Cochlear Implantation for Single-Sided Deafness in the Medicare Population

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Version Number: v.1.0

January 14, 2022

Table of Contents

LIST OF ABBREVIATIONS

Example of abbreviations included in many study protocols include:

ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
CI	Cochlear Implant
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IC	Informed Consent
IRB	Investigational Review Board
MCL	Most Comfortable Loudness
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSD	Single-Sided Deafness
SSQ	Speech, Spatial, and Qualities of Hearing Scale
UADE	Unanticipated Adverse Device Effect
UHL	Unilateral Hearing Loss

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP), as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 58, 21 CFR Part 812)
- Good Clinical Practices

All investigators involved in the conduct of this study will be informed about their obligations in meeting the above commitments.

PROTOCOL SUMMARY

Title:	Single-Sided Deafness in the Medicare Population
Study Description:	The purpose of the study is to evaluate the safety and effectiveness of cochlear implantation in adults 65 years of age and older.
Objectives:	The primary objective of this study is to evaluate the effectiveness of cochlear implantation in patients ages 65 years and older with single-sided deafness. The secondary objective of this study is to evaluate the safety of cochlear implantation in patients ages 65 years and older with single-sided deafness. Additional secondary objectives describe the effectiveness of cochlear implantation in patients ages 65 years and older with single-sided deafness.
Study Endpoint:	Primary Endpoint: 1. Improvement on AzBio sentences in noise by 12 months post-activation with the cochlear implant (CI) when speech is presented to the front and noise is presented to the acoustic (contralateral) ear, as compared to the pre-operative best-aided condition Secondary Endpoints: 2. Similar speech in noise at 6 and 12 months post-activation, with speech presented to the front and noise to the CI ear or to the front, as compared to the pre-operative best-aided condition 3. Summary of speech perception in quiet for the implanted ear alone and for the contralateral ear at the pre-operative, 6-month, and 12-month intervals 4. Subjective report of perceived benefit on the Speech, Spatial, and Qualities of Hearing Scale (SSQ) at the pre-operative, 6-month, and 12-month intervals 5. Number and proportion of subjects experiencing a device-related adverse event throughout the duration of the study
Population:	Fifteen subjects will be enrolled in this study.
Number of Sites:	The study will include three sites across the United States and Canada.
Description of Study Device:	Subjects will be implanted with an approved MED-EL cochlear implant system. After implantation, subjects will be fit with an approved audio processor.
Study Duration:	The study is anticipated to last for two years from enrollment through final data analysis.
Participant Duration:	Individual subject participation will last for approximately 12 months or one year.

1 PURPOSE

The purpose of this study is to evaluate the safety and effectiveness of cochlear implantation in adults 65 years of age and older. Data will be collected in candidates meeting the current FDA-approved indication pre-operatively for 12 months post-implantation.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Unilateral sensorineural hearing loss, also known as single-sided deafness (SSD), is defined as profound sensorineural hearing loss in one ear, with normal hearing thresholds in the opposite ear. Patients who are diagnosed with unilateral sensorineural hearing loss often experience a reduced quality of life, as well as a reduction in speech perception abilities and the ability to tell where sounds originate (Dillon, et al., 2017). Single-sided deafness can affect all ages, in some cases presenting from birth and others being acquired later in life.

Previous treatment options for single-sided deafness include CROS or BI-CROS hearing aids as well as bone conduction devices. These treatment options work by transferring the signal from the deaf side to the better hearing side and, thus, do not provide hearing sensation to the deaf ear (Niparko, Cox, & Lustig, 2003). While devices intended to transfer sound to the better hearing ear can provide some awareness of sounds on the deaf side, they do not restore binaural hearing. In fact, these devices may demonstrate head shadow detriments when a masker (noise) is present on the side of microphone, or poorer hearing ear (Arndt, et al., 2017).

