Study Protocol and Statistical Analysis Plan

Evaluate the Benefit of a BiCROS Hearing Aid Fitting – ID# 461

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1 Objectives and hypotheses of the clinical investigation

1.1 Purpose of the clinical investigation claims for clinical performance, effectiveness or safety of the investigational device that are to be verified

This study will be a PMCF study in order to substantiate the clinical benefit of a BiCROS system (regulatory requirement) and to secondly substantiate intended claims.

1.2 Primary and Secondary Objectives

The **primary objective** of this study is to evaluate whether a BiCROS fitting improves Speech Intelligibility for speech from the front and noise from the better ear's side compared to no treatment (unaided) for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear measured with the US Matrix Test.

The **secondary objectives** of this study are:

1. Evaluate whether a BiCROS fitting improves Speech Intelligibility in a setup with speech from the front and noise from the better ear's side compared to the alternative treatment of a monaural hearing aid fitting for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear measured with the US Matrix Test.
2. Evaluate whether a BiCROS fitting improves Speech Recognition Thresholds (SRT) by 1dB for speech from front in diffuse noise compared to no treatment (unaided) for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear measured with the US Matrix Test.
3. Evaluate whether a BiCROS fitting improves Speech Intelligibility in diffuse noise compared to the alternative treatment of a monaural hearing aid fitting for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear measured with the US Matrix Test.
4. Evaluate whether a BiCROS fitting results in improved subjective quality of hearing compared to no treatment (unaided) for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear measured with a questionnaire (SSQ).
5. Evaluate decrease in subjective listening effort for adults with unaidable hearing loss in one ear and aidable hearing loss in the other ear with a BiCROS fitting compared to no treatment (unaided) with a questionnaire or other means.

2 Design of the clinical investigation

2.1 General

2.1.1 Design Type

This clinical investigation is an interventional study, conducted at one investigation site, with a confirmatory design. The investigation employs a single group of participants that will be tested in all conditions (cross-over) and be blinded towards the intervention condition they are tested in as much as possible (unaided can't be blinded).

Test conditions:

- Experimental intervention: BiCROS fitting: A CROS microphone transmitter is worn on the poorer, unaidable ear and the hearing aid on the better hearing ear.
- Control intervention: Monaural hearing aid fitting: One hearing aid is worn on the better hearing ear.
- Control intervention: BiCROS fitting: A CROS microphone transmitter (with omnidirectional microphone mode) is worn on the poorer, unaidable ear and the hearing aid (with omnidirectional mode) on the better hearing ear.
- Control intervention: Monaural hearing aid fitting: One hearing aid (with omnidirectional mode) is worn on the better hearing ear.
- No intervention: No treatment (unaided), i.e. no CROS transmitter and no hearing aid are worn. (Condition not included in preference ratings because it doesn't allow for quick AB comparisons.)
- The order of conditions will be randomized.

2.2 Procedures

2.2.1 Investigation-related Procedure

Hearing test, ear Impression taking, hearing aid fitting, and outcome measures will be performed according to Table 1. The aforementioned parts of the procedures except for outcome measures may be conducted at Sonova Innovation Centre Toronto in Mississauga for participants who wish to receive fitting closer to their home to reduce the amount of travel to the London study site. The study team will be present in person for the initial hearing aid fitting. For those participants, in-between visits during the home trial period, which may be required for fine tuning, will be conducted in Mississauga, too, where a remote connection to the study team in London will be established by a Sponsor employee that is not otherwise taking part in this study. This way, the audiologist who fitted the hearing aids will be able to orchestrate the fine tune to not introduce any additional variability between fittings.

All outcome measurements will be solely conducted at the National Centre for Audiology in London.

Study Visits

Table 1 *Overview of study visits*

Visits	Tests and Procedures
Visit 1 Approximately 2 hours	• Hearing Test under the supervision of a registered audiologist. • Impressions for both ears if required. • If impressions are not required, the hearing aid fitting described in Visit 2 will begin.
Visit 2 Approximately 2 hours	Hearing Aid Fitting • Hearing Aid fitting under the supervision of a registered audiologist.

	• Probe microphone measure to ensure hearing aid is fitted properly.
Home Use	Participants will be asked to wear the BICROS hearing aid system home to use for 4-5 weeks. Participants may schedule visits to see the study audiologist if you require any adjustments during that time. Participants will be given two questionnaires and asked to complete them prior to returning to the lab for the next visit.
Visit 3 & Visit 4 (if necessary) Up to 2 hours each	In-lab Assessments: • Rating the sound quality of speech and music. • Rating the amount of effort required to listen to speech in noise without the BICROS system and while wearing the BICROS system in different hearing aid settings. • Indicating preference between different hearing aid settings for speech • Repeating speech back in quiet and in noise. • We will ask participants for their opinions of the BICROS hearing aid and document these opinions using a structured process. • Return devices to study audiologist. • Sounds will be delivered by hearing aid, headphone and speakers below uncomfortable levels. • An end of study assessment of hearing levels and ear canal status (audiometry, otoscopy) will be completed.

