predefined on a 13-point categorical scale (Luts et al, 2010) with varying difficulties (SNRs or talker distance). As speech stimuli the OLSA sentences are either presented at different levels in a background noise with fixed level or at different distances from the listener in a quiet environment. This creates different SNRs (speech levels at the position of the listener), which can be predefined or automatically adapted by the ACALES procedure (Krueger et al., 2017). ACALES adaptively chooses the SNRs or talker distances for each presentation on the basis of previous ratings. The procedure is rapid and easy to administer, resolves differences between individuals and masker conditions, and offers a high test–retest reliability (Krueger et al., 2017). Following data are provided by the ACALES procedure:

For the beamformer benefit part: for each subject the result is a two-slope curve that provides the SNR for following effort scale categorical units (ESCU) “no effort” (1), moderate effort (7), and “extreme effort” (13). The ACALES test will be repeated in 8 times: 2 test conditions (RBF and I-BF) by

two talker locations (speech from the side and speech from the back) by two test sessions (test at visit 1 and retest at visit 2).

For the Speech Enhancer part: for each subject the results are the different effort scale categorical

units (ESCU) from 1= “no effort” to 13 = “extreme effort” determined at 2m, 4m and 8m. The ACALES test will be repeated in 6 times: 2 test conditions (Speech Enhancer ON and OFF) by three talker distances (2m, 4m, 8m) in just one test session.

3) WaKo Rhyme Test : speech intelligibility

The measure of the speech perception in % is an alternative procedure to evaluate the speech intelligibility in different listening conditions. The Speech perception is defined as % correct words out of a word list of 72 words. Initially an individual presentation level is measured using adaptive procedure to determine the level necessary to understand 50% of all presented words. Afterwards the correct word score can be obtained using this individual presentation level (reduced by 1 dB) by calculating the ratio of correct words by the number of total words.

The Rhyme Test (WAKO) is a standard speech intelligibility test in German (v. Wallenberg & Kollmeier, 1989) recommended for the evaluation of hearing aid performances. The WAKO test uses words with equivalent difficulty in an open design. The WAKO test was already used for previous evaluations of the SE (Appleton-Huber, 2020). The WAKO will be repeated 4 times for the secondary objective: 2 test conditions (SE ON and SE OFF) by two listening situations (speech from adjacent room with door left ajar, speech in reverb). Following data are provided from each WAKO measure: test list number and speech score (in %).

4) Subjective assessment

In addition to the tests mentioned above a subjective assessment will be used to determine the subjective perception as this measure is often a good indication for clinical relevance. For this purpose a novel is either read by the tester aloud (with soft voice) or presented by a loudspeaker in a reverberant room in three different distances (2, 4m, 8m) and in an adjacent room with door left ajar. The subjects rates his/her perception of the presented real and recorded speech using a questionnaire on the dimensions “loudness, listen effort and speech intelligibility”. The subject will rate the perception on the same scale with pencils with different colors to get either absolute and relative ratings. The subjective assessment will be repeated 14 times for the secondary objective: 2 test conditions (SE ON and SE OFF), read out loud by the tester (with visual cues) and presented via loudspeaker (no visual cues) by three different distances (2m, 4m, 8m) and in an adjacent room with the door left ajar presented via loudspeaker. Following data are provided from assessment: rating on a 100-point scale per condition and per dimension.

7 Inclusion and Exclusion Criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Experienced (minimum use duration 6 months) and adult (minimum age: 18 years) hearing aid users,
- Written and spoken German,
- Ability to understand instruction,
- Ability to describe listening experiences,
- Ability to attend to the appointments,
- Healthy outer ear,
- Hearing loss within the fitting ranges of the investigational product,

- Informed consent as documented by signature.

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

- Clinical contraindications deformity of the ear (closed ear canal or absence of pinna)
- Known hypersensitivity or allergy,
- Not willing to wear the hearing aid,
- Fluctuating hearing that could influence the results.