Cochlear implantation for single-sided deafness has been studied for over a decade, with initial research on patients who sought cochlear implantation as a treatment for incapacitating tinnitus (Van de Heyning, et al., 2008). Due to patient reports of other benefits after implantation, the impact of CI on speech perception, localization, and quality of life has been studied extensively in this population as well. Later reports demonstrated that cochlear implantation for unilateral sensorineural hearing loss can restore some binaural benefits for speech perception, localization and quality of life both over short and long-term observation intervals (Vermeire & Van de Heyning, 2009)(Mertens et al., 2017).

Approval for cochlear implantation for single-sided deafness was obtained by MED-EL in 2019. Data from the University of North Carolina at Chapel Hill reporting on 37 clinical trial subjects with SSD or AHL provided the bulk of evidence used to support this approval. Data from this study has been published and demonstrates significant improvements in speech perception in noise, localization, and quality of life. (Dillon, et al., 2017) (Buss, et al., 2018)

2.2 POTENTIAL RISKS AND BENEFITS

2.2.1 KNOWN POTENTIAL RISKS

The known potential risks for cochlear implantation in single-sided deafness follow the known risks for cochlear implantation in the bilateral hearing loss population. These risks include:

- Vertigo, dizziness, or balance problems
- Facial nerve problems including injury and unintended stimulation
- Impaired sense of taste
- Aural fullness
- Potential for swallowing difficulties
- Meningitis
- Infection
- Cerebrospinal fluid leak
- Perilymphatic fistula
- Tinnitus
- Implant migration/extrusion
- Skin flap problems
- Numbness or pain around the incision or coil site
- Headache
- Device-related problems including programming problems
- Device failure requiring explantation/reimplantation

2.2.2 KNOWN POTENTIAL BENEFITS

Subjects may experience an improvement in speech perception in noise, as well as in spatial hearing and localization ability compared to hearing pre-operatively. (Buss, et al., 2018) Subjects may also experience an improvement in quality of life after implantation, including decreased stress and fatigue and decreased listening effort.

Subjects in this study will have prior experience with a CROS or BI-CROS aid or other relevant device, and will have documentation of limited benefit from amplification in the ear to be implanted. As potential candidates will have tried non-surgical options and lack evidence of appropriate improvement, the potential benefit of cochlear implantation outweighs the risk for this population.

3 OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the effectiveness of cochlear implantation for single-sided deafness in the approved population of adults ages 65 and older. Safety outcomes will also be evaluated in this population.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate effectiveness of cochlear implantation for single-sided deafness in the approved population of adults ages 65 and older	Improvement on speech in noise by 12 months post-activation when speech is presented to the front and noise is presented to the acoustic hearing (contralateral) ear. The pre-operative, best-aided score will be compared to the 6-month and 12-month CI score for AzBio sentences in noise. Improvement is defined as greater than or equal to 10 percentage points.	The endpoint is based on pilot data indicating this condition shows the greatest potential for improvement from baseline to the post-operative interval.
Secondary		
To summarize effectiveness outcomes of cochlear implantation for single-sided deafness in the approved population	Similar speech in noise in two spatial conditions with the CI at 6 and 12 months post-activation, compared to the pre-operative, best-aided score. AzBio sentence in noise score will be summarized for two conditions: speech and noise presented from the front as well as speech presented to the front and noise presented to the CI ear.	Speech perception in noise in two spatial conditions will demonstrate that the CI either provides benefit or results in similar performance (within 10 percentage points) post-operatively compared to the pre-operative aided condition.
	Summary of speech perception in quiet for the CI ear and for the contralateral ear at the pre-operative, 6-month, and 12-month intervals. The CI ear is expected to demonstrate improvement (greater than or equal to 10 percentage point change), while the contralateral ear is expected to demonstrate no change.	Individual-ear speech perception testing will provide verification that the implanted ear is receiving benefit from the CI while demonstrating the contralateral ear is not negatively impacted.
	Subjective report of perceived benefit on the Speech, Spatial, and Qualities of Hearing Scale (SSQ) at the pre-operative, 6-month, and 12-month intervals.	Quality of life data will provide supporting evidence that the cochlear implant is providing benefit post-operatively.
To evaluate safety of cochlear implantation for adults with single-sided deafness	Number and proportion of subjects experiencing an adverse device effect (ADE) throughout the studyexperiencing an ADE.	Safety outcomes are expected to be similar to the traditional cochlear implant population.

