

Clinical Protocol

iotaSOFT™ Insertion System for Use with Cochlear Implant Surgery in Pediatrics

Protocol: iotaSOFT000002
V4.0: 13-NOV-2023

Sponsor:

iotaMotion, Inc.
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Iowa city, IA 52240
Phone: 319-338-1492

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and good clinical practices.

Sponsor Approval:

Signature

Date

Print Name

Title

Confidential

No use or disclosure of this document is permitted without prior written authorization from Sponsor.

Confidential

Investigator Confirmation Page

iotaSOFT™ Insertion System for Use with Cochlear Implant Surgery in Pediatrics

Protocol: iotaSOFT000002, v4.0

Protocol Signature Page

I have read this protocol and agree to adhere to the requirements.

I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the governing regulatory requirements, good clinical practices and requirements outlined in this protocol and the Clinical Trial Agreement. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Clinical Site

Site Investigator Signature

Date

Printed Name

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1. Protocol Synopsis

Sponsor	iotaMotion, Inc. 14 1/2 S. Clinton Street Iowa city, IA 52240 Phone: 319-338-1492
Device	iotaSOFT™ Insertion System Indication for Use: The iotaSOFT Insertion System is intended to aid the surgeon in placement of cochlear implant electrode arrays into a radiographically normal cochlea by controlling the speed of implant insertion. The iotaSOFT Insertion System is intended for use in <i>‘...cochlear implant patients ages 9¹ months (or the current minimum indicated age per cochlear implant manufacturer) and older during cochlear implant procedures...’</i> using either a round window or cochleostomy approach. This study will seek to expand the indication to 9 months of age and older.
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 ray 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).
Objective	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.
Primary Endpoint	The primary endpoint of the study is to demonstrate safety of the iotaSOFT Insertion System through evaluation of iotaSOFT related serious adverse events through 30 days after CI surgery/activation.

¹ Currently, only the Cochlear Nucleus family of cochlear implants are approved for cochlear implantation from 9 months of age and up (P970051/172). Approval for pediatric cochlear implantation begins at 12 months of age for eligible candidates for Advanced Bionics and MedEl devices.

Additional Analyses	Additional evaluations from the study include the following: 1. Proportion of cases in which use of iotaSOFT during cochlear implantation was successful at inserting the electrode array. 2. Evaluate procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over. 3. Evaluate all adverse events (nonserious and serious) related to the iotaSOFT System.
Study Population	<u>Inclusion Criteria:</u> 1) Candidate for unilateral² or bilateral³ cochlear implantation according to indications for use with FDA approved cochlear implant devices, as listed below: a. Advanced Bionics HiFocus SlimJ b. Cochlear Slim Straight c. MED-EL Flex⁴ 2) Age 9⁵ months to less than 12 years old at the time of CI surgery. 3) Willingness to participate in the study and able to comply with the follow-up visit requirements. <u>Exclusion Criteria:</u> The subject must not have known or active medical issues that would preclude having a CI device, including: 1) Prior cochlear implantation in the ear to be implanted. 2) Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array or present an increased risk of aberrant insertion. 3) Craniofacial abnormality, temporal squamosal skull thickness less than 3mm, major cochlear lesions (e.g., fibrosis, fracture, or ossification), or cochlear malformations. 4) Deafness due to lesions of the acoustic nerve or central auditory pathway. 5) Diagnosis of auditory neuropathy. 6) Active middle-ear infection or tympanic membrane perforation in the presence of active middle ear disease. 7) Absence of cochlear development. 8) Additional medical concerns that would prevent participation in evaluations as determined by the investigator.

² Includes unilateral cochlear implant candidates diagnosed with SSD ages 5 years and older scheduled for implantation with ‘SSD approved’ MedEl or Cochlear Ltd. iotaSOFT compatible implants.

³ Unilateral cochlear implantation surgery at the time of study enrollment may include bilateral candidates undergoing sequential or simultaneous implantations.

⁴ Includes all MED-EL Flex lengths.

⁵ Currently, only the Cochlear Nucleus family of cochlear implants are approved for cochlear implantation from 9 months of age and up (P970051/172). Approval for pediatric cochlear implantation begins at 12 months of age for eligible candidates for Advanced Bionics and MedEl devices.

	9) Planned or current participation in a clinical study of an investigational device or drug.
Study Duration	Subject participation in the study is approximately three months from study enrollment through one month following cochlear implant activation. It is anticipated that enrollment will incur over a period of 9 months resulting in an expected total study duration of 12 months.

2. Introduction

2.1. Background

360 million people worldwide, or 5% of the global population, have disabling hearing loss (>40 dB). Moderate to severe hearing loss affects 6.3 million patients in the US, yet only 5-6% of people who meet cochlear implant (CI) candidacy criteria receive a CI.¹ The number of patients that could benefit from a CI is expected to dramatically rise which makes improving patient access to CI interventions of the utmost importance.

