ACES

Ambispective Clinical Evaluation of Sophono™

Statistical Analysis Plan

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Contents

1 Version History

SAP Change History				
Version	**Version Date**	**Description of Change**	**Paragraphs involved**	**Modified by**
1.0	27 Apr 2018	First Release	All	Fabio Di Piazza

2 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AC	Air Conduction
AE	Adverse Event
APHAB	Abbreviated Profile of Hearing Aid Benefit
BC	Bone conduction
CHL	Conductive Hearing Loss
CIP	Clinical Investigation Plan
CI	Confidence Interval
dB	Decibel
EC	Ethics Committee
ENT	Ear, Nose and Throat
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
HL	Hearing Loss
Hz	Hertz
IC	Informed Consent
ICH	International Conference on Harmonization
ICH E3	ICH guideline E3: Structure and content of clinical study reports
ICH E6	ICH guideline E6: Guideline for Good Clinical Practice
ICH E9	ICH guideline E9: Statistical principles for clinical trials
IRR	Incidence Rate Ratio
IQR	Interquartile Range
MPO	Maximum Power Output
NR	No Response
PTA	Pure Tone Average
PPS	Per Protocol Set
QOL	Quality Of Life
SAP	Statistical Analysis Plan
SNR	Signal-to-Noise Ratio
SRT	Speech Recognition Threshold
SSD	Single-Sided Deafness
VT	Vibrotactile

3 Introduction

The Sophono Alpha 1 processor has gone through a series of upgrades (Alpha 2 and Alpha 2 MPO) while the implant with dual magnets remains relatively unchanged. Bench audiogram research and ancillary data presented at society meetings indicate an improved feedback-free gain with the Alpha 2 MPO device over earlier versions; however, to date no studies have been published. The aim of this study is to examine the long-term (implant duration three months or longer) audiologic, safety, and quality of life outcomes of subjects implanted with the Sophono bone conduction hearing implant and to compare the Alpha 2 to the Alpha 2 MPO sound processors. This SAP is based on Protocol Clinical Investigation Plan MDT16043ENT, Version 2.0. The SAP has been prepared in agreement with Medtronic internal procedures, and using the STROBE Statement[1] and ICH guidelines E3, E6 and E9 as guidelines.

4 Study objectives

4.1 Primary objective

The primary objectives of this study are:

- To assess the safety of the Sophono implant
- To assess the effectiveness of the Sophono Alpha 2 MPO processor

in subjects diagnosed with CHL, SSD and mixed HL who currently have or have had the Sophono implant.

4.2 Secondary objectives

4.2.1 Secondary objective 1

To compare the effectiveness of the Sophono Alpha 2 processor to the Alpha 2 MPO processor

4.2.2 Secondary objective 2

To assess the effectiveness of the Sophono Alpha 2 and the Sophono Alpha 2 MPO over time.

4.2.3 Secondary objective 3

To assess subject satisfaction after system use.

4.2.4 Secondary objective 4

To assess QOL after system use.

5 Investigation Plan

5.1 Study design

This study is an ambispective, multi-center, single-blind, intra-subject controlled study to assess safety of the Sophono implant and effectiveness of the Sophono Alpha 2 MPO processor in subjects with SSD, CHL, and mixed HL.

5.2 Inclusion/Exclusion criteria

All inclusion and exclusion criteria stated in section 9.3 and 9.4 from CIP, must be met for subjects to be eligible for inclusion in the study.

5.3 Overall study design and plan-description

After informed consent is collected, the study will consist of a retrospective medical chart review to collect data on AEs for all subjects. A prospective clinic visit for subjects still implanted with the Sophono implant will be conducted to evaluate the subject's implant site and conduct hearing tests, along with a QOL and satisfaction self-assessment.

All subjects will be screened for study eligibility. A qualified member of the investigational site's research team will review the inclusion and exclusion criteria to screen each subject. Subjects will be considered enrolled into the study when they have both:

- Been informed of the study design, objectives, risks and benefits
- Confirmed interest in participation by signing an IC and Research Authorization Forms

Any subject who currently has or who has had the Sophono implant (including those who have been explanted) may be enrolled.