4 STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY DESIGN

Fifteen subjects will be recruited into this single-subject, repeated measures study to determine the safety and effectiveness outcomes of cochlear implantation for single-sided deafness in patients 65 years of age and older. Three centers across the United States and Canada will recruit subjects into this study. Each center will enroll up to 5 subjects.

Pre-operative speech perception and quality of life assessments will be conducted. All subjects will receive a MED-EL Cochlear Implant and will subsequently be fit with an approved audio processor. Post-operative evaluations will occur at 3, 6, and 12 months post-activation of the CI. Data will be analyzed from the 6- and 12-month follow-up intervals and compared to baseline data.

4.2 END OF STUDY DEFINITION

A subject's participation in the study is considered complete when he or she has completed the 12-month follow-up interval. The end of the study will occur when the last enrolled subject completes the final study visit.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Participants must meet the below inclusion criteria to qualify for this study. The below criteria follow the current FDA approval for single-sided deafness.

- 65 years of age or older at the time of implantation
- Unilateral profound hearing loss, as defined by a pure-tone average (500, 1000, 2000, and 4000 Hz) of 90 dB or greater in the ear to be implanted
- Sensorineural hearing loss in the ear to be implanted, as defined by an air-bone gap less than or equal to 10 dB at two or more frequencies out of 500, 1000, 2000, and 4000 Hz
- Normal or near-normal hearing in the non-implanted ear, as defined by a pure-tone average (500, 1000, 2000, and 4000 Hz) of 30 dB or less
- Word recognition in the ear to be implanted of 5% or less on CNC word score in quiet
- Previous experience with an appropriately-fit CROS, BI-CROS, bone conduction, or traditional hearing aid, as deemed appropriate by investigator
- Fluent in English

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual meeting one or more of the below exclusion criteria at the candidacy evaluation will not be eligible for enrollment in this study.

- Duration of profound hearing loss of 10 years or more
- Sudden onset of hearing loss within six months of implantation
- Evidence of non-functional cochlear nerve or other retrocochlear hearing loss
- Evidence of severe cochlear malformation (i.e., common cavity or ossification)
- External or middle ear infection
- Suspected cognitive concern
- Other medical contraindication for surgery or anesthesia

5.3 PARTICIPANT WITHDRAWAL OR TERMINATION

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects may voluntarily withdraw from the study at any point. The principal investigator may terminate a participant from the study for reasons outlined below.

- Lack of compliance with clinical trial protocol
- Poor physical health resulting in the inability to follow the protocol or schedule appointments at required intervals
- Any adverse event that occurs such that continued participation in the clinical trial is not in the subject's best interest

Subjects who choose to withdraw, are terminated from the study, or are considered lost-to-follow-up should be reported to MED-EL Study Monitors as soon as possible.

5.3.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Withdrawn subjects will continue to be seen by their clinical audiologist and surgeon for regular follow-ups, but no additional data will be collected. Reasonable attempts will be made to resolve adverse events reported on withdrawn subjects. Subjects may voluntarily withdraw from the study at any time without fear of repercussion or loss of benefit from the study device. When withdrawing, the subject should contact study personnel at their implanting site, who will contact the MED-EL Study Monitors.

6 STUDY DEVICE

The MED-EL Cochlear Implant System is an approved cochlear implant system consisting of the MED-EL Cochlear Implant, audio processor, programming interface, and the surgical kit. The implanted portion is surgically implanted under the skin behind the ear. It consists of a titanium housing and an active electrode array that is inserted into the cochlea during surgery.