3 Statistical design and analysis

3.1 Determination of Sample Size

Primary objective

A power analysis was conducted to apply a one-tailed paired samples t-test to compare the difference between the two conditions tested in the primary objective. The required sample size for 95% power with a one-tailed paired t-test is 19.

With additional 4 participants as backup (based on previous research experience), the required number of participants is 23. For 80% power, 12 participants are needed.

Statistical criteria of termination of trial

There are no statistical criteria for stopping the study.

3.2 Planned Analyses

3.2.1 Datasets to be analyzed, analysis population

Dataset will be the SNRs from the Matrix test across hearing aid conditions, questionnaire responses, subjective rating values, listening effort ratings, and preference ratings.

3.2.2 Primary Endpoint Analysis

Whether there is a significant benefit of the BiCROS fitting over the unaided condition in terms of SRTs will be tested using a one-tailed paired samples t-test. The assumption of normally distributed paired differences between unaided and BiCROS will be tested by visually inspecting Q-Q plots, checking skewness and kurtosis against predefined thresholds (skewness < 0.8 and kurtosis < 2) and testing for statistically significant deviations from normality (p<.05) using the Shapiro-Wilk-test. Outliers will be defined as differences that lie outside the range between 1.5 times the interquartile range below the first quartile and 1.5 time the interquartile range above the third quartile of the data. Outliers will be removed if they are ≥ 2 standard deviations from the mean. In case of a non-normal distribution, non-parametric testing will take place with a one-sided Wilcoxon rank sum test.

According to common standards, a Type I error probability of 5% is deemed to be acceptable and the null-hypothesis will be rejected if the p-value is equal to or less than 0.05.

Time point of analysis: After all data collection of the primary endpoint is completed for all participants.

Responsibility for analysis: Western University investigators will complete the statistics.

3.2.3 Secondary Endpoint Analysis

Whether there is a significant benefit of the BiCROS fitting over the unaided condition in terms of SRTs will be tested using a one-tailed paired samples t-test. The assumption of normally distributed paired differences between unaided and BiCROS will be tested by visually inspecting Q-Q plots, checking skewness and kurtosis against predefined thresholds (skewness < 0.8 and kurtosis < 2) and testing for statistically significant deviations from normality (p<.05) using the Shapiro-Wilk-test. Outliers will be defined as differences that lie outside the range between 1.5 times the interquartile range below the first quartile and 1.5 time the interquartile range above the third quartile of the data. Outliers will be removed if they are ≥ 2 standard deviations from the mean. In case of a non-normal distribution, non-parametric testing will take place with a one-sided Wilcoxon rank sum test.

Descriptive analysis with mean and standard deviations will be completed for the questionnaire results. In addition, repeated measures ANOVA with follow-up post hoc t-tests with Bonferroni correction as required will be performed comparing the responses of multiple sub-scales to 0 (“unchanged” - the questionnaire asks participants to rate their experience in terms of change (improvement vs. no improvement for each question) including an option for no change). Factors are conditions (unaided and BiCROS) and SSQ subscales (speech hearing, spatial hearing, and qualities of hearing). Violations of sphericity will be corrected by adjusting the degrees of freedom of the ANOVA using the Greenhouse-Geiser epsilon.

Sound quality ratings and listening effort ratings will be analyzed using repeated measures ANOVA with follow-up post hoc t-tests with Bonferroni correction as required. Factors are conditions (unaided, monaural with omnidirectional and beamformer, and BiCROS with omnidirectional and beamformer) and subscales (clarity, total Impression, and listening effort).

Preference ratings will be analyzed using one-sample Shapiro–Wilk test for normality to detect any significant skew toward a preferred setting, using BiCROS beamformer as the test condition for all comparisons.

According to common standards and Type I error probability of 5% is deemed to be acceptable and the null hypothesis will be rejected if the p-value is equal to or less than 0.05.

Time point of analysis: After all data collection of the primary endpoint is completed for all participants.

Responsibility for analysis: Western University investigators will complete the statistics.

3.2.4 Interim Analysis

No interim analysis is planned.

3.3 Handling of missing data and drop-outs

We will most likely not have the ability to replace dropouts if the recruited number of replacements would render the sample total to higher than the planned number of participants (23), given the recruitment limitations of the target population. Participants are permitted to remove their data and if they do so, their data will not be included in the results. Those who drop out, but do not ask for any data to be removed, will have the data up to their drop out time included.

4 Informed consent process

4.1 Process for obtaining informed consent

Participants are presented with the Letter of Information by email, mail, or in person. They are provided time to review the LOI. They are permitted to ask any questions they have about the information in the LOI. They will then sign the letter of information. A member of the study staff will also sign the LOI. A copy of the LOI is provided to the participant.