Since the first description of “atraumatic” insertion techniques in 1993,² numerous studies have shown that trauma to the cochlea during electrode insertion results in damage to delicate inner ear structures, reduced implant performance, and the potential loss of residual hearing.³⁻⁷ While electrode array insertion technique has been shown to play a critical role in implant performance, the current standard of practice remains the use of manual forceps in which the inherent limitations of human kinematics makes slow and steady insertions difficult to achieve in a consistent manner.⁸ Alternatively, there are dedicated implant-specific manual insertion tools which have limited to no ability to precisely control the insertion speed or insertion force variability. Therefore, there is a clear need for an insertion tool that performs slow and steady insertions for a more standardized and controlled technique.

Studies evaluating the effect of electrode array insertion speed on insertion forces have shown that greater speeds directly correlate with greater intracochlear forces.^{9,10} Further, multiple studies demonstrate that high insertion forces damage the delicate structures of the cochlea, limiting CI performance and increasing the likelihood of the loss of residual hearing.¹¹⁻¹³ High insertion speeds have also been shown to increase the prevalence of intracochlear pressure spikes which can cause damage to the inner ear similar to loud noise exposure.¹⁴⁻¹⁶

2.2. Technology Rationale

Known risks associated with manual cochlear implantation (the current standard of care) include electrode translocation, electrode tip fold-over, incorrect placement of electrode array, loss of residual hearing, and/or vestibular symptoms. Currently, experienced CI surgeons mitigate these risks by performing slow and steady atraumatic CI insertion techniques by hand.

The iotaSOFT Insertion System [DEN190055] provides the surgeon a standardized, more controlled, and consistent method of inserting the electrode array compared to manual insertion techniques. The system enables the surgeon to perform CI electrode array insertions more consistently and slowly than the capabilities of human motion. Literature shows consistent and slow insertions decrease the risk of additional hearing loss or vestibular symptoms from inherently uncontrolled, variable, and excessively forceful manual insertions.¹² The iotaSOFT Insertion System can provide consistency of electrode array insertions among different ENT surgeons, helping to ensure that each patient receives an equally slow and consistent insertion regardless of the surgeon performing the procedure or the electrode array used. The iotaSOFT insertion system enhances the surgeon’s ability beyond the capability of human motion during the electrode insertion and therefore has the potential to reduce the current risk profile inherent in the standard CI surgical procedure.

2.3. Device Description

The iotaSOFT™ Insertion System is designed to assist the surgeon during cochlear implantation by controlling the speed of electrode array insertion. The cochlear implant (CI) electrode array insertion system is designed to reduce electrode array insertion variability and forces. The system consists of a single-use, sterile drive unit connected to a reusable, non-sterile touch screen control console and foot pedal interface (Figure 2-1, Figure 2-2).

Currently iotaSOFT is a commercially available Class II device for use in cochlear implantation of compatible electrode arrays in patients ages 12 and older (DEN190055).



Figure 2-1 iotaSOFT Insertion System

Left: iotaSOFT Drive Unit and screwdriver in sterile packaging tray after Tyvek and sterile tray cover removed. Right: Controller and Accessories with computer console, power supply, rolling stand, foot pedal, and extension cables coiled on stand basket.

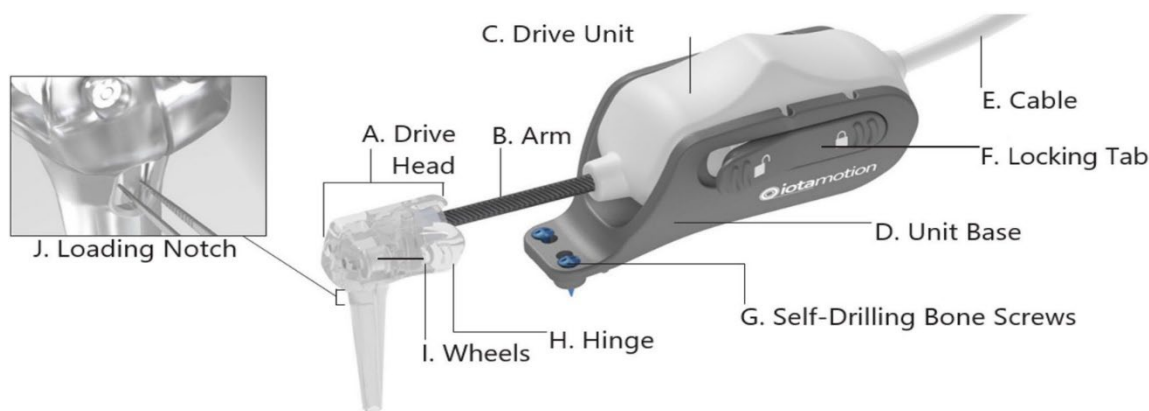


Figure 2-2 iotaSOFT Drive Unit

2.3.1. *Indication for Use*

The current indication for use in the approved population is the following:

The iotaSOFT Insertion System is intended to aid the surgeon in placement of cochlear implant electrode arrays into a radiographically normal cochlea by controlling the speed of implant insertion. The iotaSOFT Insertion System is intended for use in cochlear implant patients ages 12 years and older during cochlear implant procedures using either a round window or cochleostomy approach.