Various active electrode arrays are available as part of the MED-EL Cochlear Implant. Included in this study will be the FLEXSOFT and FLEX28 electrode arrays. The FLEXSOFT electrode array is intended to be used in open cochleae (no obliteration or ossification) for an electrode insertion depth of about 31 mm. The FLEX28 electrode array is intended to be used in open cochleae (no obliteration or ossification) for

an electrode insertion depth of about 28 mm. The FLEX28 and FLEXSOFT electrodes are currently approved by the FDA and Health Canada.

The Patient Kit consists of the Audio Processor(s) and related accessories, chosen in various combinations by the subject. Audio Processors will be selected from the current approved processors. MED-EL's MAESTRO System software must be used to program the Audio Processors. Programming will be completed using the approved coding strategies and front-end features.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES

7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures will be performed over the duration of the study and will be documented for each subject enrolled in the study.

- Informed Consent (IC): Investigators will review the IC with potential subjects and obtain signature prior to initiating study activities.
- Medical Assessment: Subjects should be evaluated for their ability to undergo surgery. This should include a chart review to document prior surgeries and known health conditions, as well as ear-related history. All subjects should also undergo a complete otologic exam and radiologic assessment, for proof of patent cochleae, if this has not already been completed.
- Surgery: Cochlear implant surgery will be performed once a subject has consented to participate in the study and completed pre-operative assessment.
- Unaided Thresholds: Unaided air conduction thresholds will be measured pre- and post-operatively in both ears. Bone conduction thresholds will also be measured pre-operatively in order to determine whether hearing loss is conductive or sensorineural. Post-operatively, bone conduction thresholds should only be measured if a change of greater than 10 dB in PTA is noted for air conduction thresholds.
- Sentence Testing in Noise: AzBio sentences in noise will be administered at 60 dB SPL with a signal-to-noise ratio of 0 dB SNR. Pre-operatively, sentence testing will occur with a CROS hearing aid. Post-operatively, testing will occur with the cochlear implant on and the contralateral ear open. Three conditions will be tested: speech and noise from the front (S0N0), speech from the front and noise to the better hearing ear (S0Ncontra), and speech from the front and noise to the profound ear (S0Nci). One list will be presented per condition.
- Monosyllabic Word Testing: CNC words in quiet will be tested in each ear pre- and post-operatively. Pre-operatively, CNC word score will be assessed under insert earphones in each ear at the subject's most comfortable loudness level (MCL). Post-operatively, the non-implant ear will be assessed under insert earphones at MCL, while the implanted ear will be assessed through direct audio input at MCL with the CI on. The contralateral ear will be masked as needed. One list will be presented per condition.

- Subjective Questionnaires: Subjects will complete the SSQ (Gatehouse & Noble, 2004) pre-operatively and post-operatively.
- Cochlear Implant Mapping: Programming of the audio processor should occur at each interval after device activation.
- Adverse Event Reporting: Adverse events should be monitored throughout the duration of the study and reported within appropriate timeframes as required.

7.1.2 STUDY INTERVALS

- Enrollment/baseline
- Surgery (within 6 months of baseline)
- Cochlear implant activation (1-6 weeks post-operative)
- 3-months post-activation (10-14 weeks post-activation)
- 6-months post-activation (20-28 weeks post-activation)
- 12-months post-activation (48 – 56 weeks post-activation)

Testing can occur outside of the provided window with prior approval from MED-EL.

7.2 STUDY SCHEDULE

7.2.1 POTENTIAL SUBJECT IDENTIFICATION

Before completing any enrollment activities, medical and audiological charts should be reviewed for potential subjects. Subjects who appear to be suitable candidates for the study should have the testing set forth in Section 7.2.2 completed. Radiologic assessment completed as part of standard of care does not need to be repeated after consent/permission is obtained.