8 Measurements and procedures

1) Otoscopy

The investigator will assess the ear and the ear canal status with an otoscope before the first hearing test. The investigator will start the assessment at the outer ear, continue with the ear canal and the ear drum in the end. Doing this, he/she will check if there are any contra indications for fitting hearing aids or further tests. The investigator has to report the amount of wax in the ear canal and also any potential irritation, inflammation, or the presence of foreign objects. A clear and clean ear canal is mandatory to fit the hearing aids and to take part to the clinical investigation.

2) Audiometry

Before the audiometry the ear canal will be inspected with a standard ear microscope. The pure-tone audiometry is common audiological measurement tool to assess a persons, frequency specific, hearing. The hearing threshold levels (HTL) are measured via air (AC) and bone conduction (BC) for each side independently as well as uncomfortable levels (UCL).

The measurement is done via headphones for the air conduction or a special transducer for the bone conduction. The measurement for the hearing threshold typically starts on the participants, subjective, better ear at 1000 Hz. The investigator presents a pure-tone and slowly increases to level, in 5 dB steps, until the participant indicate that he/she can just hear the tone. The measures are repeated 2 times to verify the reported threshold. The same procedure is repeated for each test frequency.

3) OLSA and ACALES tests (beamformer benefit)

For the beamformer benefit part: diffuse cafeteria babble noise from 11 loudspeakers at 65.0 dB (marked with “N”). Target speech material from 90° (marked with “T”) or 180° are OLSA sentences. Subjects are seated in the middle of the loudspeaker circle and are instructed to look to the front.

Material of the ACALES procedure presented via 3 loudspeakers in a distance of 2m, 4m, and 8m measured from the subject’s position in a reverberant environment.

4) WaKo speech intelligibility test (SE benefit)

Speech material of the Rhyme test procedure is presented in quiet from one loudspeaker in a distance of 4m in a reverberant environment (right part of Figure 4) and from an adjacent room with the door left ajar.

5) Subject assessment of speech in quiet in different room configurations (SE benefit)

The speech material is presented either from one loudspeaker or the tester by reading out loud in a distance of 2m, 4m and 8m in a reverberant environment and from an adjacent room with the door left ajar.

6) OLSA (hearing aid benefit)

For the hearing aid benefit part: diffuse cafeteria babble noise from 11 loudspeakers at 65.0 dB (marked with “N”). Target speech material are OLSA sentences presented from the front. Subjects are seated in the middle of the loudspeaker circle and are instructed to look to the front.

7) Real Ear Measurement

The measurements of the output of the fitted hearing aids will be conducted with a probe tube at the subject’s right and left ear drums. For input signal presented from a loudspeaker at 0° in 1 m distance the ISTS (Holube et al. 2010) is used at three different presentation levels: 50 dB SPL, 65 dB SPL and 80 dB SPL. The determined measure is REAR (Real Ear Aided Response. This is a standard measurement during hearing aid fitting. The standard measurement equipment (Aurical from GN Otometrics) is used.

9 Statistical design and analysis

9.1 Determination of Sample Size

a. Introduction and background

The sample size is computed on the primary outcome: SRTs measured in a 2 by 2 factorial design:

- 2 different test setups, talker from the side vs. from the back,
- 2 test conditions, R-BF vs. I-BF.

Traditional power analysis packages or software are unable to compute sample size calculation analytically for a two-way repeated measures design. Green & MacLeod (2016) and Kumle et al. (2021) propose an alternative power analysis based on simulations for a generalized (linear) mixed-effect model.

Mixed-effect models should be preferred over analysis of variance (Oleson et al., 2019) as it makes no assumption about the distribution of the outcome variable (only residuals should be independent and identically distributed) or sphericity (correlation between repeated measures) and allows to include random slopes in the model, assuming the fixed effects are not constant across tested subjects.

b. Principle of power analysis based on simulation

The principle for simulation-based power analysis is to 1) simulate a new dataset, 2) analysis each set and test for significance, and 3) calculate the proportion of significant to all simulations. The simulation of new data set is not trivial as it will affect the accuracy of the simulation. One possible way to generate the new data-set is to use an existing data-set from a well powered study. The power will be computed based on the reference data set in order to detect an a priori determined fixed effect, also described as the smallest effect size of interest (SESOI).

