Expanded Indications in the Adult Cochlear Implant Population

IDE: G170111

NCT: 03236909

IDE Sponsor: MED-EL Corporation

2645 Meridian Parkway

Suite 100

Durham, NC 27713

Version Number: v.1.6

August 20, 2020

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
APHAB	Abbreviated Profile of Hearing Aid Benefit
ASM	Automatic Sound Management
CFR	Code of Federal Regulations
CNC	Consonant-Nucleus-Consonant
CRF	Case Report Form
CRO	Contract Research Organization
EAS	Electric-Acoustic Stimulation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HL	Hearing Level
IC	Informed Consent
IDE	Investigational Device Exemption
IRB	Investigational Review Board
PI	Principal Investigator
PTA	Pure-tone Average
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNR	Signal-to-Noise Ratio
SOP	Standard Operating Procedure
SPL	Sound Pressure Level
SSQ	Speech, Spatial, and Qualities of Hearing Scale
UADE	Unanticipated Adverse Device Effect
WNR	Wind Noise Reduction

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

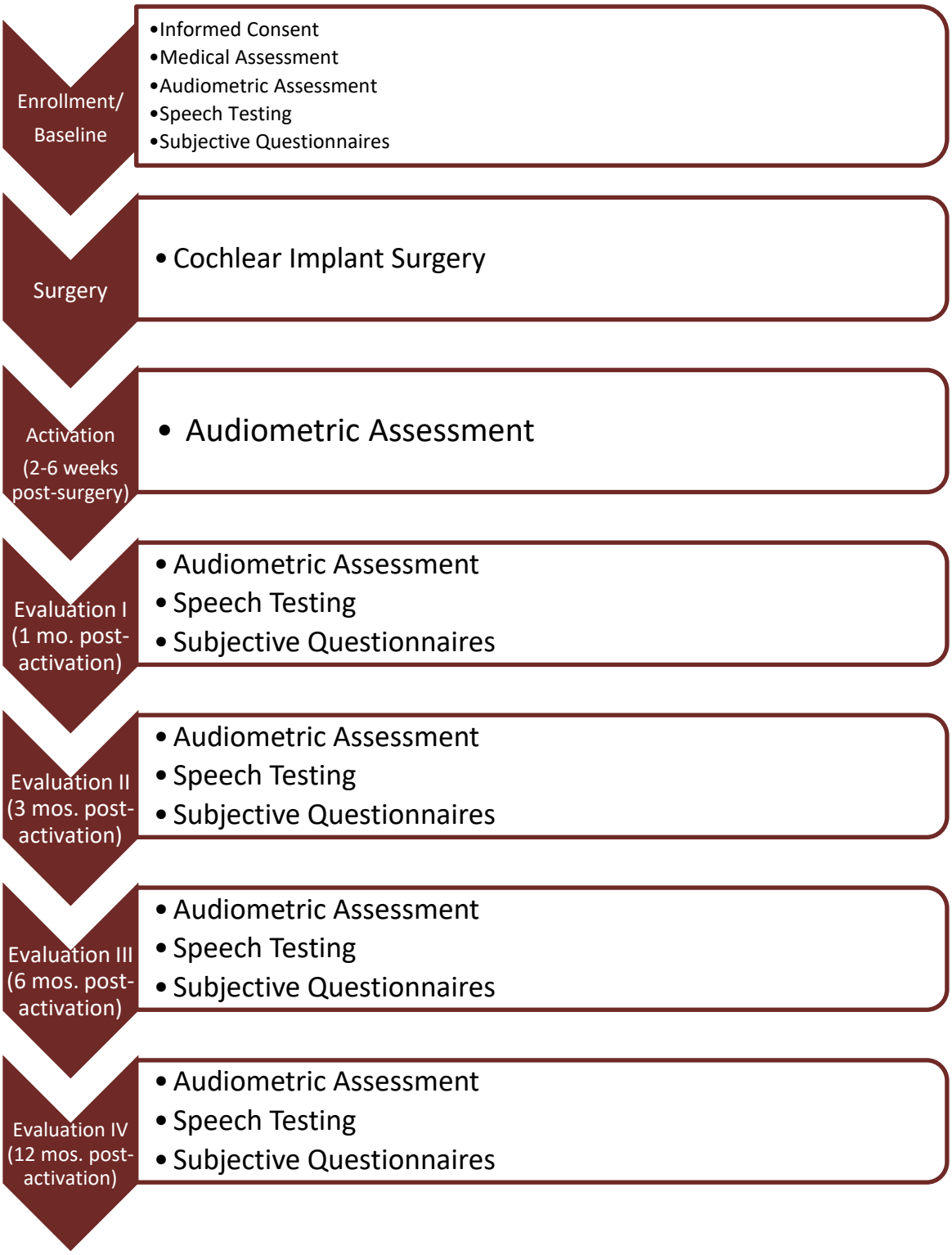
All investigators involved in the conduct of this study will be informed about their obligations in meeting the above commitments.

PROTOCOL SUMMARY

Title:	Expanded Indications in the Adult Cochlear Implant Population
Précis:	Fifty subjects with moderate to profound bilateral sensorineural hearing loss will be implanted with the MED-EL SYNCHRONY/SYNCHRONY PIN or SYNCHRONY 2/SYNCHRONY 2 PIN Cochlear Implant System. Subjects will be considered for the study if they are 18 years of age or older and demonstrate a CNC word score in quiet of 60% or less in the ear to be implanted. Subjects will be followed for six (6) months post-activation of the SONNET EAS or SONNET 2 EAS Audio Processor.
Objectives:	Co-Primary Objective: Subjects will demonstrate significant improvement in CNC word score in quiet in the implanted ear at six (6) months post-activation. Co-Primary Objective: Subjects will demonstrate significant improvement in AzBio sentence score in noise in the implanted ear at six (6) months post-activation. Secondary Objective: Subjects will demonstrate similar or better scores on AzBio sentences in noise in the everyday listening condition at six (6) months post-activation. Secondary Objective: Subjects will demonstrate similar or better responses on the APHAB and SSQ, when comparing the everyday listening condition at six (6) months to the everyday listening condition pre-operatively. Secondary Objective: Preservation of residual low-frequency hearing at six (6) months post-activation will be summarized and reported according to the HEARRING scale. Secondary Objective: Adverse events will be collected and reported by the number and proportion of subjects experiencing a device or procedure-related adverse event.
Study Endpoint:	Safety and effectiveness endpoints will be six months post-activation, with an additional follow-up visit at 12 months post-activation.
Population:	Fifty (50) subjects, 18 years of age and older, will be implanted across the United States and Canada.
Phase:	Phase 3
Number of Sites:	Six (6) sites will participate in the clinical trial.
Description of Study Device:	Subjects will be implanted with the MED-EL SYNCHRONY/SYNCHRONY PIN or SYNCHRONY 2/SYNCHRONY 2 PIN Cochlear Implant System with +FLEX^{28} or +FLEX^{SOFT} electrode arrays. Subjects will be fit with the SONNET EAS/SONNET 2 EAS (ear-level) and/or RONDO/RONDO 2/RONDO 3 (single-unit) external audio processors. Fitting parameters will include Fine Structure coding strategies as well as activation of Automatic Sound Management 2.0 within the MAESTRO System Software. All testing will be completed using the SONNET/2 (EAS) Audio Processor.
Study Duration:	Enrollment is expected to last two years, while subject follow-up will last an additional 14 months. Therefore, the study duration is anticipated to be 38 months, from enrollment to completion.
Participant Duration:	Each subject's participation in the clinical trial will last approximately

fourteen (14) months.