7.2.2 ENROLLMENT/BASELINE

Prior to completing any study-specific candidacy or baseline testing, subjects will sign an IC form.

All testing should occur in a sound-treated booth under insert earphones or in the soundfield with the subject seated one meter from the speaker, depending on the test condition.

Baseline testing will include the following outcome measures:

- Unaided audiogram, insert earphones
  - Pure-tone air conduction thresholds (125 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)
- Individual ear, speech testing in quiet, insert earphones
  - CNC Words in quiet at MCL
  - One list of 50 words will be presented to each ear individually
  - Lists will be randomized at each clinical trial site
  - Contralateral ear masked, as needed

- Bilateral, speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of 0 dB
  - Testing should be completed with a CROS or BI-CROS hearing aid, as applicable
  - One list of 20 sentences will be presented in each of three conditions, as follows:
    1. Speech and noise will be presented at 0° azimuth
    2. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the contralateral ear)
    3. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the ear to be implanted)
  - Lists will be randomized at each clinical trial site
- Subjective questionnaire
  - SSQ

7.2.3 SURGERY

Surgery will be completed within six months of the above pre-operative testing. If surgery is not completed within six months of baseline testing, the testing should be repeated to ensure accuracy. Recommended surgical steps should follow the approved Surgical Guide.

7.2.4 DEVICE ACTIVATION

Device activation will occur one to six weeks after surgery. No testing will be completed prior to fitting the device. The Audio Processor should be programmed in an approved Fine Structure coding strategy. Frequency filters should be set to 70-8500 Hz or 100-8500 Hz, or as otherwise deemed appropriate by the investigator. Default settings for front-end features should be implemented in at least one program, and the subject should be tested in that program. Programming should otherwise follow the clinical standard of care.

7.2.5 3-MONTH AND 6-MONTH FOLLOW-UP TESTING

Testing should occur as specified below. For soundfield testing, the subject should be seated one meter from the speaker.

Testing at these follow-up intervals will include the following outcome measures:

- Implant ear alone, speech testing in quiet, direct audio input
  - CNC Words in quiet at MCL
  - One list of 50 words will be presented
  - Lists will be randomized at each clinical trial site
- Bilateral, speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of 0 dB
  - Testing should be completed with the CI on and the contralateral ear unplugged or aided, as applicable
  - One list of 20 sentences will be presented in each of three conditions as follows:

1. Speech and noise will be presented at 0° azimuth
2. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the contralateral ear)
3. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the ear to be implanted)

- Lists will be randomized at each clinical trial site

- Subjective questionnaire
  - SSQ

Programming should be completed according to the recommendations from Section 7.2.4.

7.2.6 12-MONTH FOLLOW-UP TESTING

Testing should occur as specified below. For soundfield testing, the subject should be seated one meter from the speaker. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency across clinical trial sites.

Testing at these follow-up intervals will include the following outcome measures:

- Unaided audiogram, both ears, insert earphones
  - Pure-tone air conduction thresholds (125 – 8000 Hz)
  - Pure-tone bone conduction thresholds, only if shift in air conduction thresholds is noted (500 – 4000 Hz)
- Individual ear, speech testing in quiet
  - CNC Words in quiet at MCL through insert earphones to the contralateral ear
  - CNC Words in quiet at MCL through direct audio input to the CI ear
  - One list of 50 words will be presented to each ear individually
  - Lists will be randomized at each clinical trial site
- Bilateral, speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of 0 dB
  - Testing should be completed with the CI on and the contralateral ear unplugged or aided, as applicable
  - One list of 20 sentences will be presented in each of three conditions, as follows:
    1. Speech and noise will be presented at 0° azimuth
    2. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the contralateral ear)
    3. Speech presented at 0° azimuth, noise presented at 90° azimuth (toward the ear to be implanted)
  - Lists will be randomized at each clinical trial site
- Subjective questionnaire
  - SSQ

Programming should be completed according to the recommendations from Section 7.2.4.