c. Reference data set

The reference data set is taken from Latzel & Appelton (2015) who measured SRTs with different beamformers (including the R-Bf and the I-BF) and 2 test setups with different spatial configurations (noise from around vs side). Individual data from this reference study are available and show interesting properties, as the experiment was conducted on 20 hearing aid users with the same range of hearing loss degree (moderate to severe) at the same investigation site. While these test setups have always the talker in front, these data provide valuable nformation about within subject variance with hearing aid users. The reference analysis is based on a linear mixed-effect model is fitted with setup, device, and interactions as fixed effect and subject as random factor with device as

random slope. The fixed effects are sum coded to get estimate of test setup and device that are easily interpreted.

The estimated effects are:

- test setup effect -0.6 dB SNR in average with a standard error of 0.2 dB SNR,
- device effect -3.0 dB SNR in average with a standard error of 0.4 dB SNR,
- interaction setup by device -1.6 dB SNR in average with a standard error of 0.4 dB SNR.

The effects of talker location and directional microphone are in line with data from Giuliani & Brayda (2019) who report SRTs measured with a single talker from different azimuth (from the back and the side) and different beamformers. While the test was performed with a different population (normal hearing listeners), different beamformers (virtual reality glasses) and test material (SRT in Italian with the Bocca test), the effects are similar with the reference data i.e., a decrease of 0.5 dB SNR when the talker is in the back instead of the side, a decrease of 4.5 dB SNR for the wider beamformer compared to narrower one, and a negative interaction of 0.5 dB SNR.

Results from both studies are consistent in direction even if there are some differences in their amplitudes. These observations are providing enough confidence for the simulation and we can therefore estimate the power based on the reference data for different sample sizes.

d. Simulation

We will make use of the mixed power function from the mixedpower package (Kumle et al., 2018, version 0.1.0) with varying sample size, since we want to compute the power for different sample sizes. The following simulation is based on 1000 runs with a varying sample size from 16 to 28. This range of sample sizes is usually reported in published articles about the effect of directional microphones and is also acceptable from a time and resources perspective.

Simulation is repeated two times. First on original data set where simulations rely on the same effect size provided by the reference model, which might be overpowered for the device effect. This increases the risk to perform analysis with inflated effect sizes and limit the chance of reproducing the results. The alternative is to specify the smallest effect size of interest (SESOI).

Specifying SESOI makes “it possible to design studies which are worthwhile to run, as they have a predetermined power to detect an effect that is of interest” (Albers & Lakens, 2018; Kumle et al., 2021). However, prior knowledge is required to specify an effect size of interest. The SESOI for the test device will be set to 1 dB SNR difference between both tested conditions. The choice of this SESOI is based on a study review and experience from previous studies. The other SESOI are averaged between both reference studies i.e., -0.6 dB for the setup and -1.0 dB for the interaction.

e. Sample size

The power for different sample sizes is shown by fixed effect in following figure:

A sample size of 20 subjects might be sufficient to detect a difference of 1.0 dB SNR between both beamformer conditions with a power of 80%. The research question for the study focuses on the effect of the beamformer so that the decision is based on this main effect only. The sample size will be extended by 10 % to 22 participants as there is a risk of drop out during a clinical investigation with multiple visits over a longer time frame.

9.2 Statistical criteria of termination of trial

The clinical investigation is done under the constant supervision of the investigator in a controlled acoustical environment so that there is no suspicion of an unacceptable risk. There are therefore no statistical criteria who should justify the premature termination of the trial.

9.3 Planned Analyses

The statistical analysis plan includes the methods and types of the analysis, the variables the data sets and the timeframe when the (interim) analysis is planned.

9.3.1 Datasets to be analyzed, analysis population

Statistical analysis will be based on the per-protocol (PP) population. The PP population will include all participants with associated primary and secondary outcome data, excluding subjects who were deemed ineligible following screening visit, those who withdrew from the trial and were unwilling for their previously collected data to be utilized or those who failed to provide baseline.