SCHEMATIC OF STUDY DESIGN



1 PURPOSE

The purpose of this investigation is to expand FDA-approved labeling for MED-EL cochlear implants to include adults who have moderate to profound sensorineural hearing loss and obtain limited benefit from appropriately fit hearing aids. Limited benefit from amplification is defined by test scores of 60% correct or less in the ear to be implanted (70% or less in the non-implanted ear) on monosyllabic words in quiet.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Under current FDA approval, candidates for MED-EL cochlear implants (CI) include adults with bilateral severe to profound sensorineural hearing loss demonstrating limited benefit from amplification, as defined by speech understanding scores of 40% or less on Hearing In Noise Test (HINT) sentences. This candidacy criteria was established upon approval of the MED-EL Combi40+ Cochlear Implant System in 2001. Since that time, clinical criteria used to determine CI candidacy has continued to expand for both speech perception and audiometric thresholds.

Conventional materials used as tests of speech understanding pre- and post-implantation range from monosyllabic words to sentences, that can be tested either in quiet or in noise. The Consonant-Nucleus-Consonant (CNC) Word Recognition Test is validated and used to assess monosyllabic word understanding (Peterson & Lehiste, 1962). The City University of New York (CUNY) Sentence Test, the Hearing in Noise Test (HINT), and AzBio sentences are commonly used sentence test materials. CUNY sentences consist of 72 sentence lists, scored as the number of words correctly identified out of each sentence (Boothroyd, Hanin, & Hnath, 1985). HINT sentences were originally designed to be presented in an adaptive format with background noise (Nilsson, Soli, & Sullivan, 1994). More recently, a description of the development and validation of the AzBio sentence lists was provided by Spahr and colleagues (Spahr et al., 2012).

A retrospective review of 100 cochlear implantations at the University of North Carolina at Chapel Hill yielded 12 subjects with CUNY sentence score in quiet greater than 60%, HINT sentence score in quiet greater than 50%, or CNC word score in quiet greater than 20% (Cullen et al., 2004). All of the subjects included in the review reported significant self-perceived handicap, and all subjects surpassed their preoperative scores during postoperative testing. Improvements for speech understanding were seen as early as one-month post-implantation. Bassim et al., (2005) subsequently reported data on 112 adults receiving MED-EL Combi40+ cochlear implants at UNC. In this population, CUNY and HINT sentences in quiet were analyzed, however, the presence of ceiling effects made it difficult to interpret ongoing improvement in performance over many years. This investigative team concluded that monosyllabic word tests would be a better option for assessing performance across patient groups due to the difficulty level of the test and similarity across languages, allowing for wider comparisons.

Performance in cochlear implant users has improved such that test scores for many CI users have surpassed those of hearing aid users with less severe hearing loss (Gifford, Shallop, & Peterson, 2008). In order to evaluate a variety of test materials for cochlear implant users, Gifford compared performance across measures for 156 cochlear implant users. For HINT sentences in quiet, the current speech test specified in criteria for MED-EL cochlear implants, 28% of the test scores collected were at ceiling (100%). In fact, 61% of the test scores collected on HINT were above 85%. In contrast, no subjects were able to reach ceiling (100%) on CNC words, and only 8% of the scores collected were above 85%. AzBio sentences in quiet were also included as a more difficult material than HINT: only 1 score was collected at 100%. Given the expectation for postoperative speech understanding to improve greatly, Gifford concluded that CNC words would be a more useful tool to track performance pre-implant to post-implant.

In addition to considering the use of more difficult test materials to expand criteria on speech understanding measures, candidates with more low-frequency residual hearing are also being implanted. Verschuur and colleagues (2016) reported a significantly greater proportion of referred candidates with low frequency thresholds better than 80 dB HL between the years of 2011-2015, compared to referred candidates between 1990-2010. With the approval of the MED-EL EAS System, individuals with normal hearing to moderate hearing loss in the low frequencies qualify for cochlear implantation. The benefits of EAS have been reported by several research groups (Gantz, Turner, & Gfeller, 2006)(Dorman, Gifford, Spahr, & McKarns, 2007)(Von Ilberg, Baumann, Kiefer, Tillein, & Adunka, 2011)(Gifford et al., 2013). For example, Dorman demonstrated substantial improvement in performance on words in quiet and sentences in noise when adding low-frequency acoustic information ipsilaterally for 15 subjects with cochlear implants. In addition, Gifford, et.al (2007) also reported on individuals with residual low-frequency hearing and the use of a contralateral hearing aid (bimodal stimulation). For the 11 subjects included in this study, performance on CNC words was statistically better in the bimodal condition as compared to the cochlear implant alone. Ten of the 11 subjects preferred to wear the contralateral hearing aid for the majority of waking hours.

The results from a recent international survey on candidacy guidelines around the world were provided by Vickers and colleagues (2016). Results included responses from 28 individuals, representing 17 countries. Audiometric guidelines for adult cochlear implantation are present in 70% of the countries surveyed, with more emphasis on thresholds in the high frequencies as opposed to low-frequency residual hearing. Of the respondents, 85% of the countries surveyed have speech-based criteria in place for adult CI candidates. Of those countries, 40% use tests of word understanding and an additional 36% use both word and sentence understanding as part of the criteria. Tests of speech understanding using monosyllabic words can be easier to compare across languages, making evaluations of CI performance across the globe possible.

Gifford, et. al (2010) reported on 22 subjects with CNC scores greater than or equal to 30% (range 30-68%) preoperatively. Subjects in this study performed 11-25 percentage points higher than in other similar studies through that time. No subjects experienced a decrement in

performance, although two subjects did perform similarly post-implantation. Ninety-one percent of subjects in this study demonstrated significant improvement in performance on testing in either the CI-alone or bimodal conditions. Gifford did not find a correlation between preoperative audiometric thresholds and postoperative performance, and concluded that variables beyond the audiogram should be considered in determining cochlear implant candidacy.

The case to implant individuals based on significant self-perceived handicap in the best aided condition, along with speech understanding and audiometric thresholds, was made by Amoodi et al. (2012). This study reported on 27 subjects implanted with HINT scores greater than 60% preoperatively. The mean preoperative CNC score was 28.5%, with a range of 8-48% correct. Ceiling effects were evident in 30% of the study subjects on HINT in quiet, but a statistically significant improvement was noted for CNC words. Although subjects performed relatively well preoperatively on HINT sentences in quiet, subjects were dissatisfied with their performance using hearing aids. No subject in this study demonstrated a worsening of speech scores postoperatively.

Collectively, these studies suggest a strong need to expand the approved candidacy for cochlear implants. Current criteria for other FDA-approved CIs are more inclusive than the currently approved MED-EL cochlear implant indication. However, in order for continuing advancements to be made in the field of hearing technology, global expansion of cochlear implant candidacy criteria is necessary. The present study aims to expand the FDA-approved candidacy for MED-EL cochlear implants from sentence scores to word scores. This shift reflects the aforementioned concerns regarding ceiling effects present for HINT sentence in quiet testing, as well as the current accepted practice of implanting individuals with residual low-frequency hearing. Criteria of 60% or less on CNC words in quiet is representative of the move to include individuals with more low-frequency residual hearing, as well as individuals who may be performing relatively well on sentence testing in quiet but still feel a significant self-perceived handicap.

2.2 POTENTIAL RISKS AND BENEFITS

2.2.1 KNOWN POTENTIAL RISKS

The known potential risks of cochlear implantation in the currently approved population are as follows:

- Loss of residual hearing
- Increased vertigo
- Dizziness
- Delayed healing of the scar
- Impaired sense of taste
- Potential for swallowing difficulties

- Numbness around the incision or coil site
- Increased tinnitus
- Stimulation of the facial nerve
- Temporary pain
- Uncomfortable sounds during stimulation

In rare cases, post-operative device failure or decrease in device performance may occur. Some serious complications may result in revision surgery.