This study will seek to expand the indication to current age indications for use (lower it from 12 years) of the iotaSOFT Insertion System to 9 months⁶ of age and older.

2.3.2. *Use of iotaSOFT*

Study personnel should refer to the iotaSOFT Insertion System, Doc # 403-036-2000 v8 found in Appendix A for the full Instructions for Use. Pages 9 – 18 are specific to use of the iotaSOFT in electrode array insertion.

After standard mastoidectomy and facial recess approach for cochlear implantation, the surgeon secures the stage base to the skull at superior edge of mastoidectomy with two pre-loaded self-drilling bone screws (Figure 2-32 & 2-3). The drive unit is placed into the stage base and the adjustable drive head is coupled to a compatible CI electrode. Using manual manipulation, the drive unit head is positioned outside the facial recess and aligned to the surgeon-desired electrode array insertion trajectory. Before insertion begins, the surgeon selects the desired speed from 0.1mm/sec to 1.0mm/sec in 0.1mm/sec intervals. With direct access and view of the surgical site, the surgeon controls the electrode insertion forward and reverse motion via foot pedal while guiding the electrode array into the cochlea with standard CI instrumentation as necessary. Upon the completion of electrode array insertion and

⁶ Currently, only the Cochlear Nucleus family of cochlear implants are approved for cochlear implantation from 9 months of age and up (P970051/172). Approval for pediatric cochlear implantation begins at 12 months of age for eligible candidates for Advanced Bionics and MedEl devices.

securing the array at the cochlea, the drive head and unit are uncoupled from the electrode lead and removed from the patient for disposal. The surgical site is closed, and CI procedure is completed in the standard fashion.

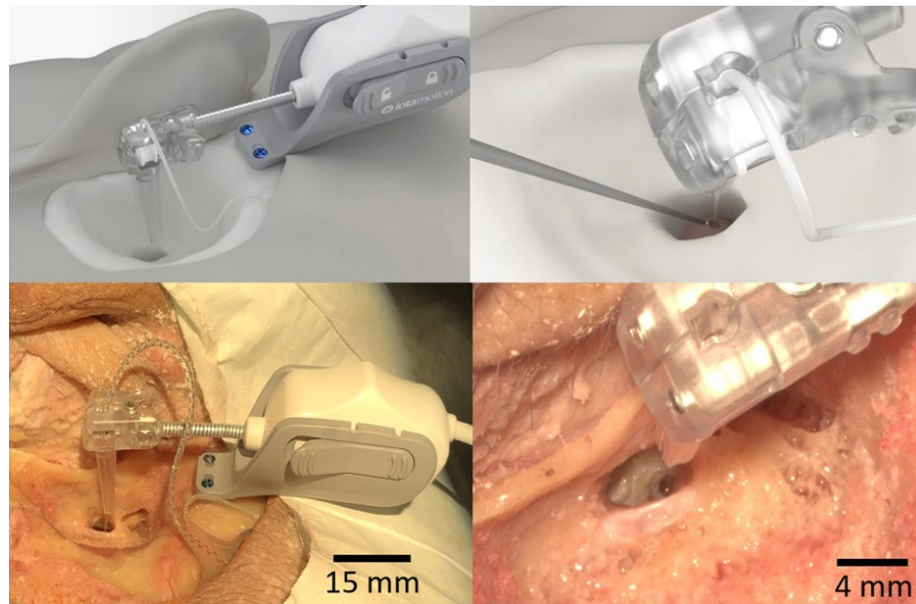


Figure 2-3. Image rendering (top) and cadaveric imaging (bottom) of iotaSOFT Drive Unit (Left: iotaSOFT Drive Unit secured at edge of mastoidectomy and electrode engaged in drive head outside the facial recess as intended during use. Right: Closer view of surgical site showing view of round window when in position during electrode array insertion.)

3. Study Design

3.1. Study Design

This is a prospective, non-randomized, open-label study 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. A goal of approximately 20-30 pediatric subjects (12 yrs of age and below to 9 mos.) scheduled for unilateral⁷ or bilateral⁸ cochlear implant surgery will be enrolled, such that a minimum of 20 sides/ears using iotaSOFT will be targeted up to 30, maximum. 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 and older.

⁷ Includes unilateral cochlear implant candidates diagnosed with SSD ages 5 years and older scheduled for implantation with ‘SSD approved’ MedEl or Cochlear Ltd. iotaSOFT compatible implants.

⁸ Unilateral cochlear implantation surgery at the time of study enrollment may include bilateral candidates undergoing sequential or simultaneous implantations.

Up to five sites in the U.S. will enroll subjects 9 months to less than 12 years old indicated for CI surgery in this study. It is anticipated that enrollment will incur over a period of 9 months resulting in an expected total study duration of 12 months.

3.2. Study 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 of age and older.

3.2.1. Primary Endpoint

The primary endpoint of the study is to demonstrate safety of the iotaSOFT Insertion System through evaluation of iotaSOFT related adverse events and serious adverse events through 30 days after CI surgery/activation.

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.