9.3.2 Primary Endpoint Analysis

All the statistical tests will be performed at two-sided $\alpha=0.05$ if not specified differently. All reported p-values greater than or equal to 0.001 will be rounded to three decimal places and p-values less than 0.001 will be displayed as "<0.001". The analysis will be run using the statistical software R, version 4.1.1 (2021) (R Core Team 2021). The statistical analysis report will be written in a Rmarkdown format and exported into an HTML document.

a) Demographic Data

The following demographic and baseline characteristics will be tabulated overall for PP population: Age (years), 4-frequency Pure Tone Average (in dB HL), and case history i.e., hearing loss onset, otalgia, otorrhea, otitis, tinnitus.

For continuous variables (e.g., age) descriptive statistics will be presented (mean, interquartile range, and number of participants with data). For categorical variables frequencies, percentages and number of participants with data will be presented. The denominator for the percentages will be the number of patients with non-missing data.

b) Primary outcome: SRT for directional benefit

The SRT is a continuous variable expressed as the signal-to-noise ratio (in dB) necessary to achieve 50% intelligibility of the presented sentences. The SRT is measured in a 2 by 2 factorial design: talker factor (from the side or from the back) and beamformer (R-BF or I-BF). These SRTs will be analyzed with a linear mixed effect model with sequence (test-retest), talker location, beamformer, and interaction between location and beamformer as fixed effects. Participants will be treated as random factor with beamformer as random slope. The fixed effects are sum coded to get estimate of talker position and beamformer that are easily interpreted. The distribution of residuals will be visually checked to be independent and identically distributed. A likelihood ratio test will be made to obtain a p-value for each fixed effect.

c) Secondary outcome: listening effort for directional benefit

The listening effort is measured in dB SNR for three effort rating: no effort (1), moderate effort (7), and extreme effort (13). Lower SNRs indicate that the participant can tolerate more noise for the same subjective rating and stand therefore for better results. The ACALES results are measured with 2 talker locations, 2 beamformer settings, and twice (test-retest). Listening effort will be analyzed with a linear mixed effect model with sequence (test-retest), talker location, beamformer, and rated effort as fixed effects. Participants will be treated as random factor with beamformer as random

slope. The fixed effects are sum coded to get estimate of talker position and beamformer that are easily interpreted. The distribution of residuals will be visually checked to be independent and identically distributed. A likelihood ratio test will be made to obtain a p-value for each fixed effect.

d) Secondary outcome: listening effort for SE benefit

The ACALES will be repeated for 3 distances and 2 conditions (SE Off vs On). The outcome is a rating on a 13 points scale, as the difficulty is fixed by the distance now. The outcome is iscrete and bounded at both ends so that a non-parametric test should be applied. Wilcoxon signed rank test will be made for each distance and Bonferroni correction for multiple comparison will be made for the three distances.

e) Secondary outcome: speech test for SE benefit

Word recognition is measured in percent for 2 conditions (SE Off vs On) and in two independent setups: 4 m distance and talker in adjacent room. Percent scores will be converted to arcsin units (Sherbecoe & Studebaker, 2004) for variance normalization. A paired t-test will be made for each condition, as the test setups address different and unrelated listening conditions.

f) Secondary outcome: subjective assessment questionnaire.

The subjective assessment questionnaire is completed for different attributes on a 100 points scale, so that the outcome, a continuous variable, is provided for both tested conditions (SE Off and SE On). The measure is repeated in multiple listening conditions: with visual cues, without visual cues, and from an adjacent room. There is no specific research question about comparing the different listening conditions, so that a single analysis will be done separately for each condition. The measures are repeated multiple times so that a linear mixed effect regression adding the subject as random effect will be used to evaluate the effect of SE for each condition. Significance will be evaluated with a likelihood ratio test and Bonferroni correction will be applied as a single evaluation is made on different attributes.

g) Secondary outcome: SRT for hearing aid benefit

SRTs are measured in 3 conditions: unaided, aided with fixed directional and aided with stereo zoom. Linear mixed effect regression will be used to model and analyze the data. The motivation for planned contrasts is given by the clinical differences between test conditions, both aided conditions are closer to the third, unaided, condition. A benefit with amplification in general can be reasonably expected. The first contrast will test if there is an overall benefit with amplification and the second will specifically look at the differences of aided SRTs.