Additional potential risks associated with the surgical procedure include:

- Facial nerve injury
- Infection
- Inflammation
- Skin irritation
- Cerebrospinal fluid leak
- Swelling around the incision or coil site
- Movement of the internal receiver
- Headache
- Meningitis

Subjects included in this study may have more residual hearing than traditional cochlear implant candidates. As such, they may be at greater risk of losing any benefit received from low-frequency hearing in the implant ear.

2.2.2 KNOWN POTENTIAL BENEFITS

Subjects may experience an improvement in speech perception abilities as compared to preoperative abilities with acoustic amplification.

Subjects may also obtain subjective benefit after cochlear implantation, as compared to their experience with acoustic amplification.

The subjects included in this study will have prior experience with acoustic amplification and will be documented as obtaining insufficient benefit from traditional hearing aids. As such, subjects in this study will not differ from the currently intended cochlear implant population. Therefore, the benefits of cochlear implantation are suspected to outweigh the risks in this population.

3 OBJECTIVES

All subjects will receive a MED-EL SYNCHRONY/SYNCHRONY PIN or SYNCHRONY 2/SYNCHRONY 2 PIN Cochlear Implant. The co-primary objectives are to demonstrate a significant improvement (greater than or equal to 10 percentage points) with the cochlear implant in CNC word score and

AzBio sentence score at six months, compared to pre-operative performance with appropriately fit hearing aids.

Other objectives are to assess AzBio sentence scores in noise post-operatively with both ears, compared to pre-operatively with hearing aids, to measure subjective improvement on the APHAB and SSQ, to summarize residual hearing, and to record and report adverse events.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Fifty subjects will be enrolled in this single-subject, repeated measures study, where each subject serves as his or her own control. Approximately five centers will be involved in this clinical trial. After undergoing enrollment/baseline assessment, qualified individuals will receive a MED-EL SYNCHRONY/SYNCHRONY PIN or SYNCHRONY 2/SYNCHRONY 2 PIN Cochlear Implant. Each subject will subsequently be fit with a SONNET EAS/SONNET 2 EAS and/or RONDO/RONDO 2 or RONDO 3 Audio Processor.

Post-operative evaluations will occur at one, three, six, and 12 months post-activation of the audio processor. Audiometric thresholds as well as word scores in quiet and sentence scores in noise will be measured at each interval and compared to the pre-operative evaluation. Adverse events will be collected and reported by the number and proportion of subjects experiencing an event. The six-month interval will be considered the primary safety and effectiveness endpoint.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

The co-primary endpoint will be the comparison of CNC word score with the cochlear implant at six months post-activation to the pre-operative aided CNC word score in the implanted ear. Improvement will be defined as equal to or greater than 10 percentage points. Testing will occur in the soundfield at 60 dB SPL. The second co-primary endpoint will be the comparison of AzBio sentence score in noise with the cochlear implant at six months post-activation to the pre-operative aided AzBio score in the implanted ear. Improvement will be defined as equal to or greater then 10 percentage points. Testing will occur in the soundfield at 60 dB SPL with a signal-to-noise ratio of +10 dB SNR.

Study success will be determined based on the analysis of both co-primary endpoints. In order for the study to be considered successful, both co-primary endpoints must be met.

4.2.2 SECONDARY ENDPOINTS

Secondary effectiveness endpoints are as follows:

- AzBio sentence score in noise with the cochlear implant at six months post-activation compared to the pre-operative aided score, in the "everyday listening condition." Scores at six months will be similar to or better than scores at the pre-operative interval. Similar is defined as within 10 percentage points, while better than is defined as equal to or greater than 10 percentage points. Testing will occur at 60 dB SPL with a signal-to-noise ratio of +10 dB SNR. The everyday listening condition is defined as the subject's daily wearing configuration, which may or may not include a hearing aid on the non-implanted ear.
- Subjective improvement will be measured on both the SSQ and APHAB questionnaires at six months in the "everyday listening condition." Responses will be compared to the pre-operative "everyday listening condition."
- Unaided, audiometric thresholds at six months post-activation will be reported. Residual hearing will be classified according to the HEARRING scale as complete hearing preservation (75-100%), partial hearing preservation (25-75%), minimal hearing preservation (1-25%), or loss of hearing (no detectable hearing).(Skarzynski et al., 2013)
- Device-related adverse events will be recorded and reported as the number and proportion of subjects experiencing an adverse device effect throughout the duration of the study. Adverse events will also be classified as anticipated or unanticipated and serious or non-serious.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Individuals must meet all of the inclusion criteria set forth below in order to qualify for inclusion in this study.

- Adults, 18 years of age or older at the time of implantation
- Moderate to profound hearing loss in the low frequencies and severe to profound hearing loss in the high frequencies, bilaterally as defined by (see *Figure 1* below for example audiogram information)
    - Low-frequency PTA (250, 500, and 1000 Hz) greater than 40 dB
    - High-frequencies not better than 65 dB (3000 Hz – 8000 Hz)
- Sensorineural hearing loss, demonstrated by an air-bone gap of less than or equal to 10 dB
- Limited benefit from appropriately fit hearing aids, defined by CNC word score in quiet of 60% or less in the ear to be implanted and 70% or less in the non-implanted ear
- CNC word score in quiet of greater than or equal to 10% in the ear to be implanted
- Evidence of appropriately fit hearing aids as determined by the audiologist
    - Bilateral hearing aids should be considered standard of care, except in situations where the audiologist, physician, or potential subject determines that unilateral fit is optimal

  - Hearing aid fit should be verified through accepted measures such as functional gain or real-ear verification
  - If appropriately fit hearing aids have not been worn within the last year, a 30-day hearing aid trial must be completed prior to enrollment in the study
- Fluent in English
- No radiological contraindications
- Ability to undergo general anesthesia
- Appropriate motivation and expectation levels
- Stated willingness to comply with all study procedures for the duration of the study

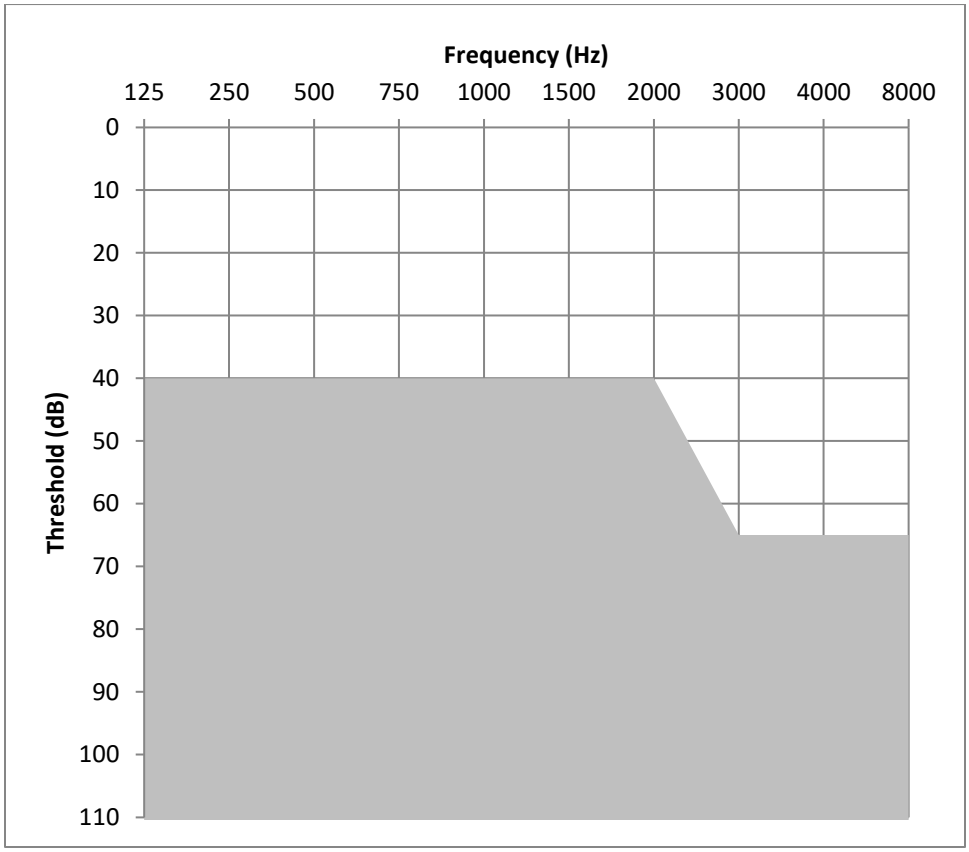


FIGURE 1 – Example inclusion audiogram showing audiometric threshold criteria.
NOTE: Subjects may fall outside of the shaded area but still meet the PTA criteria.