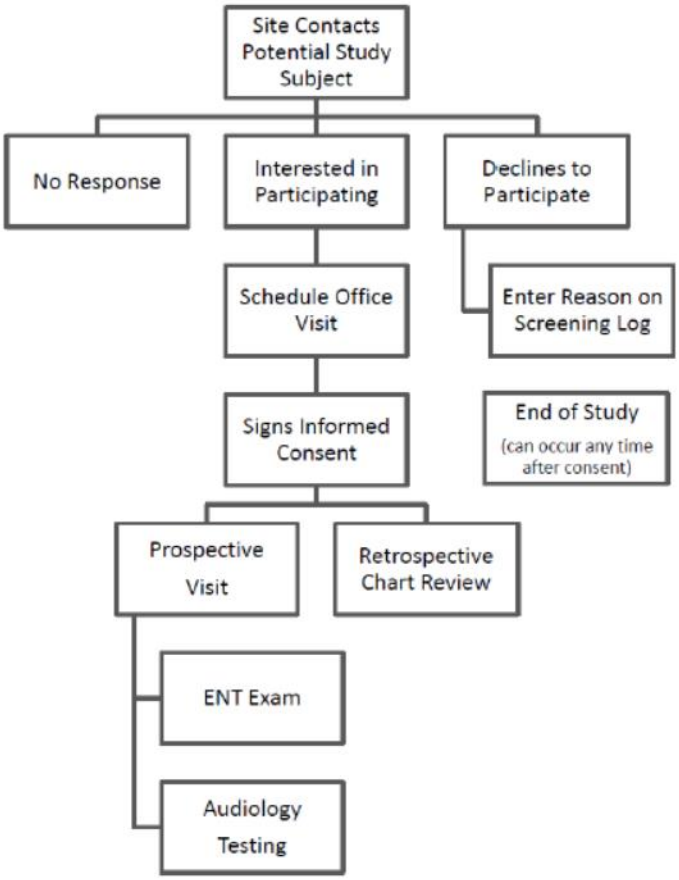
A Screening and Enrollment Log will be maintained for all subjects. For screen-fail subjects, a reason for failure will be noted.

Clinical data will be collected during:

- a retrospective review of the subject's medical chart will be performed to gather and report data on subject surgical history, reportable AEs from the time of implantation to time of chart review, previous QOL scores, and previous audiometric testing results for the Sophono processors.

- an in-office ENT exam will be conducted to gather and report data on the ear and implant site for skin complications, potential AEs and Sophono system satisfaction and QOL questions. During the in-office visit Audiology testing will be performed to collect data on: Basic Sound Field Audiology thresholds at octave intervals, Speech Reception Threshold, Word Recognition Thresholds and Hearing in Noise.

Figure x – Flow Chart



Data collection requirements are summarized in the following table:

Table x – Data Collection Requirements

Data	Baseline	Retrospective	Prospective	Study Exit
Informed Consent	X			
Inclusion/Exclusion Criteria Evaluation	X			
Demographic	X			
Medical History (including Procedure)	X	X		
Audiogram		X	X	
Speech Recognition Threshold		X	X	
Word Recognition Threshold		X	X	
Quality of Life Scores (including Additional Items)		X	X	
Product Satisfaction			X	
ENT Exam			X	
Adverse Events		X	X	X
Protocol Deviations	X		X	X

6 Determination of Sample Size

Since the primary endpoint is composed of a safety and efficacy endpoint, the sample was determined by the primary objective on safety because it requires the larger sample size. The sample size calculation was estimated using data from previous studies with a precision-based calculation considering a minimum incidence of 14% of any adverse events with a sample size of 72 subjects will be able to obtain a 95% confidence level with a precision of +/- 9% (ranging from 5% to 23%). Considering a 25% withdrawal or potential dropout rate, a total of approximately 100 subjects will be enrolled (see details in section 13.1 of the Protocol).

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Disposition of subjects will be reported following the STROBE Statement Checklist. Number of individuals at each stage of study (number of total assessed for eligibility, number enrolled and number analyzed) will be reported. Reason for non-participation at each stage will be reported where known.