9.3.3 Secondary Endpoint Analysis

The fitting data provided by the fitting software will be exported and send to the sponsor without any personal labeling. A secondary analysis is planned on the fitting data in an exploratory framework. The purpose of this analysis is to train and evaluate a predictive algorithm (Kollmeier et al., 2016). The algorithm predicts an SRT based on the audiogram and the hearing aid fitting and will be compared to the one measured in the secondary objective: SRT for hearing aid benefit.

This secondary analysis doesn't influence the objective and will not be part of the clinical investigation report. A separate report will be provided about the predictive algorithm to show that the data were used as described in this clinical investigation plan.

9.3.4 Interim Analysis

The clinical investigation has three independent parts focusing on beamformer performances, Speech Enhancer, and Hearing Aid Benefit. A separate statistical analysis for each part will be

provided as soon as all the recruited participants have completed the 2nd visit (for the beamformer and hearing aid benefit parts) and the 4th visit (for the remaining part).

9.3.5 Safety Analysis

The adverse event risks of taking part in the study have been assessed to be low. Numbers of adverse events (AE), serious adverse events (SAE) and device deficiencies (DD) will be cross-tabulated and categorized by severity. No formal statistical analysis will be conducted, but AEs SAEs, and DD will be closely monitored throughout the process. Serious Adverse Events (SAEs) will be recorded, and the site will notify the trial monitor of any SAE, who will then notify the project sponsor within one working day.

9.3.6 Deviation(s) from the original statistical plan

The description of all deviations from the original statistical plan will be provided in the Clinical Investigation Report including proper justification.

9.3.7 Handling of missing data and drop-outs

Unless specified otherwise in each objective, no statistical techniques will be used to impute missing data. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed.

10 Investigation Duration and Investigation Schedule

Total expected duration of the clinical investigation is 5 months.

Expected duration of each participant's participation is:

Screening visit: 60 minutes

Visit 1: max 120 minutes

Visit 2: max 120 minutes

Visit 3: max 120 minutes

Visit 4: max 120 minutes

11 Data Handling and Management

11.1 Data Handling and record keeping/ archiving

All data and documents recorded during the clinical investigation are only accessible to the clinical investigation team and to the monitor. The contact data from the investigational site are never used in the clinical data management system (CDMS). Source data of clinical investigation and the source documents inclusive all notes get encoded. The code list for the participant identification is safely kept within the clinical investigation team and will be deleted 3 months after the end of the clinical investigation. Investigators will preserve confidentiality of all patients taking part in the study, in accordance with ISO14155 (GCP rules) and local regulations.

All computer and software used for data collection provide a login and restricted access at different stages: any computer used on the investigational and sponsor sites is password protected and need a personal login, the access to the CDMS is also restricted to the investigator and the monitor with a password. The collected data are then exported on a server with password protected access, for the statistician.

The CDMS system IBM Clinical Development is a unified, cloud-based system that offers all the electronic data capture and study coordination capabilities needed. Each clinical investigation team member and the monitor owns an account. In this clinical investigation, the IBM Clinical Development will be used as data management system (electronic database). Clinical investigation documents will be safely stored. Only team members will have access to the data.

The anonymized data will be retained for 10 years. The study-related coding list will be deleted from the data directory and the associated backups within three months after completion of the study Case Report Forms (CRF).

Clinical investigation data will be recorded both with paper Case Report Form (pCRF) and electronic Case Report Form (eCRF). For each enrolled participant, a CRF will be maintained. All CRFs will be kept current to reflect the participant`s status at each phase during the course of this clinical investigation.

Participants cannot be identified in the CRF by name or initials and birth date but an appropriate coded identification (participant ID) is used. All clinical investigation team members are authorized for the CRF entries. If pCRFs will be used, the investigator`s acronym as well as the participant ID will be filled in and data are entered into an electronic file for analysis by the respective investigator. Data will be monitored by the assigned monitor.

In case of correction or changes in the CRF, the investigator undertakes the correction by crossing out the word/sentence with a single horizontal line and by adding the correction including their personal identifier, the date and the justification.

