

## **SUMMARY OF SAFETY AND EFFECTIVENESS DATA**

### I. GENERAL INFORMATION:

Device Generic Name:	Cochlear Implant System
Device Trade Name:	COMBI 40+ Cochlear Implant System
Applicant's Name and Address:	MED-EL Corporation 2222 East Highway 54 Suite B-180 Durham, North Carolina 27713
Date of Panel Recommendation:	None
Premarket Approval Application (PMA):	P000025
Date of Good Manufacturing Practice Inspection:	May 29 <sup>th</sup> , June 22 <sup>nd</sup> and 28 <sup>th</sup> , 2001
Date of Notice of Approval to Applicant:	August 20, 2001

### II. INDICATIONS FOR USE:

The MED-EL COMBI 40+ Cochlear Implant System, hereinafter referred to as the COMBI 40+, is intended to provide the opportunity to detect and recognize auditory information through electrical stimulation of the auditory nerve for severe to profoundly hearing-impaired individuals who obtain little or no benefit from conventional acoustic amplification in the best-aided condition.

The COMBI 40+ is indicated for the following patient populations:

Adults of eighteen (18) years of age or older who have bilateral, sensorineural hearing impairment and obtain limited benefit from appropriately fitted binaural hearing aids. These individuals typically demonstrate bilateral severe to profound sensorineural hearing loss determined by a pure tone average of 70 dB HL or greater at 500 Hz, 1000 Hz, and 2000 Hz. Limited benefit from amplification is defined by test scores of 40% correct or less in best-aided listening condition on CD recorded tests of open-set sentence recognition Hearing in Noise Test (HINT) sentences.

Children aged eighteen (18) months to seventeen (17) years eleven (11) months must demonstrate a profound, bilateral sensorineural hearing loss with thresholds of 90 dB or greater at 1000Hz and above. In younger children, little or no benefit is defined by lack of progress in the development of simple auditory skills in conjunction with appropriate amplification and participation in intensive aural habilitation over a three (3) to six (6) month period. In older children, lack of aided benefit is defined as < 20% correct on the Multi-syllabic Lexical Neighborhood Test (MLNT) or Lexical Neighborhood Test (LNT),

depending upon the child's cognitive ability and linguistic skills. A three (3) to six (6) month hearing aid trial is required for children without previous experience with hearing aids. Radiological evidence of cochlear ossification may justify a shorter trial with amplification.

### III. CONTRAINDICATIONS:

The Implant C40+ must not be implanted in situations where there is acute or chronic middle ear pathology, lesions or agenesis of the 8th cranial nerve, pathologies of the central auditory pathway, or Michel deformity present.

The patient should not be implanted if the individual is known to be intolerant of the materials used in the implant, there is an absence of cochlear development, the tympanic membrane is perforated, deafness is attributed to central damage of the acoustic nerve or the central auditory pathway, or if external or middle ear infections are present.

### IV. WARNINGS AND PRECAUTIONS:

The complete list of warnings and precautions can be found in the COMBI 40+ labeling (attached).

### V. DEVICE DESCRIPTION:

The COMBI 40+ Cochlear Implant System is a cochlear implant system consisting of the Implant C40+, all components of the CIS PRO+ Patient Kit and/or all components of the TEMPO+ Patient Kit for the patient, and the Diagnostic Interface Box (DIB) System, the Detector Box, and the Surgical Kit for the clinic.

#### A. General function of the COMBI 40+:

The external microphone picks up sound from the environment and sends it to the speech processor. The speech processor analyzes the sound signal from the microphone according to the selected speech coding strategy, and transforms it into a coded electrical signal that is sent to the externally worn coil. This coded signal contains information about how to stimulate the individual electrodes so changes in pitch and loudness can be perceived. The coil, which is magnetically held in place over the implant, sends the coded signal across the skin to the implant package via an inductive link. The energy necessary for stimulation is also sent via the inductive link. The implant decodes the signal and sends a corresponding pattern of rapid stimulation pulses to the individual electrodes on the electrode array. These stimulation pulses travel along the auditory nerve to the brain, where the brain can categorize the sound and assign meaning. The COMBI 40+ collects sound, processes the information, delivers instructions to the implant, and stimulates the electrodes with the appropriate pulse at a speed of up to 18,180 times per second. All electrode channels of the Implant C40+ are individually capacitively coupled to provide maximum protection against the accumulation of unintended Direct Current (DC)-charge.