7.2.7 SCHEDULE OF EVENTS TABLE

		Enrollment/ Baseline	Surgery	Activation	3 months post-activation	6 months post-activation	12 months post-activation
	Informed Consent	X					
	Medical Assessment	X					
	Surgery		X				
	Unaided thresholds	X					X
Implant Ear	CNC Words MCL	X			X	X	X
Non-implant Ear		X					X
Bilateral	AzBio 60 dB SPL 0 dB SNR S0N0, S0Ncontra, S0Nci (CROS)	X					
Everyday Condition	AzBio 60 dB SPL 0 dB SNR S0N0, S0Ncontra, S0Nci (CI on, aided if appl.)				X	X	X
	SSQ	X			X	X	X

(Figure 1)

7.3 PRECAUTIONARY PROCEDURES

The MED-EL Cochlear Implant is MR conditional. Subjects in the study may undergo an MRI at 1.5 or 3.0 Tesla, if required, over the duration of the study. Additional details on MRI scanning procedures can be found in the Medical Procedures Manual, available at: *http://www.medel.com/us/isi-cochlear-implant-systems/*.

8 ASSESSMENT OF SAFETY

8.1 DEFINITIONS AND CLASSIFICATIONS

As noted in Section 3, device-related adverse events will be recorded throughout the duration of the study to satisfy the safety endpoint. Reportable events and procedures are described below in Sections

8.1.1 through 8.1.3, 8.2, and 8.3. Specific adverse events of interest are those listed in Section 2.2.1 as known potential risks.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any unfavorable change in the health of a participant, including abnormal test results, that happens during a clinical study or immediately after the study has ended.

8.1.2 DEFINITION OF ADVERSE DEVICE EFFECTS (ADE)

Adverse events will be reported as related to the device if the event is known to occur with cochlear implant use or if there is a reasonable possibility that the cochlear implant caused the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the device and the event. Events occurring immediately after implantation or use of the device may also suggest a device-related adverse event.

Events can also be noted as procedure-related complications. Procedure-related events are those that do not directly result from use of the device. Examples of procedure-related complications include anesthetic-related complications associated with cochlear implantation.

8.1.3 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse events are considered serious when they result in death or any injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.

Examples of serious adverse events that would be reportable include infection or device failure requiring explantation of the cochlear implant.

8.1.4 DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

Unanticipated adverse device effects are defined as any event not previously in the investigational plan or IC. Risks associated with the device and procedure are detailed in Section 2.2.1 above. Events can be unexpected in nature, severity, or degree of incidence. This definition could include an unanticipated adverse device effect or other serious adverse effect associated with the device, if the problem was not previously identified in nature, severity, or degree of incidence.

8.2 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event may be brought to the attention of the investigator during study visits, interim visits, or phone conferences over the duration of the study. All adverse device effects will be reported on the Adverse Event Report Form CRF. Information to be collected on the Adverse Event Report Form CRF includes: event description, date of onset, time of onset, seriousness, relationship to the device, unexpectedness, and the date/time of resolution (if applicable). Adverse events will continue to be followed until reaching adequate resolution or stabilization.

8.3 REPORTING PROCEDURES

Any adverse device effect discovered in the course of the study should be reported on the Adverse Event CRF by an investigator according to Section 8.1 and reported to MED-EL. Investigators are responsible for determining whether or not the adverse event meets the definitions for device-related, serious, and/or unanticipated. Questions regarding classification should be brought to the attention of the MED-EL Study Monitors. All AEs should be reported to the MED-EL Study Monitors in a timely manner.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of subjects are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the trial is being conducted in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements. MED-EL Corporation personnel will be responsible for monitoring this investigation according to MED-EL Corporation's SOPs.