Table x - Number of Subject Screened and Enrolled by Site

Figure x – Flow diagram of Patient Disposition

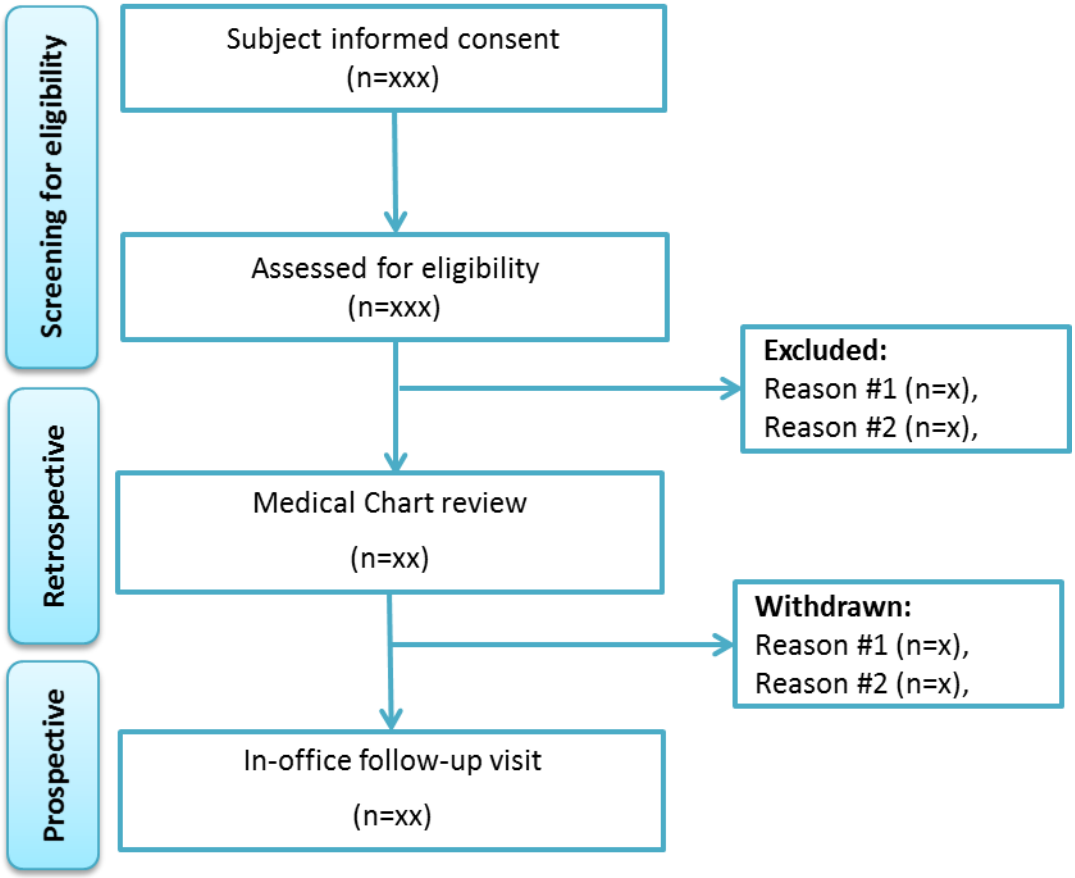


Table x - Screening for Eligibility by Inclusion and Exclusion Criteria

7.1.2 Clinical Investigation Plan (CIP) Deviations

All deviations will be collected in the case report form, with the type of the deviation and the reason for the deviation. All deviations will be reviewed by the clinical study team. The following tables will describe study deviations:

Listing x - Protocol Deviation term and reason

7.1.3 Analysis Set

The following subject set will be used for the analysis:

- The Full Analysis Set (FAS) includes **all** patients enrolled in the study who sign Patient Informed Consent and fulfill the inclusion and exclusion criteria. The FAS will be used to evaluate the primary safety endpoint.
- The Per Protocol Set (PPS) includes all patients enrolled in the study who sign Patient Informed Consent, fulfill the inclusion and exclusion criteria, and perform prospective activities. The PPS will be used to evaluate the primary effectiveness endpoint and secondary endpoints.