## B. System Components:

### Implant C40+ and Inductive Link:

The Implant C40+ consists of the implant package, the active electrode and the reference electrode. The Implant C40+ package measures approximately 1.3 by 0.9 inches, and is approximately 5/32 of an inch in thickness. All implant electronics, including the internal inductive link coil, are hermetically sealed in a ceramic ( $\text{Al}_2\text{O}_3$ ) package that provides feed-throughs to the active electrode and the reference electrode.

The minimum duration of one biphasic pulse is  $53 \frac{1}{3} \mu\text{s}$  ( $26 \frac{2}{3}$  per phase). The available current amplitude covers a 60 dB range from approx.  $1.8 \mu\text{A}$  to approximately 1.8 mA of peak stimulation current per phase for monopolar stimulation. The energy necessary for operation of the implanted electronics as well as for generating the stimulus currents is contained in the inductively transmitted carrier signal. Data transmission is digital and generally takes place at a rate of 600 kbits/s.

The use of digital information transmission provides robustness against interference from external electromagnetic fields. The use of a robust data format for pulse definition and the particular choice employed for pulse word format assures appropriate data synchronization. The implant contains safety logic that requires recognition of several sequential words with the correct format before the first stimulation pulse can occur. A new cycle of full safety synchronization occurs every time the implant powers up.

To avoid DC components in the stimulation current, each electrode channel is coupled to the current source via a capacitor. The construction of the implant logic guarantees that the pulses do not overlap. A facility for back-telemetry is implemented in the implant electronics to allow measurement of impedance and voltage levels from the outside.

## C. Active Electrode:

The active electrode contains a total of twenty-four (24) electrode contacts arranged as paired interconnected surfaces, resulting in twelve (12) monopolar stimulation channels. It is surgically inserted into the scala tympani via a small cochleostomy. The distance between the channels is approximately 2.4 mm with the first channel located approximately 1 mm from the tip. The electrode contacts span a distance of approximately 26.4 mm. The active electrode is designed to be inserted up to 31 mm into the human cochlea with a minimum amount of trauma. Mechanical features of the array include an oval cross-section, a soft consistency, and a smooth surface.

The material of the electrode contacts is platinum and the electrode wires are platinum iridium (Pt-Ir 90/10). The electrode body is made of medical implant grade silicone rubber and the connecting wires are completely embedded inside the silicone and therefore not in contact with the tissue.

#### D. Reference Electrode:

The reference electrode provides completion of the electrical path from the active electrode back to the implant electronics. The reference electrode is formed by a 3-fold multi-strand Pt-Ir wire (90/10) in silicone tubing. Three (3) disk-shaped flat spots are at the end of each wire. They serve as the contact surface and form a clover-like structure. Each disk has a diameter of approx. 1.5 mm. The reference electrode is placed outside the cochlea between the temporalis muscle and the cranium.

#### E. CIS PRO+ Patient Kit:

The key components of the CIS PRO+ Patient kit are the CIS PRO+ Speech Processor, the CIS PRO+ Headset, and the COMT+ Coil.

#### F. CIS PRO+ Speech Processor:

The CIS PRO+ Speech Processor measures approximately 3 1/2 x 2 5/8 x 6 inches. It requires two (2) rechargeable AA-type batteries for an average of one (1) full day of operation. Two (2) programmable indicator lights and an alarm buzzer give a visual or auditory indication of processor, program, cable, and battery status. Volume and program selection controls are provided for the user. The speech processor memory holds up to three (3) different programs, which can meet a variety of patient needs related to different preferences and listening situations. The CIS PRO+ Speech Processor also has an audio input port for connection to assistive listening devices, such as compatible FM systems. When an assistive listening device is connected to the audio input port, an input mixing selector is available to allow the user to choose between hearing from the device alone, or to mix the information with the signal coming from the BTE (Behind-The-Ear) microphone. The CIS PRO+ Speech Processor provides up to 18,180 sequential, non-overlapping stimulation pulses. The CIS PRO+ Speech Processor implements both the CIS strategy and the n-of-m strategy.