5.2 PARTICIPANT EXCLUSION CRITERIA

Any individual meeting the below exclusion criteria at the candidacy evaluation will be excluded from study participation.

- Evidence that hearing loss is retrocochlear in origin
- Active middle ear infection
- Skin or scalp condition precluding use of external audio processor
- Suspected cognitive impairment or organic brain dysfunction

- History of prior use of a hearing implant

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants in the study will be enrolled at the six clinical trial sites involved. Each site should aim to recruit 10 subjects in order to reach the sample size of 50 subjects. Sites may review their existing database to look for patients who previously did not meet cochlear implant candidacy criteria or may screen new patients seen at the clinic for the first time.

Five clinical trial sites from within the United States will be included; one clinical trial site will be located outside the United States (Canada). It is anticipated that approximately 10 study subjects will be recruited from Canada, while the other 40 will be recruited from within the United States.

Subject recruitment is expected to take approximately two years. Each site should expect to enroll five subjects in year one and five subjects in year two. At this rate, we expect to have 50 subjects enrolled in the trial within two years.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 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
- Post-enrollment evidence of not meeting candidacy criteria
- Implantation of cochlear implant in the contralateral ear
- 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 or are terminated from the study should be reported to study monitors as soon as possible. Subjects who are considered lost-to-follow-up should also be reported to study monitors immediately. A letter describing why and when the withdrawal occurred must be signed and dated by an investigator.

5.4.2 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 study monitor.

Reasons for withdrawal will be described in study reports as required. For subjects who are lost-to-follow-up, every effort will be made to determine the reason for non-compliance with study scheduling. A subject will be considered lost-to-follow-up (requiring withdrawal from the study) if that subject does not return to the clinical for six months or longer at one time. Appointments scheduled outside of the testing interval to the extent that the following interval will be impacted will result in consideration for withdrawal.

6 STUDY DEVICE

6.1 STUDY DEVICE DESCRIPTION

6.1.1 CLASSIFICATION

This clinical trial is intended to change indications on a currently-approved, class III medical device.

6.1.2 DETAILS OF MANUFACTURER

The device is manufactured by MED-EL Elektromedinische Geraete GmbH. MED-EL Corporation is the US importer and the sponsor of this clinical trial.

6.1.3 GENERAL DESCRIPTION

The MED-EL SYNCHRONY/SYNCHRONY 2 Cochlear Implant System is a currently FDA-approved cochlear implant system consisting of the MED-EL SYNCHRONY/SYNCHRONY PIN or SYNCHRONY 2/SYNCHRONY 2 PIN Cochlear Implant, SONNET/SONNET 2 (EAS) processor, the MAX programming interface, and the surgical kit. The implanted portion, the MED-EL SYNCHRONY implant, 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. The MED-EL SYNCHRONY PIN is a variant of the MED-EL SYNCHRONY which has two pins on the bottom of the implant stimulator housing for fixation.

Various active electrode arrays are available as part of the MED-EL SYNCHRONY series of Cochlear Implants. Included in this clinical trial will be the SYNCHRONY +FLEX^{SOFT} and SYNCHRONY +FLEX^{28}. The SYNCHRONY +FLEX^{SOFT} is intended to be used in open cochleae (no obliteration or ossification) for an electrode insertion depth of about 31 mm. The SYNCHRONY +FLEX^{28} is intended to be used in open cochleae (no obliteration or ossification) for an electrode insertion depth of about 28 mm.The +FLEX^{28} and +FLEX^{SOFT} electrodes are currently approved by the FDA.

The Patient Kit consists of two Audio Processors (SONNET EAS/SONNET 2 EAS/RONDO/RONDO 2/RONDO 3) and related accessories, chosen in various combinations by the subject. Each subject must select at least one SONNET EAS/SONNET 2 EAS processor in their patient kit configuration. The FDA-approved SONNET EAS and SONNET 2 EAS Audio Processors include a modular design, and can be worn entirely at ear level. SONNET/SONNET 2 (EAS) is a variant of the also FDA-approved SONNET/SONNET 2 Audio Processors – both contain the same components, with the addition of an acoustic unit in the EAS variant. SONNET EAS and SONNET 2 EAS also require use of an acoustic ear hook, upon which an earmold can be attached. The SONNET/SONNET 2 (EAS) Audio Processors use the FDA-approved DL-coil to transmit the signal across the skin. RONDO/RONDO 2/RONDO 3 are single-unit audio processors worn on the head at the location of the implant. MED-EL's MAESTRO System software must be used to program the SONNET EAS/SONNET 2 EAS and RONDO/RONDO 2/RONDO 3 Audio Processors.

The acoustic unit of the EAS variant is intended for use by patients with functional low-frequency hearing. Post-operative acoustic amplification (combined electric-acoustic stimulation) is indicated for hearing losses between 30 dB HL and 80 dB HL in the frequency range between 125 and 1700 Hz. Subjects who do not have post-operative unaided thresholds between 30 dB HL and 80 dB HL will use the SONNET EAS/SONNET 2 EAS processor without the acoustic unit enabled. Without the acoustic unit enabled, the SONNET EAS/SONNET 2 EAS processor will have the same performance as the also FDA-approved SONNET/SONNET 2 Audio Processor.

Subjects will be fit using the FDA-approved MAESTRO System Software. Programming will be completed using the approved Fine Structure coding strategies, as well as Automatic Sound Management (ASM) 2.0. ASM 2.0 includes the use of two front-end noise reduction features for the microphones' signal path. First, microphone directionality that is able to operate in an Omni-directional, Natural, or Adaptive Mode. Secondly, a wind noise reduction algorithm that will reduce wind noise picked up by the microphones.

6.2 STUDY DEVICE CONTROL

6.2.1 ACQUISITION

MED-EL SYNCHRONY/SYNCHRONY 2 Cochlear Implant System and audio processors will be sent to clinical trial sites from MED-EL Corporation. Devices will be ordered by the clinical trial site and processed and shipped according to relevant SOPs at MED-EL. A primary and a back-up cochlear implant will be provided for each subject. Devices will not be shipped until the proper documentation from enrollment/baseline testing has been received.

6.2.2 LABELING

Packaging will be affixed with a label stating: "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." Both the primary and back-up cochlear

implants will be labeled for investigational use only. The patient kit will also be labeled accordingly.

6.2.3 STORAGE

All devices related to the study will be stored separately from approved cochlear implant systems not involved in the clinical trial. There are no additional requirements for storage of the device.

6.2.4 ACCOUNTABILITY

MED-EL will be responsible for creating and storing records related to device accountability and traceability. Records of shipment, including the name and address of the investigative site, subject ID, device information, date of shipment, and serial numbers, will be stored at MED-EL according to the relevant SOPs. Devices returned to MED-EL as unused back-up devices or repairs will be properly documented and stored. Implants requiring explantation will be reported to FDA and documented according to internal procedures.