The following table shows how each population set will be used for analyses:

Table x – Analysis steps by population set

Population set	Baseline assessment*	Primary Safety Endpoints	Primary Effectiveness Endpoints	Secondary Endpoints
FAS	√	√		
PPS	√		√	√

*According to the clinical study team, baseline assessment on PPS will only be performed after evaluating the difference in sample size of FAS and PPS.

For those patients who drop out of the study, the analyses will include all data up to the point of their last data collection.

7.2 General Methodology

For all analyses descriptive statistics will be used to summarize patient characteristics. This will include mean, standard deviation, median, IQR, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. It is anticipated that SAS (SAS Institute Inc., Cary, NC, USA) will be used to perform all statistical analyses. Statistical tests will be based on a two-sided significance level of 0.05.

7.3 Center Pooling

Enrollment at any single site will not be limited. Based on the number of subjects enrolled by center an investigation of center effect will be performed by means summary statistics if needed.

7.4 Handling of Missing Data and Dropouts

No imputation of missing data will be performed.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons or multiple looks at data will be performed.

7.6 Derived variables

The statistical evaluations could use some derived variables calculated from collected data. All derived variables will be listed and reported.

New Variable	Derivation
Age at implant (years)	(Procedure date-Date of Birth)/365.25*
Time Diagnosis-Implant (months)	(Diagnosis date-Date of Implant)/365.25*
Device Exposure (days)	Study Evaluation/explant date – Procedure date*
Time to explant (days)	Explant date - Procedure date*
Derived Hz variables – method I	In order to obtain the PTA for all the subjects, we will derive the Hz values according to the following rules: If the Hz value is collected in the OC CRF then the derived dB variables will be equal to the collected dB value. Otherwise for the subjects that have no response (NR) at the limits of audiology testing for non-aided testing, we will derive the value, as agreed with the study team and audiologists, substituting a conservative dB value. In particular, if the NR limit is indicated then the derived Hz variable will be equal to the tested limit (e.g. if Hz value= NR105 then the derived Hz variable will be equal to 105), otherwise if the NR limit is not indicated then the derived Hz value will be equal to 100dB for the AC test and equal to 65dB for the BC test).
Derived Hz variables – method II	Also, a second method will be applied. As agreed with the study team we will derive the Hz values according to the following rules: If the Hz value is collected in the OC CRF then the derived dB variables will be equal to the collected dB value. Otherwise, for the subjects that have no response (NR) at the limits of audiology testing for non-aided testing, we will calculate the mean and standard deviation values on the entire cohort of responders at any Hertz level (e.g. 500Hz, 1000Hz, ect.) taking into account the type of test (AC or BC).Then we will derive the values substituting the mean + 2 * Standard deviation at any NR measure (both NR and NRxxx) according to the test type (AC or BC) for the SSD cohort. We will use these measures to perform analysis on SSD subset and we will compare graphically these results with the results of the same cohort (SSD subjects) evaluated with the first substitution method.

New Variable	Derivation
PTA (dB)	The PTA will be calculated as average of the derived audiogram Hz values. For the AC test all the available values at 250Hz, 500Hz, 1000Hz, 2000Hz, 3000Hz, 4000Hz and 8000Hz will be considered in the calculation. For the BC or Aided tests all the available values at 500Hz, 1000Hz, 2000Hz, 3000Hz and 4000Hz will be considered in the calculation. Missing or VT values will not be considered in the calculation.
Gain (dB) in the free-field pure tone audiometry	Absolute difference between PTA values
Time to first AE (days)	Study Evaluation- First AE occurrence date[1]
Total time in hospital (days)	Discharge date – Admission date

[1] if more than one procedure or event, consider the date of the first one.