#### G. CIS PRO+ Headset:

The CIS PRO+ Headset, which contains the external microphone and pre-processing electronics, is connected to the CIS PRO+ Speech Processor by a single, detachable cable and is worn like a conventional hearing aid. The sensitivity control, which can be used to adjust for different listening environments, is mounted on the headset to allow easy access.

#### H. COMT+ Coil:

The high-resolution stimulation code generated by the processor is transmitted to the implant via an inductive link between the external coil and the implant. The coil also contains a magnet, which couples with the magnet in the implant to keep the coil in place.

#### I. TEMPO+ Patient Kit:

##### TEMPO+ Speech Processor:

The TEMPO+ Speech Processor is approximately 2 5/8 x 1/2 x 3/8 inches in the straight configuration and can store up to nine different fitting programs. The TEMPO+ Speech Processor provides up to 18,180 sequential, non-overlapping stimulation pulses according to the CIS+ coding strategy. The CIS+ strategy includes the Hilbert transform for envelope detection, which eliminates the unwanted effects of aliasing and provides a more accurate representation of the sound signal.

The TEMPO+ Speech Processor is powered by three (3) high power zinc-air batteries, which typically need replacing after approximately thirty-six (36) hours of operation.

The TEMPO+ Speech Processor is provided with three (3) different battery packs: straight, angled, and children's. The control unit can be separated from the battery pack so that the battery pack may be exchanged. FM systems and other assistive listening devices can be connected to the TEMPO+ Speech Processor through the angled battery pack. Features of the TEMPO+ Speech Processor include a sensitivity control, an indicator light, a locking battery compartment, and an on/off switch.

#### J. COMT+ Coil:

The high-resolution stimulation code generated by the processor is transmitted to the implant via an inductive link between the external coil and the implant. The coil also contains a magnet, which couples with the magnet in the implant to keep the coil in place. Coils produced for the TEMPO+ Speech Processor (Serial number above 10,000) may also be used with the CIS PRO+ Speech Processor.

Several accessories are delivered with the patient kits, including battery chargers, cables, Speech Processor Test Devices, ear hooks, attachment clips, and carrying pouches.

#### K. DIB System:

The primary components of the DIB System are the DIB (Diagnostic Interface Box), the DIB Coil, the CM4.02 fitting software, ZEBRA 3.0 software for Electrically-evoked Auditory Brainstem Response (EABR) and Electrically-evoked Stapedius Reflex Threshold (ESRT) measurements, TM3.0a telemetry software, and the Detector Box. The

DIB System is used to program the TEMPO+ and the CIS PRO+ Speech Processors as well as to perform telemetry, EABR, and ESRT with the implant.

L. COMBI 40+ Surgical Kit:

The COMBI 40+ Surgical Kit contains recommended tools for use during the surgical implantation of the Implant C40+. These include a surgical claw, surgical forceps, C40+ template – external outline, C40+ template – internal outline, and the TEMPO+ headset template.

VI. ALTERNATIVE PRACTICES AND PROCEDURES:

Alternative treatments to a multi-channel cochlear implant for severe to profoundly hearing impaired adults and profoundly hearing impaired children include the use of conventional hearing aids, vibrotactile aids, the use of lip-reading, manual communication or sign language, or combinations of these alternatives. These treatments do not involve surgery and the risks associated with a surgical procedure. Patients are considered for treatment with a cochlear implant only if they do not obtain adequate benefit from appropriately fitted conventional hearing aids. Tactile aids convert sound waves into vibrations or electrical current which is felt on the skin, but do not provide the resolution necessary to understand speech. Manual communication is possible only with other persons who understand manual communication. Lip-reading is only possible when the speaker is directly facing the reader, vision and lighting conditions are adequate, and requires a level of skill that many are unable to attain.