Training will be conducted prior to initiation of the investigation. Upon completion of training, investigators will have documented understanding of the following information:

- Obligation to conduct the study in accordance with the investigator agreement, GCP, and other applicable regulations
- Requirements for a well-controlled study
- Investigator's role in the process of obtaining IC
- Obligation to obtain and maintain IRB approval
- Importance of complete and accurate study records, including source documentation
- Required monitoring and clinical monitor access to the study records
- Time commitments for investigators involved in the study
- Details specific to the investigational plan

Case report forms and other related study documentation will be reviewed as MED-EL receives the completed documentation throughout the duration of the study. Completed study records will be reviewed 100% for missing data entries. Accuracy of study records will be monitored based on the investigator's history, accuracy of study records, the rate of adverse events, and the occurrence of protocol deviations.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A statistical analysis plan (SAP) will be created prior to the final analysis being performed for the study and will provide further detail to the statistical techniques that will be used for the analysis of the study endpoints.

10.2 STATISTICAL HYPOTHESES

The primary endpoint to be tested is performance on AzBio sentences in noise in the speech front, noise to the better hearing ear condition; the pre-operative, best aided condition will be compared to the 6-month post-operative, CI plus better hearing ear (unplugged or aided, as applicable) condition. Improvement will be defined as equal to or greater than a 10 percentage point increase in the score. The specific hypotheses being tested are:

$$Ho: \mu_{\Delta AzBio} \leq 10$$
$$Ha: \mu_{\Delta AzBio} > 10$$

where $\mu_{\Delta AxBio}$ is the average of the differences between a subject's 6-month AzBio sentence score and their aided baseline AzBio sentence score. The number 10 represents the superiority margin of 10 percentage points.

The analysis will utilize a standard one-sided paired T-test if the data are normally distributed or the Wilcoxon Signed Rank test if the data are not normally distributed. A resulting p-value of 0.05 or less will be considered significant and the null hypothesis will be rejected.

This analysis will be repeated using the results from the 12-month follow-up visit.

The secondary endpoints and the safety endpoint will be summarized using descriptive statistics such as the mean and standard deviation for continuous measures and a count and percentage for categorical measures.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documentation should be kept as part of the subject's medical records. Source documentation (e.g., medical history, audiologic history, audiograms) should be accessible to the MED-EL Study Monitors, as needed, for comparison to CRFs. Medical records kept on each subject will include information about the subject's participation in the clinical trial.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigator will ensure that the study is conducted in accordance with regulations for the protection of human subjects found in 21 CFR Part 50, 21 CFR Part 56.

12.2 INSTITUTIONAL REVIEW BOARD

The protocol, IC form, and any recruitment or participant materials will be submitted to the IRB for review and approval. IRB approval of both the protocol and IC must be obtained prior to beginning

enrollment. Any amendment to the study protocol must also receive IRB approval before those changes are implemented in the study. Changes to the consent form will also be submitted to the IRB; at that time, a determination as to whether or not previously consented subjects need to be re-consented will be made.

12.3 INFORMED CONSENT PROCESS

A consent form with detailed descriptions of the study device, study procedures, and risks will be given to study participants. Written documentation of IC is required prior to initiating any study-related activities. Template IC forms will be provided to each investigative site.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study protocol, documentation, data, and all other information generated will be kept in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of MED-EL. The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the clinical trial subjects.

All parties involved in a clinical investigation will maintain strict confidentiality to assure the protection of privacy of a subject participating in the clinical investigation. Likewise, appropriate measures will be taken to avoid the access of non-authorized persons to the clinical trial data.

All information provided to the investigator by MED-EL will be kept strictly confidential and confined to the personnel involved in conducting the trial. Such personnel will be informed of the confidential nature of the information. It is recognized that this information may be communicated in confidence to the relevant IRB. In addition, no reports or information about the trial or its progress will be provided to anyone not involved in the trial, other than MED-EL or the relevant IRB, except if required by applicable law or regulation.