3.2.2. Additional Analyses

Additional evaluations from the study include the following:

1. Proportion of cases in which use of iotaSOFT during cochlear implantation was successful at inserting the electrode array.
2. Evaluate procedural characteristics such as electrode array insertion time, electrode array insertion speed, electrode positioning, and rate of tip-fold-over.
3. Evaluate all adverse events (nonserious and serious) related to the iotaSOFT System.

3.3. Subject Population

Subjects will be screened to verify that they meet all inclusion and no exclusion criteria prior to being enrolled in the study. Informed consent will be obtained from every subject or their parent/legal guardian before they are considered enrolled in the study. Subjects will be recruited into the study sequentially to represent the general pediatric population of those with hearing loss. Potential subjects must meet all of the inclusion criteria and none of the exclusion criteria to participate in the study.

3.3.1. Inclusion Criteria

- 1) Candidate for unilateral⁹ or bilateral¹⁰ cochlear implantation according to indications for use with FDA approved cochlear implant devices¹¹, as listed below:
 - a. Advanced Bionics HiFocus SlimJ
 - b. Cochlear Slim Straight
 - c. MED-EL Flex¹²
- 2) Age 9¹³ months to less than 12 years old at the time of CI surgery.
- 3) Willingness to participate in the study and able to comply with the follow-up visit requirements.

3.3.2. Exclusion Criteria

The subject must not have known or active medical issues that would preclude having a CI device, including:

- 1) Prior cochlear implantation in the ear to be implanted.
- 2) Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array or present an increased risk of aberrant insertion.
- 3) Craniofacial abnormality, temporal squamosal skull thickness less than 3mm, major cochlear lesions (e.g., fibrosis, fracture, or ossification), or cochlear malformations.
- 4) Deafness due to lesions of the acoustic nerve or central auditory pathway.
- 5) Diagnosis of auditory neuropathy.
- 6) Active middle-ear infection or tympanic membrane perforation in the presence of active middle ear disease.
- 7) Absence of cochlear development.
- 8) Additional medical concerns that would prevent participation in evaluations as determined by the investigator.
- 9) Planned or current participation in a clinical study of an investigational device or drug.

⁹ Includes unilateral cochlear implant candidates diagnosed with SSD ages 5 years and older scheduled for implantation with 'SSD approved' MedEl or Cochlear Ltd. iotaSOFT compatible implants.

¹⁰ Unilateral cochlear implantation surgery at the time of study enrollment so does not preclude bilateral candidates undergoing sequential implantations.

¹¹ With a cochlear implant model compatible with the iotaSOFT System per DEN190055.

¹² Includes all MED-EL Flex lengths.

¹³ Currently, only the Cochlear Nucleus family of cochlear implants are approved for cochlear implantation from 9 months of age and up (P970051/172). Approval for pediatric cochlear implantation begins at 12 months of age for eligible candidates for Advanced Bionics and MedEl devices.

4. Study Procedures

4.1. Informed Consent and Screening

The written Informed Consent forms will meet requirements for subject information, as outlined in FDA regulations (21 CFR Part 50) and the Declaration of Helsinki. Informed consent will be obtained from every subject and/or their legal guardian in a manner compliant with regulations before any study related procedures are performed. Subjects/guardians must be informed about the study and the potential benefits and risks of participation. Only those subjects/guardians who voluntarily provide written consent to participate will be allowed to continue in the screening process. A potential subject/guardian must go through the informed consent process per the governing Institutional Review Board (IRB) regulations for pediatric consent and sign and date an IRB approved consent document. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject/guardian.

Once a subject has been determined a candidate for cochlear implantation, according to approved indications, the subject will be invited to participate in this study. After documenting informed consent, the unique subject identifier will be assigned in a sequential manner for each subject. A sample Informed Consent form is found in Appendix B.

4.2. Baseline Procedures

Subjects that qualify for the study will have the following data collected and reported on the Baseline case report form:

- Confirmation of inclusion/exclusion criteria
- Age at time of CI surgery, demographics
- Otologic medical history and etiology
- Medication regimen

4.3. CI with iotaSOFT Procedure

Only FDA approved cochlear implants¹⁴ for approved indications and patient age will be used in this study.

Preparation and surgical procedures include institutional standard of care in addition to the use of the iotaSOFT system for electrode array insertion rather than manual insertion. Use of iotaSOFT will be according to the system instructions for use to ensure the sterile field is not compromised and system is operational. Preoperative preparations are also recommended to follow cochlear implant manufacturers' recommendations and professional organizations' standard of care steps including imaging studies, especially with pediatric candidates.

Study personnel should refer to the iotaSOFT Insertion System, Doc # 403-036-2000 v8 found in Appendix A for the full Instructions for Use. Pages 9 – 18 are specific to use of the iotaSOFT in electrode array insertion.

¹⁴With a cochlear implant model compatible with the iotaSOFT System per DEN190055.