VII. MARKETING HISTORY:

The COMBI 40+ Cochlear Implant System is sold in over fifty (50) countries worldwide for both children and adults. The device has not been withdrawn from any market for any reason related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

Patients who undergo cochlear implantation are subject to the same risks as other surgical procedures conducted under general anesthesia, and other routine surgical interventions of the middle or inner ear. During cochlear implant surgery any residual hearing in the implanted ear will probably be permanently destroyed. There is a risk of facial nerve injury, numbness, stiffness, tinnitus, vertigo, pain, and taste disturbances or wound infection. Device placement might be incorrect, which could require a second surgery for repositioning. Although the Implant C40+ can usually be completely recessed in the bone, there is the possibility a lump may be palpable behind the ear. A leakage of perilymphatic fluid could potentially occur, which might make additional treatment necessary and could result in meningitis.

The device may not restore hearing to a level achieved by other cochlear implant users. Facial twitching could be caused by the activation of some electrodes, which would require an adjustment in the program of the device. When such program adjustments are not

successful in resolving the facial twitching, those electrodes may need to be eliminated from the program. Failure of component parts could result in uncomfortably loud or painful stimulation. The cochlear implant could cause a further degeneration of nerve cells in the ear or the hearing nerve. Very long-term effects of stimulation of the hearing nerve with a cochlear implant are not fully known to date.

Removal of the cochlear implant requires a surgical intervention that is similar in scope to the initial placement of the device. Device removal might become necessary due to an electrical or mechanical failure of the implant, an infection at the site of the surgical wound or at the site of the device that cannot be successfully treated with medication, or because of migration of the device or the electrode array. There is a risk that removal of the cochlear implant may cause damage to the inner ear. There may be additional risks related to cochlear implant surgery and the COMBI 40+ that are yet unknown.

## IX. SUMMARY OF NON-CLINICAL LABORATORY STUDIES :

The COMBI 40+ Cochlear Implant System, including the Implant C40+, CIS PRO+ Speech Processor, TEMPO+ Speech Processor, and the DIB, fulfills the essential requirements of Annex I of AIMD 90/385/EEC.

### A. Microbiological studies:

#### 1. Sterility Assurance:

Three (3) half ( $\frac{1}{2}$ ) cycles and one (1) full cycle of ethylene oxide sterilization were performed in accordance with European Normative EN 550: 1994, Method C, half cycle method, for a Sterility Assurance Level (SAL) of  $10^{-6}$ . The validation was performed utilizing a standard sterilization box containing twenty (20) COMBI 40/40+ cochlear implants. All three (3) half ( $\frac{1}{2}$ ) cycle and full cycle sterilization runs were 100 per cent lethal to the biological indicator. Sterilization is routinely performed according to EN 550.

#### 2. Shelf life:

Accelerated shelf life testing has been conducted according to the Q10 theory to validate a shelf life of two (2) years from the date of sterilization.

#### 3. Ethylene Oxide Residual Analysis:

In accordance with ISO 10993-7, ethylene oxide residuals were determined by headspace gas chromatography on three (3) samples for single and multiple sterilization runs after twenty-two (22) hour aeration. All residual values were below the acceptance criteria.

### B. Pyrogenicity:

1. Pyrogen level was determined by Limulus Amebocyte Lysate (LAL) Gel Clot testing. An Implant C40 was incubated in water for injection and the extract was used for the assay. The LAL test showed no signs of pyrogenicity.
2. A saline extract was injected intravenously into three (3) rabbits, and showed no signs of pyrogenicity.

### C. Biocompatibility:

The materials of construction for the Implant C40+ are the same as those for the previously manufactured Implant C40. Data from a series of in-vitro and in-vivo studies demonstrate the biocompatibility of the following tissue contacting components of the Implant C40+:

Material	Device Component
High strength RTV silicone Adhesive	coating of stimulator
Liquid silicone rubber LSR 40	overmold and active electrode lead
Platinum, Platinum/Iridium (90/10%)	Electrode wires, electrode contacts
Silicone tube, HCRA 50	Reference electrode lead

The manufacturer of the silicones has performed detailed biocompatibility studies of the material. The materials were designed to meet ISO 10993 requirements for long term implantation. The testing confirmed the biocompatibility of these materials.