7.7 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristic variables for FAS and PPS (baseline assessment on PPS will only be performed after evaluating the difference in sample size of FAS and PPS). This will include mean, standard deviation, median, IQR, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. Demographic and Baseline variables will be collected through: Demographic information, Diagnosis History, Procedure, Audiograms, Speech Recognition Threshold and Word Recognition, Quality of Life Scores, Additional items and Patient Satisfaction. The following tables will be reported:

Table x - Subject Demographic Characteristics
Table x - Diagnosis History by Ear
Table x - Procedure information by Ear
Table x - Audiograms (Retrospective)
Table x - Speech Recognition Threshold and Word Recognition Score (Retrospective)
Table x - Quality of Life (APHAB) (Retrospective)
Table x - Additional Items (APHAB) (Retrospective)
Table x - Audiograms (Prospective)
Table x - Speech Recognition Threshold and Word Recognition Score (Prospective)
Table x - Quality of Life (APHAB) (Prospective)
Table x - Additional Items (APHAB) (Prospective)
Table x - ENT Exam
Listing x - Outcome (if ENT Physical Exam Ear or Skin over Implant Abnormal)

7.8 Treatment Characteristics

Duration of **Device Exposure** will be measured for FAS and PPS, in days starting from the implant through and including the time of last evaluation: Duration of device exposure (days) = (Study evaluation/explant date – Procedure date). Extent of device exposure will be presented in a summary table and supporting data listing.

Table x - Device Exposure

7.9 Interim Analyses

Interim analyses are not planned for this study.

7.10 Evaluation of Objectives

In this section, detailed information about each objective is included together with calculations and derivations of outcome parameters (see table in section 7.6), analysis methods, datasets analyzed (FAS or PPS) and additional analyses where applicable.

7.10.1 Primary endpoint

The primary safety endpoint is the proportion of AEs related to the Sophono implant or surgery, which will be assessed through retrospective surgical chart review and prospective ENT exam. The primary safety endpoint will be evaluated on FAS. The AEs used for this endpoint are according to Investigator's determination of the event's relatedness to the device or surgery.

Adverse Event rates will be displayed together with their 95% confidence interval (95%CI) overall, by site and by type of event.

A time to first Adverse Event will be performed using survival analysis. The analysis will be supported by a Kaplan Meier curve indicating the number of patients at risk and any possible comparison of curves between groups will be done using the Log-Rank Test where appropriate.

Table x - Primary safety endpoint – Sophono Implant related Adverse Events rates
Figure x - Kaplan Meier estimate of first Sophono Implant related Adverse Event occurrence
Table x - Kaplan Meier estimate of first Sophono Implant related Adverse Event occurrence

The primary effectiveness endpoint is the absolute difference (gain) in the free-field pure tone audiometry assessed by PTA unaided (AC) and aided by the Alpha 2 MPO processor. The primary effectiveness endpoint will be evaluated on PPS.

The difference between unaided and aided measurements will be analyzed by means of paired (samples) t-test or Wilcoxon signed rank sum test according to the normal or non-normal distribution.

Additional analysis will be performed on:

- the "within indication" subset will exclude from the analysis subjects whose Prospective AC & BC tests do not meet the device indications for use.

- The subsets defined by implanted ear diagnosis. For the subject affected by SSD, analyses will be performed for both the derived variables (both NR substitution methods).

Table x - Primary effectiveness endpoint - Difference in PTA between unaided (AC) and aided by the alpha 2 MPO Processor (Audiogram Results Gain)

7.10.2 Secondary endpoints

For secondary endpoints the PPS population will be used for analysis.

7.10.3 Secondary endpoint#1

The secondary objective#1 will be evaluated as the difference in the free-field pure tone audiometry assessed by PTA aided by Alpha 2 processor compared to the PTA aided by Alpha 2 MPO processor. The difference between Alpha 2 and Alpha 2 MPO measurements will be analyzed by means of paired (samples) t-test or Wilcoxon signed rank sum test according to the normal or non-normal distribution.

Table x - Difference in PTA by device (Audiogram Results Gain)
Figure x - PTA by device type

7.10.4 Secondary endpoint#2

The secondary objective#2 will be evaluated as the change over time in the free-field pure tone audiometry assessed by pure tone average (PTA) aided in the Sophono Alpha 2 and Alpha 2 MPO.
The change over time (Retrospective vs Prospective data) of the PTA measurements will be analyzed by means of paired (samples) t-test or Wilcoxon signed rank sum test according to the normal or non-normal distribution and reported for each processor (Alpha 2 and Alpha 2 MPO).
The plots for the mean change over time will be reported.