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 participating in the study and completed pre-operative assessment.
- Tympanometry: Middle ear function will be measured by the use of tympanometry to determine whether or not middle ear status disqualifies the subject from participation in the study.
- Unaided Thresholds: Unaided air conduction thresholds will be measured pre- and post-operatively. Bone conduction thresholds will also be measured in order to determine whether hearing loss is conductive or sensorineural.
- Monosyllabic Word Testing: CNC words in quiet will be administered at 60 dB SPL as the co-primary outcome measure. Word testing will occur in the aided condition, either with

hearing aids (preoperatively) or the cochlear implant (postoperatively). One list will be presented per condition.

- Sentence Testing (implanted ear): AzBio sentences in noise will be administered at 60 dB SPL with a signal-to-noise ratio of +10 dB SNR. as the co-primary outcome measure. Sentence testing will occur in the aided condition, either with hearing aids (preoperatively) or the cochlear implant (postoperatively). Two lists will be presented per condition.
- Sentence Testing (both ears): AzBio sentences will be administered at 60 dB SPL with a signal-to-noise ratio of +10 dB SNR. Sentence testing will occur in the aided condition, either with hearing aids, the cochlear implant, or both. Two lists will be presented per condition. (OPTIONAL: time permitting, testing can also be completed with a signal-to-noise ratio of +5 dB SNR.)
- Subjective Questionnaires: Subjects will complete the APHAB questionnaire (Cox & Alexander, 1995) and 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. Documentation of programs will be sent to the MED-EL Study Monitor.
- 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 4 months of baseline)
- Cochlear implant activation (2-6 weeks post-operative)
- 1-month post-activation (3-6 weeks post-activation)
- 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.

7.2.2 ENROLLMENT/BASELINE

Prior to completing any 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. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency across clinical trial sites. During soundfield measures, the contralateral ear should be plugged or masked, as needed, except when testing is completed in the bilateral condition.

Baseline testing will include the following outcome measures:

- Tympanometry
- Unaided audiogram, insert earphones
  - Pure-tone air conduction thresholds (125 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)
- Individual ear, aided speech testing in quiet, soundfield
  - CNC Words in quiet at 60 dB SPL
  - One list of 50 words will be presented to each ear individually
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Individual ear, aided speech testing in noise, soundfield
  - Az Bio Sentences in noise at 60 dB SPL with an SNR of +10 dB
  - Speech and noise will be presented at 0° azimuth
  - Two lists of 20 sentences each will be presented to the implant ear only
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Bilateral, aided speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of +10 dB
  - Speech and noise will be presented at 0° azimuth
  - Two lists of 20 sentences each will be presented
  - Lists will be randomized at each clinical trial site
  - *OPTIONAL: testing can also be completed with an SNR of +5 dB*
- Subjective questionnaires
  - APHAB
  - SSQ

This documentation should be received by the MED-EL Study Monitor before MED-EL will ship the investigational device.

At the baseline interval, an earmold impression should also be taken if the following criteria are met:

- The subject does not currently have a well-fitting earmold
- Unaided thresholds at 125 – 1000 Hz are 80 dB HL or better in the ear to be implanted

7.2.3 SURGERY

Surgery will be completed within four months of the above pre-op testing. If surgery is not completed within four months of baseline testing, the testing should be repeated to ensure accuracy. A soft surgery technique will be followed for all subjects. The surgical steps to be followed are drawn from the MED-EL Surgical Guide. These same steps are also detailed in *Appendix A*.

7.2.4 DEVICE ACTIVATION

Device activation will occur two to six weeks after surgery. Prior to fitting the device, the following testing should be completed:

- Unaided audiogram, insert earphones
  - Pure-tone air conduction thresholds (125 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)

If at least one unaided air conduction threshold between 125 – 1000 Hz is 80 dB or better, investigators should proceed with fitting SONNET EAS/SONNET 2 EAS according to the recommendations in Appendix B, Electric + Acoustic Fitting.

If all unaided air conduction thresholds between 125 – 1000 Hz are poorer than 80 dB, investigators should proceed with fitting SONNET EAS/SONNET 2 EAS according to the recommendations in Appendix B, Electric Only Fitting.

If the subject has also selected a RONDO/RONDO 2/RONDO 3 processor, investigators should program the device according to the recommendations in Appendix B, Electric Only Fitting.

A copy of the programs created for each processor should be sent to the MED-EL Study Monitor at the completion of this interval.

7.2.5 FOLLOW-UP INTERVALS

Follow-up testing will occur at 1 month, 3 months, 6 months, and 12 months post-activation. 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. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency across clinical trial sites. During soundfield measures, the contralateral ear should be plugged or masked as needed.

All testing should occur with an ear-level processor and be completed prior to making programming changes to the subject's processors. Additionally, processor settings should be verified prior to testing, with testing conducted using the patient's preferred program position and preferred volume and sensitivity settings.

Follow-up intervals will include the outcome measures below, which are also listed in *Table 1*:

- Unaided audiogram, insert earphones

  - Pure-tone air conduction thresholds (125 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)
- Aided speech testing in quiet, implant ear only, soundfield
  - CNC Words in quiet at 60 Db SPL
  - One list of 50 words will be presented to the implant ear at each interval
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided speech testing in noise, implant ear only, soundfield
  - Az Bio Sentences in noise at 60 Db SPL with an SNR of +10 Db
  - Speech and noise will be presented at 0° azimuth
  - Two lists of 20 sentences each will be presented to the implant ear at each interval
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided speech testing in noise, "everyday listening condition," soundfield
  - AzBio Sentences in noise at 60 Db SPL with an SNR of +10 Db
  - Speech and noise will be presented at 0° azimuth
  - Two lists of 20 sentences each will be presented in the "everyday listening condition" at each interval
  - Lists will be randomized at each clinical trial site
  - *OPTIONAL: testing can also be completed with an SNR of +5 Db*
- Subjective questionnaires
  - APHAB
  - SSQ

Programming should be completed according to the recommendations in *Appendix B*. A copy of the maps created in each processor should be sent to the MED-EL Study Monitor at the completion of each interval.

7.2.6 SCHEDULE OF EVENTS TABLE

		Candidacy/ Pre-op	Surgery	Activation	1 month post-activation	3 months post-activation	6 months post-activation	12 months post-activation
	Informed Consent	X						
	Medical Assessment	X						
	Surgery		X					
	Tympanometry	X						
	Unaided thresholds	X		X	X	X	X	X
Implant Ear	CNC Words 60 Db SPL (Aided)	X			X	X	X	X
Non-implant Ear		X						
Implant Ear	AzBio 60 Db SPL +10 Db SNR (Aided)	X			X	X	X	X
Everyday Condition	AzBio 60 Db SPL +10 Db SNR (Aided)	X			X	X	X	X
Everyday Condition	*OPTIONAL: AzBio 60 Db SPL +5 Db SNR (Aided)*	*X*			*X*	*X*	*X*	X
	APHAB	X			X	X	X	X
	SSQ	X			X	X	X	X

(TABLE 1)

7.3 PRECAUTIONARY PROCEDURES

The MED-EL SYNCHRONY/SYNCHRONY PIN and SYNCHRONY 2/SYNCHRONY 2 PIN 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/*.

7.4 PROHIBITED PROCEDURES

Subjects may not receive an additional hearing implant on the contralateral ear during the course of the study.

In cases where residual hearing should be preserved, the Insertion Electrode is also contraindicated as a tool for assessing insertion depth.

8 ASSESSMENT OF SAFETY

8.1 DEFINITIONS AND CLASSIFICATIONS

As noted in Section 4.2, device-related adverse events will be recorded throughout the duration of the study to satisfy the safety endpoint. Adverse device effects will be reported as the number and proportion of subjects experiencing device or procedure-related adverse events. Reportable events and procedures are described below in Sections 8.1.1 through 8.1.3, 8.2, and 8.3.