The following biocompatibility studies were conducted on COMBI 40 cochlear implants. All materials in contact with body fluids are identical for the Implant C40 and the Implant C40+:

1. Cytotoxicity (based on ISO 10993-5 guidelines):

A saline extract of the implant (4g/20ml) was mixed with Minimum Essential Medium. This test extract, negative, reagent and positive control were each placed onto confluent monolayers of L-929 mouse fibroblast cells. The monolayers in the test, negative, and reagent control flasks were examined microscopically at 48 hours to determine any change in cell morphology. The monolayer in the positive control flasks was examined at 24 hours. The saline test extract showed no evidence of causing cell lysis or toxicity.



## 2. Mutagenicity:

Saline and dimethyl sulfoxide (DMSO) extracts of implants (4g/20ml) were used to conduct an Ames mutagenicity standard assay to determine whether they would cause mutagenic changes in five histidine-dependent *Salmonella typhimurium* tester strains. The saline extract and the DMSO extract were not considered mutagenic.

## 3. Acute Systemic Toxicity (according to United States Pharmacopeia (USP)):

Saline and cottonseed oil extracts of implants (4g/20ml) were injected into mice (five mice per extract). The mice were observed immediately and at 4, 24, 48, and 72 hours. There was no mortality or evidence of significant systemic toxicity.

## 4. Intracutaneous toxicity (according to USP):

Saline and cottonseed oil extracts of implants (4g/20ml) were injected intracutaneously into rabbits (two rabbits per extract). The rabbits were observed at 24, 48, and 72 hours. There was no evidence of significant irritation or toxicity from the extracts.

## 5. Implantation Study:

Implants were implanted in subcutaneous tissue of rabbits for 7 days (6 samples), 30 days (4 samples), and 90 days (6 samples). There were no adverse effects. The test articles did not produce significantly greater biological reactions than did the negative control.

## 6. Hemolysis:

A saline solution containing the implant was shown to be non-hemolytic.

## 7. Sensitization:

Saline and cottonseed oil extracts from implants (4g/20ml) were shown to be non-sensitizing (Magnusson and Kligman maximation method). Positive controls validated the test procedure.

## 8. External Devices:

Some external parts, such as the CIS PRO+ Headset, the small CIS PRO+ Headset, the COMT+ Coil and the TEMPO+ Speech Processor come in contact with intact skin. The materials chosen for these parts comply with food contact regulations and have historically been used for similar applications for many years with no adverse reactions reported.

#### D. Cochlear histopathology:

The electrode of the Implant C40+ has been designed as a soft, tapered array with an oval cross-section to allow insertion up to 31 mm into the human cochlea with a minimum of trauma to intracochlear structures.

#### E. Electromagnetic Compatibility and Electrostatic Discharge testing:

The COMBI 40+ Cochlear Implant System has been tested for ESD and EMC immunity according to EN 60601-1-2. All applicable requirements are fulfilled.

In addition, testing on immunity against radiation from cellular telephones in the 1800 and 1900 MHz band up to 100 V/m has been tested. The system can easily withstand this emission without damage. Some COMBI 40+ users have reported a disturbance of the sound signal from particular models of digital telephones, which is corrected by changing the position or the model of the telephone.

#### F. Environmental testing:

Components of the COMBI 40+ Cochlear Implant System have been tested to verify their ability to withstand conditions, which can occur during manufacture, shipping, and use. These tests were conducted according to the International Safe Transit Authority Procedure 2A or 2B.

#### G. Active electrode testing:

Three (3) active electrode arrays were subjected to coiling of the entire length around a three (3) mm diameter rod. The acceptance criterion was set at ten (10) complete coilings for each electrode array, which far exceeds the maximum that could occur in clinical practice. All electrodes passed this test.

Three (3) active electrodes were subjected to flex testing of +/- 15 degrees around a diameter of five (5) mm. The criterion for acceptance was set at 10,000 cycles. All three (3) electrodes passed this test.

Three (3) electrodes were subjected to a twisting test. The electrode was fixed at the implant package side and twisted one (1) complete turn (360 degrees) in one direction and then 360 degrees in the opposite direction for each cycle. Fifty (50) complete cycles was set as the acceptance criteria. All electrodes passed this test.

Three (3) electrodes were subjected to a pull test where the electrode length was elongated by ten (10) mm. All electrodes passed this test.