CI surgery will be conducted per each surgeon's standard clinical practice and surgical approach including cortical mastoidectomy and facial recess approach to the cochlea for cochlear implantation. The surgeon will secure the stage base to the skull at superior edge of mastoidectomy with two pre-loaded self-drilling cortical bone screws and supplied sterile screwdriver. The drive unit is placed into the stage base and the adjustable drive head is coupled to a compatible CI silicon lead by clasp clip action onto the CI excess silicone lead away from the electrode array. With manual surgeon manipulation, the drive unit head is positioned outside the facial recess and aligned to the surgeon-desired electrode array insertion trajectory.

Microscope video recording will be conducted during the electrode insertion while using iotaSOFT.

Before insertion begins, the surgeon selects the desired speed from 0.1mm/sec to 1.0mm/sec in 0.1mm/sec intervals using foot pedal controller. With direct access and microscopic view of the surgical site, the surgeon advances or retracts the electrode array via foot pedal while guiding the electrode array into the cochlea with standard manual CI instrumentation as necessary. Upon the completion of electrode array insertion and securing the array at the cochlea, the surgeon unclips the drive head and unit from the excess silicone lead then removes the device and screws from the patient for disposal.

Should the surgeon need to quickly revert to alternative standard manual insertion techniques at any point during a CI procedure, this can be accomplished immediately without the need to modify the surgical approach or perform additional surgical steps aside from uncoupling of the iotaSOFT drive head from the CI lead in seconds.

For bilateral CI procedures, one ear will be implanted using the iotaSOFT drive unit and data will be collected for the enrolled ear.. For unilateral procedures or staged CI procedures, iotaSOFT will only be used and data collected for one side.

The following information will be documented and reported on the Procedure case report form:

- Surgeon experience survey of use of iotaSOFT, such as estimation of electrode array insertion time, insertion speed, successful use of the device, electrode positioning, malfunctions, etc.
- Procedure duration, estimated blood loss, CI device models, implant success, length of hospital stay
- Intraoperative X-ray¹⁵ evaluation of electrode position
- Adverse event assessment

Additionally, if available, the microscope video recording of electrode insertion will be submitted to the sponsor for evaluation of insertion duration.

¹⁵ If consistent with surgeons' standard of clinical practice, otherwise is optional.

4.4. Follow-Up Procedures

Subjects will be followed per institutional standard of care. For purposes of this study, subject data collection will occur at the CI activation visit and 1 month after CI surgery/activation.

Activation visit: The timing of the activation visit will be institutional standard of care.

1 month follow-up visit: 30-60 days after CI surgery

Post-surgery impedance will be collected at the initial activation visit of the CI and at 1 month post-CI surgery/activation using the site standard of care non-invasive measurement techniques per CI manufacturer guidelines. The following data will be documented and reported to the study sponsor on the Follow-Up case report form:

- Impedance: within normal limits or abnormal at activation and 1 month
- Neural telemetry: if collected as standard of care, report normal/abnormal, if abnormal provide report or reasoning why
- Adverse event assessment including readmissions since CI surgery

4.5. Data Collection Summary

Table 4-1 summarizes the data to be collected during the study.

Table 4-1 Summary of Data Collection Timeline

	Baseline Within 30 days	Procedure Day 0	Activation Visit Day 14- 28 ± 5 days)	1 Month Post- Op Visit Day 35-56 (± 5 days)
Consent, I/E confirmation	X			
Otologic history, demographics	X			
iotaSOFT user questionnaire		X		
Intraoperative X-ray		X ¹⁶		
Microscope video recording		X ¹⁷		
Impedance			X	X
Neural telemetry			As SOC	As SOC
AE assessment		X	X	X

4.6. Data Collection Methods

To ensure data quality and completeness, all required data will be reported via electronic case report forms (eCRF). The investigator will identify personnel responsible for recording data onto the case report forms (CRFs). Case report forms should be completed accurately and

¹⁶ If consistent with surgeons' standard of clinical practice, otherwise is optional.

¹⁷ Recorded during electrode insertion and use of iotaSOFT if available intraoperatively

completely and in a timely manner after each study visit. The Investigator will review the case report forms and sign them certifying their accuracy. Completed CRFs are to be submitted to the Sponsor or designee within two weeks of completion of a study visit or made available for review during a monitoring visit. The following types of eCRFs will be available for this study:

- Baseline
- Procedure
- Follow-up
- Adverse Event
- Protocol Deviation
- Study Exit

Personnel at the site responsible for data entry will receive training on the electronic database system prior to first use.

4.7. Early Discontinuation

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the Investigator must ensure that there is documentation for the reason for the withdrawal (e.g., a signed note from either the subject or the Investigator stating the reason for withdrawal) on the Study Exit CRF. The Investigator should attempt to determine the status of unresolved adverse events (AEs) and the subject's medical status at the time of discontinuation. The Investigator can decide to terminate a subject's participation due to safety reasons or if the relation between benefit and risk is no longer acceptable. If the subject had any unresolved AEs at the time of withdrawal, the Investigator should request continued communication with the subject until resolution of the AE, if possible.

Given the short follow-up duration of the study, every effort by site investigators should be made to retain subject participation for the duration of the study.

Subjects should only be considered lost to follow-up after significant effort has been made to contact the subject. At a minimum there should be 3 documented telephone contact attempts and one certified letter sent to the subject's last known residence.