11.2 Procedures to maintain and protect participant privacy.

The Sponsor and Principal investigator affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual participant medical information obtained as a result of this clinical investigation is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files. For data verification purposes, authorized representatives of the Sponsor, the monitor, CA or a EC may require direct access to parts of the data records relevant to the investigation team. The investigator should provide adequate time and facilities for monitoring visits.

Actions taken to guarantee participant privacy:

- Participant names and details, accessible for monitor, appropriate investigators and Principle Investigator are documented in the Participant Identification log. There is no disclosure of personal information to no one else but the investigation team.
- Participant paper based files will be safely stored. Only members of the investigation team have access to these documents.
- Electronical data is uploaded in project files in CDMS and on SharePoint and just permitted to access by monitor, principal investigator and investigators.
- Source data is encoded and will be archived encoded as well. None of the participant names will be revealed to anyone than the clinical investigation team. Participants and their respective data will be tracked on source data and source documents via their participant

12 Amendments to the CIP

Substantial amendments are only implemented after approval by the EC. The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

13 Deviations from clinical investigation plan

Deviations from the CIP to protect the rights, safety and well-being of human participants under emergency circumstances may proceed without prior approval of the sponsor and the EC – such deviations will be documented and reported to the sponsor representative (Study Manager) and the EC as soon as possible. Apart from that the investigator is not allowed to deviate from this CIP unless that deviation does not influence the investigation data.

14 Device accountability

The accountability for investigational device will align to the procedures in Chapter 7.9 of ISO_14155, 2020. A device accountability log will be used to track the distribution of the investigational devices during the clinical investigation. In addition, information whether a device deficiency has occurred during the clinical investigation or not will be kept on the device accountability log.

15 Informed consent process

15.1 Process for obtaining informed consent

The investigators will explain to each participant the nature of the study, its purpose, and the procedures, involving the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that they may withdraw from the study at any time and that withdrawal of consent will not lead to consequences for the participant. The participant must be informed that their medical records may be examined by authorized individuals.

All participants for the clinical investigation will be provided a participant information sheet, and a consent form describing the clinical investigation and providing sufficient information for participant to make an informed decision about their participation in the clinical investigation. The participants will be given enough time (minimum time frame for this study: 1 week) for their participation decision.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any clinical investigation procedure. The participant should read and consider the statement before signing and dating the informed consent form and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or their designee) and it will be retained as part of the study records. Complementary to the other documents, the participant will receive an additional information regarding the general data protection regulation following the European Union law.

16 Adverse events, adverse device effects and device deficiencies

Device deficiencies and all adverse events (AE) including all serious adverse events (SAE) as defined in ISO 14155:2020 are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from participant's informed consent until the last protocol-specific procedure, including a safety follow-up period (ISO-14155, 2020). Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or investigation procedure.

The causality assessment of the SAEs will be conducted according to MDCG 2020-10/1 Safety Reporting in Clinical Investigations of Medical Devices under Regulation (EU) 2017/745.

The reporting of Serious Adverse Events and Device Deficiencies follows the Regulation (EU) 2017/745 and the MDCG 2020-10/1 Safety Reporting in Clinical Investigations of Medical Devices under Regulation (EU) 2017/745.

17 Vulnerable Populations

Vulnerable population is not included in this clinical investigation.

18 Suspension or premature termination of the clinical

18.1 Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.

The clinical investigation will be suspended if the numbers of corona cases peak in Germany again at any time, and also in case if an unacceptable risk is identified related to the investigational device or clinical investigation procedure. The Sponsor may terminate the clinical investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively, e.g. traveling to the investigational site (due to COVID- 19),
- alterations in accepted clinical practice that make the continuation of a clinical investigation unwise,
- early evidence of benefit or harm of the experimental intervention.

18.2 Requirements for participant follow-up

In case of a premature termination, the participants are invited by the investigator for a final appointment. In this visit, an audiogram will be recorded and the outer ear will be checked to ensure that there are no damages caused by the clinical investigation procedure.

19 Publication policy

The clinical investigation will be registered in clinicaltrials.gov, a publicly accessible database, as required by ISO 14155.

The results of the clinical investigation will be published as white paper.