#### H. Destructive testing:

The coiling test was performed to destruction on one sample. After 53 complete coilings around the three (3) mm diameter rod there was a breakage of the electrode.

The flex test was performed to destruction on four (4) electrodes. The mean number of cycles to failure was 890,000.

The pull test was also performed to destruction on the three (3) electrodes. The mean elongation length to the first electrode wire breakage was 15.9 mm.

#### I. Impact Testing:

Impact testing: Three (3) implants were subjected to impact testing to simulate hitting the head against a wall. It was determined that if the implant could withstand an impact that resulted in breakage of the wall, then a sufficient safety margin was inherent. All three (3) implants survived this test without damage.

A second impact situation was designed to simulate a young child falling from a counter top (1.2 meters) onto a cement floor directly impacting the implant site. Three (3) implants were subjected to this test. All three (3) survived the test without damage.

#### J. Crush Testing:

Crush testing was performed on twenty (20) implant housings. The average pressure required to damage the device was 1464 N. This corresponds to a weight of approximately 149 Kg or 328 lbs.

#### K. Hermetic Sealing:

Hermetic sealing of the implantable device is performed using a validated laser welding process in a specified protective atmosphere. The validation was performed utilizing a representative sample size of implant housings to demonstrate repeatability. All established laser welding parameters were proven to be effective. Hermetic seal integrity is verified on each device with a calibrated helium leak test.

### X. SUMMARY OF THE CLINICAL INVESTIGATION:

#### Study Design

In addition to the US clinical trial data, data have been supplied from European studies to support the safety of the COMBI 40+ Cochlear Implant System.

The following patient Inclusion and Exclusion Criteria were used:

A. Children - Inclusion Criteria:

1. All subjects aged eighteen (18) months through seventeen (17) years eleven (11) months must demonstrate a profound, bilateral sensorineural hearing loss with thresholds of 90 dB HL or greater at 1000 Hz and above, and must demonstrate minimal functional benefit from conventional amplification.
  - a) Electrophysiologic assessment: All children under the age of two (2) years must have electrophysiologic evidence of profound, bilateral hearing loss, i.e., absent acoustic reflexes and auditory brainstem response to click stimuli.
  - b) All children must have completed a three (3) to six (6) month trial with appropriate binaural amplification coupled with an intensive habilitation program that focuses on the development of auditory-based skills.
  - c) Demonstrated lack of acquisition or plateau of auditory skills as noted on an accepted inventory, such as Meaningful Auditory Integration Scale (MAIS) inventory or Central Institute for the Deaf (CID) performance categories, or in an individualized habilitation program over a three (3) to six (6) month period. A summary of habilitative history will be submitted to the sponsor prior to acceptance into the study.
  - d) Children under the age of five years who have the linguistic and cognitive ability to take the Multisyllabic Lexical Neighborhood Test (MLNT), Level 1, may not exceed a pre-operative score of 20% in the best-aided condition. Children age five years and older will be given the Lexical Neighborhood Test, Level 1, in the best-aided condition and must demonstrate a pre-operative word score of 20% or less.
2. Radiological evidence of cochlear ossification will justify a shorter trial with amplification, and may override other inclusion criteria.
3. English must be the primary language spoken in the home.
4. Subjects with an existing cochlear implant may be included if the cochlear implant is a) a functional single-channel cochlear implant, b) a functional multi-channel cochlear implant that is no longer manufactured or supported as a commercial product, or c) a non-functional single- or multi-channel cochlear implant.

B. Adults -Inclusion Criteria:

1. 18 years of age or older.
2. Severe to profound sensorineural deafness.

3. Fluent English speaker with good competence in reading and writing.
4. No functional cochlear implant usage in either ear, except in cases where:
  - a) The existing cochlear implant is no longer functional (i.e. due to device failure).  
Note: devices may be considered nonfunctional if required external system components (i.e. cables, headsets, speech processors) are not manufactured and cannot be obtained by the patient, despite the presence of an intact and functional internal implant package.
  - b) The existing cochlear implant is a single channel device.
5. Patients will typically demonstrate bilateral severe to profound sensorineural hearing loss determined by a pure tone average of 70dB HL or greater at 500 Hz, 1000 Hz, and 2000 Hz.
6. Hearing aid assessment.
7. No significant benefit from acoustic amplification in the best-aided condition: a score of  $\leq 40\%$  in the Hearing in Noise Test (HINT) sentences, audition only.
8. Radiological evaluation showing no obstacles to full electrode insertion and providing screening against central auditory lesions.