In the event of subject death during the study, the Study Exit eCRF should be completed.

4.8. Adverse Event Reporting

Adverse Events will be reported and documented throughout the duration of the study. All reported events will be recorded on case report forms and determinations will be made as to the whether the events are Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Effects, and/or related to the IotaSOFT device.

Surgical revisions during the follow-up period will be reported via Adverse Event case report forms.

4.8.1. AE Definitions

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

Adverse Device Effect (ADE): AE related to the use of an investigational device.

Serious Adverse Event (SAE): Any AE that led to death, or led to a serious deterioration in the health of a subject that either resulted in a life-threatening illness or injury, permanent impairment of a body structure or a body function, in-patient or prolonged hospitalization or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.8.2. Adverse Event Relatedness

The relatedness of the AE to iotaSOFT will be determined by the Investigator using the following definitions:

Related: The AE follows a reasonable temporal sequence from the time of index procedure. This includes an AE that occurs during the index procedure and during the follow-up period.

Probable: The AE follows a reasonable temporal sequence from the time of index procedure and the possibilities of factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded.

Possible: The AE follows a reasonable temporal sequence from the time of index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.

Unlikely: The AE has an improbable temporal sequence from the time of index procedure, or it can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Not related: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

4.9. Protocol Deviation Reporting

A protocol deviation refers to a study-related activity that is not in compliance with the investigational protocol. Deviations that are required to protect the life or well-being of a subject do not require prior approval from the Sponsor and should be implemented immediately. The IRB and Sponsor must be notified within 5 (five) days of such an event.

5. Study Management

5.1. Product Training

Recommended training specific to use of the iotaSOFT Insertion System is conducted by iotaMotion personnel and includes both classroom instruction and hands-on simulated surgeon use of the iotaSOFT in either synthetic or cadaveric temporal bones with the indicated electrode arrays. The iotaSOFT Insertion System should be used by surgeons who have a) developed adequate skills to perform the tasks associated with the cochlear implantation procedure, b) read and followed the iotaSOFT Instructions for Use, and c) completed a recommended training session in the use of this device and demonstrated proper use in synthetic or cadaveric temporal bone prior to use in patients.

The recommended training provided by iotaMotion is limited to the use of the iotaSOFT Insertion System and does not replace the necessary medical training and experience required to perform cochlear implant surgery. The iotaSOFT Insertion System is a surgical instrument designed to provide assistance to the surgeon during cochlear implantation; it is not a substitute for the surgeon's experience and skill. As an adjunct surgical assist instrument that may be used during cochlear implantation electrode array insertion, the surgeon should determine its suitability for use with each surgical candidate based on anatomical characteristics of a patient which may preclude using the iotaSOFT Insertion System. The surgeon may elect to default to a manual insertion technique based on their best medical judgement at any time prior to or during the procedure.

5.2. Devices

Device accountability records will be maintained for iotaSOFT devices during the study. Upon receipt of devices at the clinical site, the lot and serial numbers will be recorded on the Device Accountability Log and devices will be maintained in a secured location with access only available to the investigator.

Once used, the subject ID number, date of use, and disposition of each device will be recorded on the Device Accountability Log. At the conclusion of enrollment, all unused devices will be returned to the sponsor.

5.3. Monitoring

The Sponsor or designee will monitor the progress of the study as required by Good Clinical Practices (GCP) and as specified by a separate study monitoring plan. This will include routine, periodic visits to study sites to compare reported results with source documentation.

The Investigator and site personnel will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data as requested. Each site will be monitored at least once during the study according to the Monitoring Plan. Monitoring will consist of reviewing of subject records, source documents, and other required documentation, including IRB approvals and correspondence. Site personnel must be available to meet with the monitor or other study Sponsor designee during site visits.

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

5.4. Confidentiality

All information and data sent to the Sponsor or designee concerning subjects or their participation in this study will be considered confidential. Subjects' names or identifying information should not be used on any correspondence to the Sponsor. Subjects will be assigned an identification number instead, for their participation in the study.

Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to a patient. The Investigator consents to the visits by the Sponsor and its representatives and the FDA or any other governmental body to review the study subjects' medical records.

5.5. Ethical Considerations

This study will be conducted in accordance with Good Clinical Practices, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements. The protocol and Investigator will comply with International Standards, and the site's respective institutional review board.

Procedures required for this protocol will not begin until the required approval from the IRB has been obtained. Any additional requirements imposed by the IRB shall be followed. The reviewing IRB will be an independent review panel responsible for ensuring the protection of the rights, safety and well-being of study subjects.

Investigators must submit the study protocol to their IRB and obtain the IRB's written approval before being allowed to conduct and participate in the study. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc. The Investigator will provide the Sponsor or designee with copies of such approvals and reports.

The Sponsor or designee will maintain a list of Investigators, locations, and qualifications for participation in this study. Training of the Investigator will be documented and include adherence to GCP.