All data provided to MED-EL will be identified by a unique subject ID, thereby ensuring that the subject's identity remains unknown. The subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with applicable regulations.

The subjects should also be informed that authorized representatives of MED-EL and/or regulatory authorities may require access to parts of the site records (relevant to the study), including medical history, for data verification. The investigator is responsible for keeping a subject identification list of all subjects screened and enrolled.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Prior to initiation of the study, investigators who may complete CRFs and are responsible for maintaining appropriate documentation will be identified. The investigator will be responsible for

maintaining complete and accurate documentation of study procedures and medical records, including IC, for the duration of the study. Data on subjects will be collected in an anonymous manner, and any records sent to MED-EL should be de-identified.

The investigator is responsible for ensuring completeness, legibility, and accuracy of the recorded data. Source documentation should be completed in a neat, legible manner to ensure accurate interpretation of the data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, write over, or use correction fluid or tape on the original document.

13.2 PROTOCOL DEVIATIONS

Any noncompliance with the protocol or with GCP requirements will be reported to MED-EL in the protocol deviation log as a protocol deviation. Protocol deviations may be on the part of the investigator, participant, or other study staff. Corrective actions will be implemented based on the type and frequency of protocol deviations from each site. It is the responsibility of the investigator to be familiar with the protocol and regulations and to be vigilant regarding potential protocol deviations. Deviations should be submitted to MED-EL and the IRB in a timely manner, as required.

14 LITERATURE REFERENCES

Arndt, S., Laszig, R., Aschendorff, A., Hassepass, F., Beck, R., & Wesarg, T. (2017). Cochlear Implant Treatment of Patients with Single-Sided Deafness of Asymmetric Hearing Loss. *HNO, 65*(Suppl 2), 98-108.

Arndt, S., Prosse, S., Laszig, R., Wesarg, T., Aschendorff, A., & Hassepass, F. (2015). Cochlear implantation in children with single-sided deafness: does aetiology and duration of deafness matter? *Audiol Neurotol, 20*(Suppl 1), 21-30.

Buss, E., Dillon, M. T., Rooth, M. A., King, E. R., Deres, E. J., Buchman, C. A., . . . Brown, K. D. (2018). Effects of Cochlear Implantation on Binaural Hearing in Adults with Unilateral Hearing Loss. *Trends Hear, 22*, 1-15.

Dillon, M. T., Buss, E., Rooth, M. A., King, E. R., Deres, E. J., Buchman, C. A., . . . Brown, K. D. (2017). Effect of Cochlear Implantation on Quality of Life in Adults with Unilateral Hearing Loss. *Audiology & Neurotology, 22*, 259-71.

Mertens G., De Bodt M., Van de Heyning P. (2017) Evaluation of long-term cochlear implant use in subjects with acquired unilateral profound hearing loss: Focus on binaural auditory outcomes. Ear and Hearing 38: 117–125.

Niparko, J. K., Cox, K. M., & Lustig, L. R. (2003). Comparison of the Bone Anchored Hearing Aid Implantable Device with Contralateral Routing of Offside Signal Amplification in the Rehabilitation of Unilateral Deafness. *Otology & Neurotology, 24*, 73-8.

Tavora-Vieira, D., & Rajan, G. P. (2015). Cochlear Implantation in Children with Congenital and Noncongenital Unilateral Deafness: A Case Series. *Otol Neurotol, 36*, 235-9.

Van de Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., & De Ridder, D. (2008). Incapacitating Unilateral Tinnitus in Single-Sided Deafness Treated by Cochlear Implantation. *Ann Otol Rhinol Laryngol, 117*(9), 645-52.

Vermeire, K., & Van de Heyning, P. (2009). Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. *Audiol Neurotol, 14*(3), 163-71.

Version	Date	Significant Revisions
1.0	13JAN2022	Original version