C. Adult and Children - Exclusionary Criteria:

Medical conditions that contraindicate cochlear implantation or surgical intervention (i.e. acute or chronic middle ear pathology, lesions or agenesis of the VIIIth cranial nerve, pathologies of the central auditory pathway, or Michel deformity).

D. Study Population and Study Period:

1. Children:

Eighty-two (82) children were implanted with the Implant C40+ standard electrode array at eighteen (18) sites in the United States between April 1, 1998 and March 1, 2000. The cumulative implant experience was 553 months. Data from fifty-five (55) subjects who have at least six (6) months device experience were used to support device efficacy. Of these, thirty-four (34) were younger than five (5) years and twenty-one (21) were older than five (5) years of age.

Of the twenty-seven (27) children that were not used to support efficacy, eighteen (18) subjects had not reached the six (6) month follow-up. Four (4) implanted patients did not meet the inclusion criteria for the investigational protocol, and five (5) patients were exempted due to health issues or inability to comply with the protocol requirements.

## 2. Adults:

One hundred and six (106) adults were implanted with the Implant C40+ standard electrode array at twenty-six (26) sites in the United States between November 10, 1997 and September 29, 2000. The cumulative experience was 713 months. Data from forty-five (45) post-linguistically deafened and eighteen (18) pre-linguistically deafened patients who have at least six (6) months device experience were used to support device efficacy.

Of the 43 adults that were not used to support efficacy, thirty-five (35) had not reached the six (6) month follow-up. Five (5) implanted patients did not meet the inclusion criteria for the investigational protocol, and three (3) patients were exempted due to health issues or inability to comply with the protocol requirements.

## E. Safety data

In addition to the monitoring of all complications and adverse events, fifty (50) children and fifty (50) adults with a minimum of one (1) year device experience were used to evaluate device safety. These were comprised of fifty (50) US children, forty (40) US adults, and ten (10) European adults. The analysis for the fifty (50) US pediatric and forty (40) US adult patients was comprised of evaluating the stability of the threshold (THR) charges, the most comfortable level (MCL) charges and the dynamic range, the stability or increase of auditory perceptual measures over time, medical/otological evaluation, and monitoring of adverse events.

The safety data analysis for the ten (10) European adults consists of the evaluation of the stability of the threshold (THR) charges, and the most comfortable level (MCL) charges and dynamic range over time using initial stimulation (one (1) month), and post one (1) year data points.

The possibility of electrode instability or neural damage was considered to exist if either the threshold (THR) charge (THR\* pulse duration) increased by more than 50% from one programming session to the next, or if the dynamic range decreased by more than 30%. It has been shown that some patients benefit from higher stimulation rates, which is achieved by deactivation of channels. Deactivation of channels was not included in the analysis if it was done intentionally to increase the stimulation rate in order to increase performance for the individual.

There were no US pediatric or adult patients demonstrating evidence of electrode instability or neural damage according to the defined criteria. There were no European adult patients demonstrating evidence of electrode instability or neural damage according to the defined criteria.

## 1. Adverse Events and Complications:

All patients implanted in the United States with the Implant C40+ standard electrode array during the Investigational Device Exemption (IDE) trial were included in the safety analysis. A total of 188 patients have been followed for a total experience of 1,266 months. Adverse events were classified as medical/surgical or device related. Complications were classified as major if they required surgical intervention and minor if they resolved spontaneously or with non-invasive medical treatment. There were no internal device failures in children or adults during the study period.

## 2. Adults:

Twenty (20) patients out of 106 experienced twenty-two (22) adverse events or complications during the study period. One (1) event was classified as major because the resolution required revision surgery. The remaining twenty-one (21) events were classified as minor. All adverse events or complications have been resolved.

### a) Medical/Surgical Complications: Adults

One (1) patient reported uncomfortable stimulation. This event was classified as major because the patient required revision surgery and was re-implanted due to the frequency and severity of the symptoms (the implant was fully functional).