5.6. Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. Records are subject to inspection by the monitor and regulatory agencies. The Investigator should maintain the following records related to the study:

- Signed Clinical Trial Agreement and recent curriculum vitae
- Written copy of the IRB approval, informed consent document, recruiting materials and IRB correspondence
- Signed copy of the study protocol and amendments, if any

- All significant correspondence which pertains to the investigation
- Subjects' case history records, including signed subject informed consent form; all relevant observations; observations of adverse device events; medical history; completed worksheets; documentation of the dates and reasons for any deviation from the protocol
- Copy of the Delegation of Authority Log
- Curricula vitae of the Investigator and sub-investigators
- Device Accountability Logs
- Signed financial disclosure forms, if applicable

5.7. Investigator Reports

A list of Investigator required reports is outlined in Table 5-1.

Table 5-1 Investigator Reports

Investigator Report	Submit To	Description
Withdrawal of EC approval	Sponsor	Notification within five working days.
Serious AEs	Sponsor	Immediately and no later than 24 hours
Serious AEs	IRB	As required
Progress Report	IRB	The Investigator must submit this report at regular intervals, but not less than once per year per IRB.
Deviations from protocol	Sponsor	Report of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Notification within five working days.
Deviations from protocol	IRB	As required
Final Report	IRB	Within three months of study termination or completion as required by IRB.

5.8. Sponsor Responsibilities

The Sponsor's or its designee's responsibilities in the study include:

- Provide training to Investigators and study site staff
- Select the Investigator, and other consultants (e.g., monitors) who participate in the study
- Provide financial support to each study site
- Ensure completion of site monitoring of clinical data at clinical study sites
- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes
- The Sponsor or designee will maintain records of the name and address of the reviewing IRB, documentation of their decisions regarding the study, and approved consent document.

5.8.1. Site and Investigator Selection

Each clinical investigator and site will be qualified through the sponsor qualification procedure. The clinical study sites will be selected based on the availability of the subject pool to be included in the study. The selected Investigators must be specialists in CI surgery of pediatric patients. Healthcare professionals or site staff that assist with the study-related data collection do not need to be trained for standard of care practices. Delegation of duties will be authorized by the Investigator and documented on a Delegation of Authority Log. A copy of the sample Clinical Trial Agreement with the investigator is found in Appendix D.

5.8.2. Amending the Protocol

Any changes to the protocol must be submitted to the FDA and IRB for review and approval prior to incorporating them into study. Any change that would require alteration of the ICF must receive approval from the IRB prior to implementation. Following approval, the protocol amendment will be distributed to all protocol recipients at the site.

5.9. Publication

Results from this study may be submitted for publication. The Sponsor will retain the rights to the data for use for regulatory approval and/or publication. Publication or presentation of the study data, study procedure, or related items may not be created or distributed without the Sponsor's written consent.

6. Risks and Benefits

6.1. Risks

The risk profile of the iotaSOFT Insertion System is predicated on the fact that the vast majority of the CI implantation procedure remains unchanged from manual CI insertion techniques. Likewise, the critical risks associated with use of the iotaSOFT Insertion System are also associated with manual insertion, meaning the iotaSOFT Insertion System does not add critical risk to the surgical procedure. Use of the device also does not prevent a surgeon from stopping at any time and immediately reverting to manual insertion techniques, and therefore the risk to the patient does not exceed the current gold standard of care.

In a prior clinical study of 21 adult CI surgery cases in subjects 25 years and older, there were no clinically significant patient safety or iotaSOFT outcomes differences based on surgeon years of practice experience nor cochlear implantation experience. Consistent with the device's intended use, no residual hearing measures, vestibular outcomes, and speech recognition metrics were reported in the clinical study. Furthermore, electrode array impedance measures were within normal limits as of one month follow-up, and adverse events were generally unremarkable. One event of CSF leak was reported when an otologic drill was used to create a pilot hole, although use of drill is not according to the iotaSOFT instructions for use.

The risks associated with use of the study device, iotaSOFT, for the implant procedure will be included in the subject informed consent document and may include the following:

- Inability to utilize the iotaSOFT for electrode array insertion due to anatomical constraints resulting in manual insertion techniques
- Damage to dura resulting in CSF leak
- Further loss of residual hearing at the implant ear.

6.1.1. Risks Associated with CI Surgery

Risks associated with all operations include pain, scarring, bleeding, and infection. The use of medicine to help you sleep (anesthesia) during the operation also has risks for the heart, lungs, kidneys, liver, and brain and, in rare cases, can result in death.

Possible risks associated with all ear operations include:

- damage to the facial nerve
- damage to dura resulting in CSF leak
- dizziness
- infection
- bleeding
- numbness or stiffness around your ear
- things may taste different
- increased ringing in your ear (tinnitus)
- neck pain
- skin reactions

Risks associated with implantation of the CI include:

- A lump behind the CI ear
- The skin near the CI may become irritated, red, or breakdown
- The electrode may move in the inner ear, and speech understanding may become poorer
- The electrode may move and come through the eardrum or ear canal wall which may result in additional surgery
- Tinnitus may get worse
- Facial twitching, tingling
- Dizziness or pain caused by electrical stimulation
- Leakage of inner ear fluid, which may result in meningitis
- If there are surgical or other complications, the electrode may have to be taken out.
- Inability to use future CIs
- During insertion of the electrode in surgery, tip of the electrode array may fold over in your inner ear (less than 3% chance)

The long-term effects of electrode insertion and electrical stimulation of the cochlea are unknown beyond 20 years. Such effects may include new bone growth in the cochlea or deterioration of the nerve cells. The effects may be such that it is not possible to replace the electrode. The effects may also lead to an eventual decrease in your ability to hear.

