

Statistical Analysis Plan (V1 14-AUG-2024)

Clinical Investigation Plan (CIP) Title:	iotaSOFT™ Insertion System for Use with Cochlear Implant Surgery in Pediatrics
CIP Number:	Protocol: iotaSOFT000002/ICI2301 V4.0: 13-NOV-2023
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1 INTRODUCTION

This document is a companion document to the Clinical Investigation Plan (CIP). It includes a comprehensive description of the intended statistical analyses to be performed and the presentation of the results and data collected for the study.

This Statistical Analysis Plan (SAP) is based on the approved CIP, document number iotaSOFT000002, V4.0, 13-NOV-2023.

Any deviation from the Statistical Analysis Plan that occurs after database lock will be reported in the Clinical Investigation Report (CIR) providing a justification for the deviation.

1.1 Study Design

This is a prospective, non-randomized, open-label study to evaluate the safety and effective use of the use of the iotaSOFT® Insertion System when used to assist with electrode array insertion during cochlear implant surgery in a pediatric population. Approximately 20-30 pediatric subjects scheduled for unilateral or bilateral cochlear implant surgery will be enrolled, such that a minimum of 20 sides/ears using iotaSOFT will be attempted. Enrolled subjects with one of the compatible cochlear implant models per iotaSOFT labelling, will be treated and followed through 1 month after CI surgery to provide safety and efficacy information on use of iotaSOFT. The device is currently approved for use in patients 12 years and older.

Up to five sites in the U.S. will enroll subjects 9 months up to 12 years old indicated for CI surgery in this study. Data may be analyzed and submitted to FDA after a minimum of 20 cochlear implant sides/ears with the assistance of iotaSOFT have been evaluated through the one-month follow-up visit. Up to 30 subjects may be evaluated to provide a variety of pediatric CI models and age groups. Subjects will be stratified across the proposed age range to accurately represent the target population with emphasis on the younger population (24 months and younger).

1.2 Study Objectives and Endpoints

The objective of the study is to evaluate safety and the effective use of the iotaSOFT Insertion System when used per intended use for insertion of a cochlear implant electrode array in a pediatric population. The purpose of the study is to allow for expanded indication for the use of iotaSOFT in patients 9 months and older. The primary endpoint of the study is device related-serious adverse events through 30 days after CI surgery/activation. Other endpoints include 1) Proportion of cases in which use of iotaSOFT during cochlear implantation was successful at inserting the electrode array, 2) Procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over, and 3) All adverse events (nonserious and serious) related to the iotaSOFT System.

1.3 Sample Size Justification

The total sample size will be a minimum of 20 uses of iotaSOFT. Subjects may have unilateral or bilateral implantation (per terms of inclusion criteria) with a new iotaSOFT System used for each cochlear implant. Therefore, it is expected that 20-30 subjects may be enrolled, with only one procedure performed per subject. In a previous study with iotaSOFT, there were 0 out of 21 subjects with an iotaSOFT-related SAE. Using an example of n=20, we can consider potential

results from the primary endpoint analysis. If there are 0 out of 20 iotaSOFT-related SAEs in this study, the 95% confidence interval for this rate would be (0, 0.168). If there is 1 iotaSOFT-related SAE out of 20 uses, the estimated rate would be 0.050 (5%) and the confidence interval would be (0.001, 0.249).

As detailed in the sections below, our formal primary analyses will be based on the entire sample. For purposes of descriptive and exploration, we will stratify the data according to the following ages groups: 9 to 24 months, >24 to 48 months, and >4 to 12 years. The samples sizes will be too small to provide meaningful results within strata. For example, the best-case scenario of observing 0 out of 4 subjects with an SAE would result in a 95% confidence interval for the underlying SAE rate that is very imprecise: 0 to 60.2%.

2 ENDPOINTS

2.1 Primary Endpoint

The primary endpoint of the study is iotaSOFT related-serious adverse events (SAEs) through 30 days after CI surgery/activation, measured by calculating the proportion of subjects with one or more SAEs.

2.2 Secondary Endpoints

Other endpoints include 1) Proportion of cases in which use of iotaSOFT during cochlear implantation was successful (defined below) at inserting the electrode array, 2) Procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over, 3) device deficiencies, and 4) All adverse events (nonserious and serious) related to the iotaSOFT System. The definition of “successful” is based on the following questions from the Surgeon Questionnaire: Were any electrode contacts extracochlear?, What was the desired estimated insertion depth?, and Was the desired insertion depth achieved?