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. This change may or may not be caused by the intervention studied.[1]

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

[1] *https://clinicaltrials.gov/ct2/about-studies/glossary*

surgical intervention to prevent permanent harm to the body. Serious adverse events will only be reported if they are deemed related to the device or procedure.

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.

Investigators should record all reportable events with start dates occurring any time after the IC is obtained. Any medical condition that is present at the enrollment/baseline evaluation will not be reported as an adverse event. If the subject's condition deteriorates at any time during the study, however, the event will be reported.

Adverse events recorded as intermittent or fluctuating require documentation of onset and duration of each episode. This will be in addition to the original onset date of the event. Aes should not be recorded as resolved unless the reported event is no longer present and is not expected to reoccur.

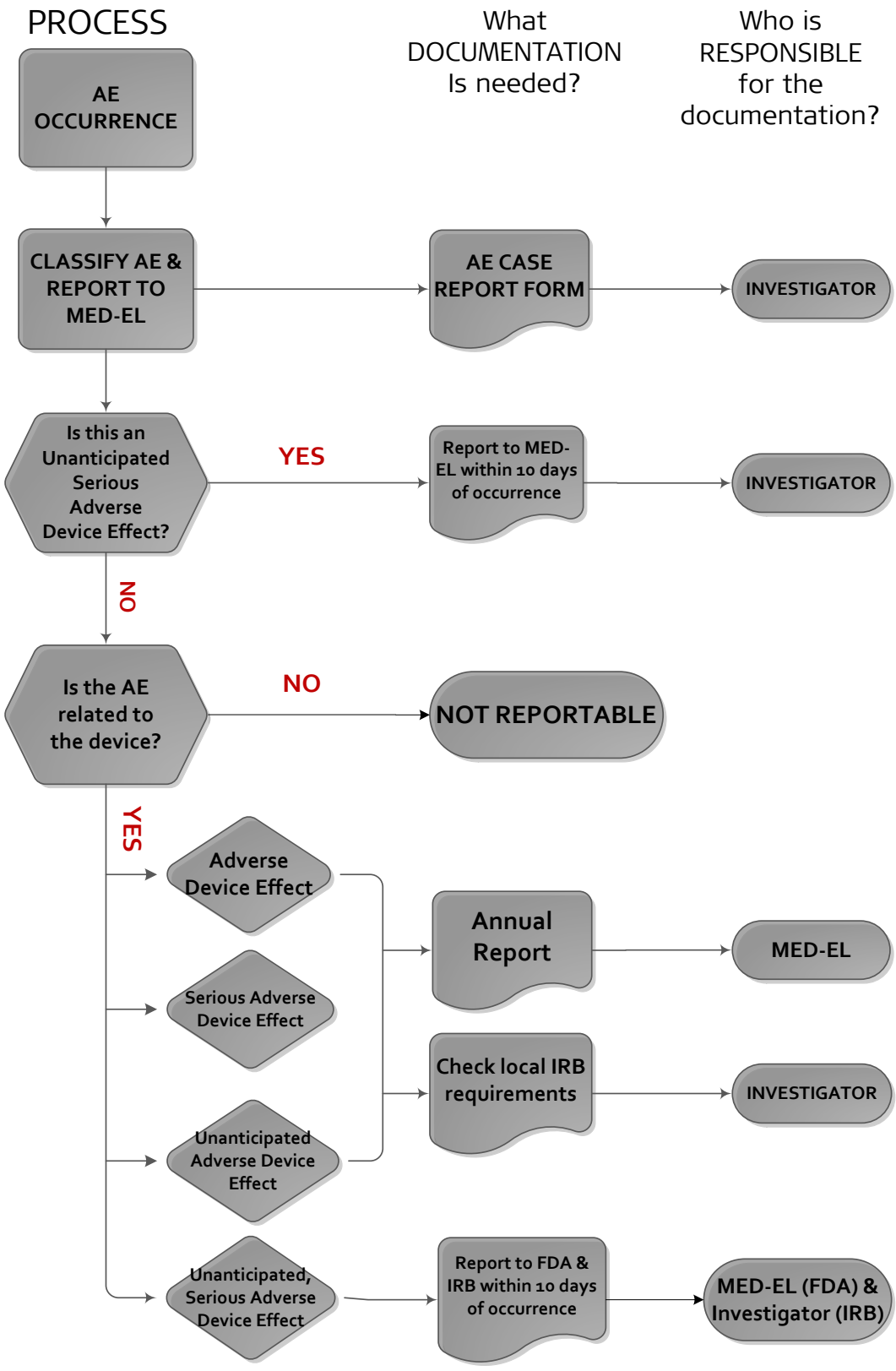
8.3 REPORTING PROCEDURES

8.3.1 ADVERSE EVENT REPORTING

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 Clinical Monitor. All Aes should be reported to

the MED-EL Clinical Monitor in a timely manner. All adverse events deemed related to the device or procedure will be reported to the FDA and to relevant IRBs in the annual report.

Investigators should reference the below flow chart (*Figure 2*) as well as Section 8.3.2 to determine appropriate reporting procedures, depending on AE type.


PROCESS
What DOCUMENTATION Is needed?
Who is RESPONSIBLE for the documentation?
AE OCCURRENCE
CLASSIFY AE & REPORT TO MED-EL
AE CASE REPORT FORM
INVESTIGATOR
Is this an Unanticipated Serious Adverse Device Effect?
YES
Report to MED-EL within 10 days of occurrence
INVESTIGATOR
NO
Is the AE related to the device?
NO
NOT REPORTABLE
YES
Adverse Device Effect
Serious Adverse Device Effect
Unanticipated Adverse Device Effect
Unanticipated, Serious Adverse Device Effect
Annual Report
MED-EL
Check local IRB requirements
INVESTIGATOR
Report to FDA & IRB within 10 days of occurrence
MED-EL (FDA) & Investigator (IRB)

(FIGURE 2)

8.3.2 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT REPORTING

If the investigator determines that the adverse device effect is unanticipated and serious, the CRF should be submitted to the MED-EL Study Monitor no later than 10 working days after becoming aware of the event. Additionally, the investigator should notify the reviewing IRB of the unanticipated serious adverse device effect within 10 working days.

Upon receiving this documentation, MED-EL will review the information contained in the CRF. After completing this review, MED-EL will submit the information to FDA, as well as all principal investigators for submission to reviewing IRBs within 10 working days. Additional reports concerning the effect will be submitted upon FDA request.

8.4 STUDY HALTING RULES

Adverse events will be reviewed by MED-EL throughout the duration of the study. Review of serious, unexpected, and device related adverse events by MED-EL will determine whether the study should continue per the protocol, be modified, or be discontinued.

Examples of findings that would trigger a safety review are the number of serious adverse events occurring overall, the number of occurrences of a particular type of serious adverse event, or increased frequency of events (e.g. device deficiencies). If findings indicate the study or protocol should be reconsidered, MED-EL will inform FDA of the disposition of the study.

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 and/or a qualified Contract Research Organization (CRO) will be responsible for monitoring this investigation according to MED-EL Corporation's SOPs.

Clinical monitors will conduct on-site pre-investigation site visits at each prospective site. During this visit, the monitor will evaluate the facilities and staff and review study-specific details and obligations with the investigators. Investigators will demonstrate understanding of the following information at the conclusion of the pre-investigation site visit:

- Obligation to conduct the study in accordance with the investigator agreement, GCP, and other applicable regulations
- Device accountability and traceability requirements for investigational devices
- 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

Once the study has been initiated and enrollment has begun, periodic on-site monitoring visits will occur. The frequency of these visits will depend on the number of subjects enrolled, the completion or accuracy of study records received by MED-EL, and the occurrence of adverse events and protocol deviations. These periodic on-site visits will evaluate whether:

- The facilities continue to be acceptable for the study
- The investigational plan is being followed
- Changes to the investigational plan have been reported to and approved by the IRB
- Records are accurate, complete, and current
- Reports to the Sponsor and IRB are accurate, complete, and on time

After completion of any monitoring visit, the clinical monitor will document the observation, conclusions, and corrective actions taken to address any findings. The documentation will include the visit date, name of the monitor, name of the investigator and site, and address of the site.