Table x - Change over time of PTA Aided by Alpha2 processor by time and Aided by Alpha2 MPO processor by time
Figure x - Change over time of PTA Aided by Alpha2 processor by time
Figure x- Change over time of PTA Aided by Alpha2 MPO processor by time

7.10.5 Secondary endpoint#3

The secondary objective #3 and secondary objective #4 will be evaluated as the subject satisfaction, via non-validated satisfaction questions and QOL assessment through validated Abbreviated Profile of Hearing Aid Benefit (APHAB) ™ assessment.
The analysis of this endpoint will be performed using descriptive statistics to summarize results of the questionnaires overall and by each item. This will include

mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.
The data will be summarized on the overall set of patients and by APHAB version (pediatric or adult version).

Table x - Subject Satisfaction and product features
Table x - Quality of Life - APHAB
Table x - Quality of Life – APHAB Adult version
Table x - Quality of Life – APHAB Pediatric version

7.10.6 Secondary endpoint#4

The secondary objective#2 will include the change over time in speech reception threshold and word recognition scores in the Sophono Alpha 2 and Alpha 2 MPO.
The change over time (Retrospective vs Prospective data) of the SRT (dB), WRS (%) and SNR Loss (%) measurements will be analyzed by means of paired (samples) t-test or Wilcoxon signed rank sum test according to the normal or non-normal distribution and reported for each processor (Alpha 2 and Alpha 2 MPO).
The plots for the mean change over time will be reported.

Table x – Change over time in speech reception threshold and word recognition scores aided by Alpha2 processor by time and by Alpha2 MPO processor by time
Figure x – Change over time of SRT (dB) aided by Alpha2 processor by time
Figure x – Change over time of WRS (%) aided by Alpha2 processor by time
Figure x – Change over time of SNR Loss (dB) aided by Alpha2 processor by time
Figure x – Change over time of SRT (dB) aided by Alpha2 MPO processor by time
Figure x – Change over time of WRS (%) aided by Alpha2 MPO processor by time
Figure x – Change over time of SNR Loss (dB) aided by Alpha2 MPO processor by time

7.11 Safety Evaluation

Adverse events will be presented using the MedDRA coding and with the following summary table and supporting data listing:

Table x – Adverse Event Summary

7.12 Study Exit

Descriptive statistics will be used to summarize the study exit reasons.
Table x –Study Exit

7.13 Changes to Planned Analysis

The analysis described in the CIP could differ from that presented in this SAP due to data availability.

Any possible comparison of Adverse Event rates will be compared by means of a mixed Poisson model. In the presence of over dispersion, negative binomial regression will be used. Over dispersion will be assessed both with a goodness-of-fit test and a likelihood ratio test for alpha=0. The incidence rate ratio (IRR) and 95%CI will be reported [IRR=rate group1 / rate group2].

Any specific events will be analyzed using survival analysis. The analysis will be supported by a Kaplan Meier curve indicating the number of patients at risk and comparison of curves will be done using the generalized Log-Rank Test where appropriate.

8 Validation Requirements

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment on the data. To ensure the quality of the results provided for the study in the form of tables, listings and figures, and the derived datasets the following processes are used:

- Statistical programming and analysis will be done by qualified programmer(s) and statistician(s) following applicable procedures and best practices.
- The derived datasets will be validated by a second programmer or statistician.
- The tables will be validated by a second programmer or statistician.
- Statistical results will be reviewed and confirmed by a second statistician.

The entire set of tables, listings, and figures (TLF) will be 100% checked for accuracy, completeness, and consistency prior to inclusion in the interim or final clinical study report. According to Medtronic SOPs the level II validation (the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output) will be implemented for both Datasets and TLFs.

9 References

1. http://www.strobe-statement.org/index.php?id=available-checklists

10 Statistical Appendices

10.1 Tables, Listings and Figures

Details for all tables, listings and figures that will be produced for the final report, are reported in the document SPR_ACES_v1_27APR2018 or subsequent.