2.3 Safety Endpoint(s)

The Primary Endpoint and many of the Secondary Endpoints are safety endpoints, as describe in 2.1 and 2.2. No additional safety endpoints outside of those identified in section 2.1 will be analyzed.

3 STATISTICAL ANALYSES

All data, including demographics and endpoints, will be recorded and analyzed. Descriptive statistics will be reported including mean, standard deviation, corresponding confidence interval, minimum, and maximum for continuous variables. Frequency and percentages/proportions will be used to summarize categorical variables.

3.1 Primary Endpoint

The primary endpoint is the iotaSOFT-related SAEs through the 30-day follow-up visit. The classification of related will be accepted if the relationship is reported as “related”, “probable”, or “possible” vs. “unlikely” or “not related”. Hence, for a particular SAE, this will be binary (relationship status is yes or no), and at the person level we plan to compute the proportion (rate)

of subjects who have at least one such SAE. Due to the modest sample size and likely rarity of the event, the normal approximation to the binomial is unlikely to be feasible. Thus, we will use the exact “test-based” approach, also called the Clopper-Pearson method, to calculate our confidence intervals. For example, in a previous study we observed 0 of 21 subjects with SAEs, which gives an estimated SAE rate of 0 and a 95% confidence interval of (0, 0.161). We intend to use SAS for these and other analyses.

In addition to our formal analyses on the overall dataset, for descriptive purposes we will also stratify our calculations to give estimated rates and confidence intervals for each group. Binary outcomes across strata will be compared using Fisher’s Exact test for binary outcomes. We will also consider age as a continuous variable and related that to presence of iotaSOFT-related SAEs via logistic regression. Because of the modest sample size, we will use the “exact” permutation-based method for this, which is available in SAS’s Logistic procedure using the “Exact” command.

3.2 Secondary Endpoints

Secondary endpoints include 1) Proportion of cases in which use of iotaSOFT during cochlear implantation was successful at inserting the electrode array (defined above in Section 2.2), 2) Procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over, 3) device deficiencies, and 4) All adverse events (nonserious and serious) related to the iotaSOFT System. Hence, additional analyses entail the proportion of cases in which use of iotaSOFT during electrode array insertion was successful at advancing the electrode array; procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over; the prevalence of device deficiencies; and all adverse events related to the iotaSOFT System. Some of these are binary (yes/no) outcomes and will be analyzed using the same “exact test-based” method described in Section 3.1. Others, such as array insertion time and speed, are numeric variables that will use standard t-based methods to estimate means and confidence intervals. If any of these numeric distributions are skewed, mathematical transformations (e.g., log or square root) will be used to compute the estimates and confidence intervals and then reverse transform them back to the original scale.

As in the case of the primary endpoint, we will test whether the secondary endpoints are related to age strata and/or actual age. For binary outcomes, the methods to do so are identical to those described for the primary endpoint (i.e., Fisher’s Exact test and exact logistic regression). For numeric secondary endpoints, age groups will be compared using one-way Analysis of Variance Models for normal data or the Kruskal-Wallis non-parametric test for non-normal data. To see if numeric secondary endpoints are correlated with numeric age, we will use Pearson correlation estimates for normal data or Spearman correlation estimates for non-normal data.

4 INTERIM ANALYSES AND PROTOCOL DEVIATIONS

4.1 Interim Analyses and Unblinding

We have no plans to perform interim analyses. We will analyze the entire dataset of 20-30 subjects after they have completed the study.

4.2 Protocol Deviations

We plan to analyze data from all subjects, including those where a protocol deviation occurred. In the analyses and reports, we will examine how protocol deviations may have affected our results.

5 REFERENCES

5.1 Internal References

Document Title	Number
Clinical Investigation Plan – November 2023	V4.0
ICI2301 Case Report Forms	V1.0
Study Data Validation Report	V1.0

5.2 External References

Document Title	Number
G220049 FDA Approval Letter	NA

6 CHANGE HISTORY

Version	Change	Author	Date
1.0	Initial Document Draft	Jeffrey D. Dawson, ScD	14-AUG-2024