Case report forms and other related study documentation will be reviewed as MED-EL receives the completed paperwork 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 statistical hypothesis for the superiority of the cochlear implant in CNC word score and AzBio sentence score at six months, compared to pre-operative performance with appropriately fit hearing aids by a margin of 10 percentage points can be written as follows:

H_o: $\mu_\Delta \leq 10$

H_a: $\mu_\Delta > 10$,

where μ_Δ is the mean change in the CNC word score or AzBio sentence score from baseline to 6-months and 10 is the superiority margin representing a 10 percentage point change in mean CNC word score or AzBio sentence score.

10.3 ANALYSIS DATASETS

Analysis datasets will be created using SAS format. These SAS datasets will be used for the final analysis of the study and will be archived at the end of the study.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Continuous variables will be summarized using mean, median, inter-quartile range, minimum, and maximum values. Categorical variables will be summarized using counts and percents. Testing of the primary endpoint will be done at the 0.025 level of significance. Additional detail regarding the statistical methods will be included in the SAP.

10.4.2 ANALYSIS OF THE PRIMARY EFFECTIVENESS ENDPOINT

The mean change in CNC word score or AzBio sentence score from baseline to 6-months will be summarized as a continuous variable using the descriptive statistics described in section 10.4.1. Additionally, a one-sided, paired t-test comparing the mean change in CNC word score or AzBio sentence score to the superiority margin of 10 will be performed and the corresponding p-value will be reported. A p-value less than 0.025 will result in rejection of the null hypothesis indicating that the mean change in CNC word score or AzBio sentence score was greater than 10 percentage points.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will not be formally tested but will be summarized using appropriate descriptive statistics. Details of the methods used will be laid out in the SAP.

The number and percentage of subjects performing similarly or better on AzBio at 6 months post-operatively compared to the pre-operative aided condition will be summarized. Responses from the APHAB and SSQ questionnaires will also be summarized descriptively. The number and percentage of subjects with complete hearing preservation, partial hearing preservation, minimal hearing preservation, and loss of hearing (according to the HEARRING classification) will also be summarized. Adverse events will be summarized by the number and percent of subjects experiencing adverse events.

10.4.4 SAFETY ANALYSES

Adverse events will be listed and summarized based on the type and severity of the event.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Adherence will be defined as those subjects who adhered to all protocol requirements. A per protocol analysis population will be defined in the SAP and the primary endpoint of change in CNC word score will be assessed.

Subjects lost to follow-up or terminated early for other reasons will be tabulated and summarized. For those subjects without a 6 month follow-up visit, the six month CNC word score or AzBio sentence score will be imputed using last observation carried forward. Only a small number of subjects are expected to be lost and benefit from the implant should be immediate making this imputation method reasonable.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will be summarized and reported for all subjects with available baseline data. All demographic and medical history information will be tabulated and presented as described in section 10.4.1 above.

10.4.7 PLANNED INTERIM ANALYSES

No interim analyses are planned for this study.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

The change in CNC word score and AzBio sentence score will be summarized by electrode array. Those subjects receiving the SYNCHRONY +FLEX^{SOFT} electrode array will form one group while those receiving SYNCHRONY +FLEX^{28} will form the other. No formal statistical comparison will be done between these two groups.

Likewise, the change in CNC word score and AzBio sentence score will also be summarized by sex. Again, no formal statistical testing will be done.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Both co-primary enpdoints are being tested at the 0.025 level of significance. Testing at this level for the individual endpoint wil control the overall Type I error rate to the 0.05 level.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

An overall list of each subject with his or her CNC word score and AzBio sentence score at baseline, 1 month, 3 months, 6 months, and 12 months along with the change in CNC word score and AzBio sentence score from baseline to 6 months, will be provided.

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses in the form of a repeated measures analysis will be done for the primary, secondary, and subjective questionnaire scores to characterize any changes over time.

10.5 SAMPLE SIZE

The sample size estimate is based on attaining adequate power to test the co-primary endpoint of the study. The hypothesis test is a paired one-sample T-test of superiority of the mean change in CNC word score from baseline to 6-months with a superiority margin of 10 percentage points. The test will be performed at the one-sided alpha = 0.025 level. A sample size of 50 would yield approximately 90% power assuming the true change in mean CNC word score is 24.4 with a standard deviation of 21.9.

The paired T-test will also be used to test for superiority of the mean change in AzBio sentence score from baseline to 6-months with a superiority margin of 10 percentage points. The test will be performed at the one-sided alpha = 0.025 level. A sample size of 50 would yield approximately 83% power assuming the true change in mean AzBio sentence score is 15 with a standard deviation of 8.4.

The estimates used for the sample size calculation came from the results for the Electric-Acoustic System (EAS) Investigational pivotal trial.

10.6 SAMPLE STRATIFICATION

In order to ensure that subjects enrolled in the study fill the entire range of candidacy scores from 0 to 60% correct on CNC words, minimum sample sizes of 10 subjects will be established across the following ranges: 0 to 20%, 21 to 40%, and 41 to 60% correct.

10.7 MEASURES TO MINIMIZE BIAS

Because this is a one-arm trial with all subjects receiving the same treatment, measures to minimize bias in the form of randomization and blinding are not relevant. However, one form of bias control implemented in this trial is that the presentation order of the CNC word lists is randomized at each follow up visit.

10.8 SITE POOLABILITY

Poolability across site of the data used for analysis of the primary endpoint will be established. For each subject, the change from baseline to 6 months in CNC word score and AzBio sentence score will be computed. The changes in CNC word score and AzBio sentence score will be analyzed using a one-way analysis of variance in which site forms the levels of the single factor. The overall F-test will be used to demonstrate poolability of the primary endpoint data. If the p-value for the overall F-test is greater than or equal to 0.10 then the data will be considered

poolable. If the p-value is less than 0.10, then additional methods may need to be employed in the analysis of the primary endpoint. These methods will be detailed in the SAP.

10.9 PROPENSITY SCORE ANALYSIS

The primary endpoints of this trial were also measured in the Electric-Acoustic Stimulation clinical trial. The results from the current study will be compared back to the EAS pivotal trial via use of a propensity score analysis. Propensity scores for the subjects in each trial will be generated using a logistic regression which estimates the probability that a subject was treated in the current or previous study. The baseline variables used to generate the propensity score are age, sex, CNC word score, and low-frequency hearing loss. Combining the propensity scores from both trials, five strata will be formed using the quintiles of the scores. The analysis of CNC word score will be done using generalized linear models. Differences from baseline in the CNC scores will be the dependent variable while study (a coded value) and the propensity quintile will act as the independent predictors. Use of the quintile in the model adjusts the estimates of treatment effect for the propensity score.

A propensity score analysis of this type requires that there is good overlap of the propensity scores from the original EAS pivotal trial and the current expanded indications trial. In the absence of good overlap, estimate of the treatment effect can still be made, but may be severely biased.

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 clinical study monitors, as needed, for comparison to CRFs. Additionally, the FDA may audit any investigational site and would require access to source documentation at that time. Medical records kept on each subject will include information about the subject's participation in the clinical trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

MED-EL will implement all necessary procedures to ensure the integrity of CRFs. As part of the periodic on-site monitoring visits, the clinical monitor will compare a sample of the CRFs to the source documents to verify accuracy. When CRFs are received, the forms will be reviewed for completeness and to identify any inconsistencies or errors.