6.2. Mitigation of Risks

The iotaSOFT Insertion System was evaluated against the current techniques to ensure no new risks (not listed above) were added. The current known risks associated with manual cochlear implantation, including electrode translocation, electrode tip fold-over, incorrect placement of electrode array, loss of residual hearing, or vestibular symptoms, are currently attempted to be reduced by experienced CI surgeons performing slow and steady atraumatic CI insertion techniques by hand. The iotaSOFT insertion system enhances the surgeon's ability beyond the limits of human motion capabilities and stabilization during CI insertions and therefore has the potential to reduce the current risk profile inherent in the standard CI surgical procedure. The risks associated with the iotaSOFT Insertion System have been successfully mitigated and are no worse than manual insertion. The iotaSOFT Insertion System is designed to not obstruct the view of the round window or cochleostomy site through the facial recess in adults and children. If the view is obstructed the surgeon should reposition the iotaSOFT drive head or revert to manual insertion. Skull thickness at the site of device placement can be verified on preoperative imaging studies or other methodologies per surgeon and institutional standard of care (e.g. measurement of skull thickness after mastoidectomy).

6.3. Benefits

The benefits of the device outweigh the minimal risks associated with the device. The iotaSOFT Insertion System provides the benefit of a 70% reduction in insertion force, 30% reduction in force variation (jerk), 180% reduction in variation between insertions with different surgeons or with different electrodes, and reduction in occurrence of electrode scala

translocations and tip fold-over when compared to manual insertion. The iotaSOFT Insertion System is not statistically different than standard manual insertion techniques related to insertion angle, intracochlear scala position, and electrode electrical functionality. The risks associated with the device are not a significant clinical risk and are further mitigated by device completed design verification and validation testing as well as training provided to surgeons before the device can be used on patients.

It is possible there may not be any benefit to the patient by participation in the study.

7. Statistical Methods

All data related to primary and additional analyses will be recorded. Descriptive statistics will be reported including mean, standard deviation, corresponding confidence interval, minimum, and maximum for continuous variables. Frequency and percentages will be used to summarize categorical variables.

7.1. Primary Endpoint Analysis

The primary endpoint is the evaluation of iotaSOFT-related adverse events and SAEs through the 1-month follow-up visit. This will be determined by the classification of an AE and an SAE per 4.8.1, and a relationship to iotaSOFT classified as related (reported as related, probable or possible) or not related (reported as unlikely or not related). This is a binary (yes or no) outcome for each person, so the estimated parameter is the probability (rate) of such events. 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 report the simple proportion as our estimate of the underlying probability, and then use the exact “permutation test-based” approach available in most statistical packages (SAS, Stata, R, etc.) to calculate our confidence intervals.

7.2. Sample Size Determination

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. 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).

7.3. Additional Analyses

Additional evaluations include 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; 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 permutation test-based” method describe in Section 7.1. 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. For the purposes of labeling, only descriptive statistics will be utilized in presentation of the ‘Additional Analyses’ as described in the introduction paragraph to **Section 7.0 Statistical Methods**.

7.4. Analysis Populations

The Intention-to-Treat (ITT) notion is not directly applicable to this setting since this is not a comparative study. However, the ITT principle of accounting for all subjects will be followed and subject withdrawal from the study will be described.

An age-stratified analysis will be performed per the breakdown as described below.

Up to 30 subjects with the following stratification:

- 8-10 subjects ages 9 – 24 months
- 8-10 subjects ages 24+ - 48 months
- 5 – 10 subjects ages 4 years – 12 years

Outcomes across strata will be compared using Fisher's Exact test for binary outcomes and two-sample t-tests (or Mann-Whitney-Wilcoxon Rank-Sum tests, if non-normal) for numeric outcomes.

7.5. Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed.

8. Abbreviations

Table 8-1 List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
CI	Cochlear Implant
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICF	Informed Consent Form
IRB	Institutional Review Board
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

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10. Protocol Revision History

Table 10-1 Protocol Revision History

Revision	Revisions
V1	Initial Release
V2.0	Revised with FDA requested changes/14MAR2022
V3.0	Revised with FDA additional requested changes/16MAR2022
V3.1	Revised with FDA final requested changes/17MAR2022
V3.2	Minor changes not implemented/released
V3.3	Annual reportable changes to date but not distributed
V3.4	Inclusive of annual reportable changes (V3.3) and changes to protocol per 5 day notice requirement

11. Appendices to Protocol

Appendix A: Instructions for Use

Appendix B: Sample Informed Consent Document

Appendix C: Sample Case Report Forms

Appendix D: Sample Clinical Trial Agreement