Investigators will be trained to make corrections only by approved methods (i.e., a single line through the incorrect entry, correction, initialed, and dated). Any discrepancies found in the CRFs by the Clinical Monitor should be brought to the attention of the investigator.

For the data management process, data may be entered into a database using accepted data entry techniques. A sample of the database will be compared to the CRFs during internal audits to ensure accuracy of the database. More comprehensive evaluation of the database will be performed as required.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 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.

13.2 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.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT DOCUMENTS PROVIDED TO PARTICIPANTS

A consent form with detailed descriptions of the study device, study procedures, and risks will be given to the participant. Written documentation of IC is required prior to initiating any study-related activities. The IC template included with this protocol will be provided to each investigative site.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The IC process will be initiated prior to the participant's involvement in any study-related activities. Potential participants must be informed as to the purpose of the study and the potential risks and benefits known, or that can be reasonably predicted or expected. These risks are described in the written consent form.

Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and will answer any questions that may arise. All participants will receive a verbal explanation of the purpose, procedures, and potential risks of the study, as well as their rights as research participants.

The participant will sign the IC prior to being enrolled in the study. The investigator administering the IC will sign and date the form to indicate the document was sufficiently

explained to the subject and their signature was witnessed. Consent may be withdrawn at any time during participation in the study. A copy of the signed IC will be provided to the subject, while the original will be retained by the investigator in the study file.

13.4 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.

14 DATA HANDLING AND RECORD KEEPING

14.1 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 forms, for the duration of the study. Correspondence with the IRB, Clinical Monitor, and MED-EL in general should also be maintained. 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.

Copies of the electronic CRF will be provided for use as source documents, as needed, and maintained for recording data for each subject enrolled in the study. Data reported in the electronic CRF derived from source documents should be consistent with the source document. Any discrepancies should be explained and captured in a note and maintained in the subject's official study record.

14.2 STUDY RECORDS RETENTION

Upon completion of the study, it is the investigator's responsibility to maintain all study records in a safe and secure location. Study-related documents should be kept for the duration of the study as required by 21 CFR Part 812.40 and the institution's IRB. No study documents will be destroyed during this period of time. If the documents must be moved to a different storage location during this period, the investigator will contact MED-EL.

14.3 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.

15 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or other aspect of this trial will be disclosed and managed.

16 LITERATURE REFERENCES

Amoodi, H. A., Mick, P. T., Shipp, D. B., Friesen, L. M., Nedzelski, J. M., Chen, J. M., & Lin, V. Y. W. (2012). Results With Cochlear Implantation in Adults With Speech Recognition Scores Exceeding Current Criteria. *Otology & Neurotology*, *33*(1), 6–12.

Bassim, M. K., Buss, E., Clark, M. S., Kolln, K. A., Pillsbury, C. H., Pillsbury 3rd, H. C., & Buchman, C. A. (2005). MED-EL Combi40+ cochlear implantation in adults. *Laryngoscope*, *115*(9), 1568–1573.

Boothroyd, A., Hanin, L., & Hnath, T. (1985). A Sentence Test of Speech Perception: Reliability, Set Equivalence, and Short Term Learning. *City University of New York*, *Internal R*.

Cox, R. M., & Alexander, G. C. (1995). the Abbreviated Profile of Hearing-Aid Benefit. *Ear and Hearing*, *16*(2), 176–186.

Cullen, R. D., Higgins, C., Buss, E., Clark, M., Pillsbury, H. C., & Buchman, C. A. (2004). Cochlear Implantation in Patients with Substantial Residual Hearing. *The Laryngoscope*, *114*(12), 2218–2223.

Dorman, M. F., Gifford, R. H., Spahr, A. J., & McKarns, S. A. (2007). The Benefits of Combining Acoustic and Electric Stimulation for the Recognition of Speech, Voice and Melodies. *Audiology and Neurotology*,

Gantz, B. J., Turner, C., & Gfeller, K. E. (2006). Acoustic plus electric speech processing: Preliminary results of a multicenter clinical trial of the Iowa/Nucleus Hybrid implant. *Audiology and Neurotology*, *11*(SUPPL. 1), 63–68.

Gatehouse, S., & Noble, W. (2004). The Speech, Spatial and Qualities of Hearing Scale (SSQ). *International Journal of Audiology*, *43*(2), 85–99.

Gifford, R. H., Dorman, M. F., McKarns, S. A., & Spahr, A. J. (2007). Combined electric and contralateral acoustic hearing: word and sentence recognition with bimodal hearing. *Journal of Speech, Language, and Hearing Research : JSLHR*, *50*(4), 835–43.

Gifford, R. H., Dorman, M. F., Shallop, J. K., & Sydlowski, S. A. (2010). Evidence for the expansion of adult cochlear implant candidacy. *Ear and Hearing*, *31*(2), 186–194.

Gifford, R. H., Dorman, M. F., Skarzynski, H., Lorens, A., Polak, M., Driscoll, C. L. W., … Buchman, C. A. (2013). Cochlear implantation with hearing preservation yields significant benefit for speech recognition in complex listening environments. *Ear Hear*, *34*(4), 413–425.

Gifford, R. H., Shallop, J. K., & Peterson, A. M. (2008). Speech recognition materials and ceiling effects: Considerations for cochlear implant programs. *Audiology and Neurotology*, *13*(3), 193–205.

Nilsson, M., Soli, S. D., & Sullivan, J. A. (1994). Development of the Hearing in Noise Test for the measurement of speech reception thresholds in quiet and in noise. *The Journal of the Acoustical Society of America*, *95*(2), 1085–99.

Peterson, G. E., & Lehiste, I. (1962). Revised CNC lists for auditory tests. *The Journal of Speech and Hearing Disorders*, *27*(February), 62–70.

Skarzynski, H., van de Heyning, P., Agrawal, S., Arauz, S. L., Atlas, M., Baumgartner, W., … Mertens, G. (2013). Towards a consensus on a hearing preservation classification system. *Acta Oto-Laryngologica. Supplementum*, *133*(564), 3–13.

Spahr, A. J., Dorman, M. F., Litvak, L. M., Van Wie, S., Gifford, R. H., Loizou, P. C., … Cook, S. (2012).

Development and validation of the AzBio sentence lists. *Ear and Hearing*, *33*(1), 112–7.

Verschuur, C., Hellier, W., & Teo, C. (2016). An evaluation of hearing preservation outcomes in routine cochlear implant care: Implications for candidacy. *Cochlear Implants International*, *17 Suppl 1*(August), 62–5.

Vickers, D., De Raeve, L., & Graham, J. (2016). International survey of cochlear implant candidacy. *Cochlear Implants International*, *17*(sup1), 36–41.

Von Ilberg, C. A., Baumann, U., Kiefer, J., Tillein, J., & Adunka, O. F. (2011). Electric-acoustic stimulation of the auditory system: A review of the first decade. *Audiology and Neurotology*, *16*(SUPPL. 2), 1–30.

Version	Date	Significant Revisions
1.0	28 April 2017	Original version
1.1	21 June 2017	Updated to reflect recommendations from FDA: stratification of pre-op CNC scores, comparison to EAS Clinical Trial outcomes, and addition of optional 12-month follow-up visit.
1.2	13 July 2017	Updated to include required 12-month follow-up visit.
1.3	20 December 2018	Added RONDO 2 Audio Processor and sixth investigative site
1.4	8 August 2019	Updated for the addition of the SYNCHRONY 2 Cochlear Implant
1.5	18 December 2019	Updated for the addition of the SONNET 2 EAS Processor
1.6	20 August 2020	Updated for the addition of the RONDO 3 Audio Processor