One (1) patient has experienced episodic vertigo accompanied by a sensation of fullness and tinnitus and has been diagnosed with vestibular neuritis. A Computer Tomography (CT) scan and diagnostic testing of the device yielded no evidence of abnormality with the device or device placement. The patient recently reported that his symptoms are much better and have begun using his device eight (8) to twelve (12) hours per day.

One (1) patient was able to create an air pocket over the implant caused by vigorous nose blowing. This was resolved through counselling.

One (1) patient developed a facial weakness two weeks post-surgery. This was treated with steroids and anti-inflammatory medication, and resolved prior to first-fitting.

Two (2) patients developed post-operative swelling at the implant site. One (1) was treated with the use of additional magnets to hold the external coil in place. The other wore a headband to keep the external coil in place. Both patients swelling decreased. One (1) patient has no problem with the magnet and one (1) patient now wears a headband intermittently.

One (1) device case was reversed in the bone bed, resulting in the external coil magnet repelling rather than attracting. The patient received an external coil that was modified by reversing the coil magnet. The physician was subsequently re-instructed on proper implant procedure.

b) Device Related Adverse Events: Adults

Six (6) patients reported uncomfortable stimulation. Five (5) were resolved through reprogramming and exchange of external equipment. One (1) patient required a modified coil with a silicone coating to protect from moisture.

Two (2) patients reported a constant buzzing sound from the processor, one (1) of which experienced headaches and general discomfort.

One (1) patient reported a strong metallic taste sensation from stimulation to the external auditory canal (example: water from shower in ear, finger touching canal).

Two (2) patients reported tinnitus.

One (1) patient reported a two-week period of dizziness post-operatively.

Two (2) patients experienced probable facial nerve stimulation. One (1) manifested as a twitching sensation while the other felt a sensation in a tooth.

One (1) patient experienced a tickling sensation in the ear.

3. Children:

Nineteen (19) out of eighty-two (82) implanted children experienced nineteen (19) adverse events or complications. Three (3) were considered major, requiring surgical intervention, [one (1) explantation and two (2) re-suturing] and 16 were considered as minor. All have been resolved.

a) Medical/Surgical Complications: Children

Two (2) patients presented with post-operative infection. They were treated with intravenous antibiotics and no further problems have been reported.

Three (3) patients presented with middle ear infections, which were resolved with medical treatment.

Three (3) patients' scalp incisions opened during the post-operative healing period (two due to impact, one unknown cause). Two (2) of these required re-suturing. All incisions have healed properly and no further difficulties were encountered.



One (1) patient with a history of recurrent Acute Otitis Media (AOM) developed chronic otorrhea and granulation tissue. At the time of the cochlear implant surgery, there was granulation tissue in the middle ear and mastoid. There was also erosion of the stapes' superstructure. There was no evidence of an inflammatory polyp in the ear canal, as was noted to be present six (6) months post implant. The patient was treated with aggressive local management, which was unsuccessful. The device has been explanted. The patient has subsequently been re-implanted.

Two (2) patients had erythema at the implant site.

b) Device Related Adverse Events: Children

Three (3) children had facial nerve stimulation, which was resolved by programming.

Three (3) children had vertigo accompanied either by tinnitus or nausea.

One (1) child was only able to use five (5) stimulation channels.

One (1) child presented with skin irritation at the implant site as a result of continuing to wear a cracked coil.

F. Study Outcomes and Statistical Considerations:

1. Children:

Device efficacy was defined as improved performance on any measure of the speech perception battery in quiet after six (6) months of device use as compared to the best-aided pre-surgical condition on age-appropriate measures. Because children express improvement in speech recognition differently due to age, maturation, language and cognitive development, a different test battery was used for younger children (ages eighteen (18) months through four (4) years eleven (11) months) than for older children (ages five (5) years through seventeen (17) years eleven (11) months). In addition to speech perception measures, the Meaningful Auditory Integration Scale (MAIS) scale was administered as a measure of the child's ability to integrate auditory information into daily routines, enabling evaluation of children who have difficulty taking standardized tests due to maturational factors. Sound-field warble tone, speech detection and speech recognition thresholds were measured to complement the assessment of auditory performance. An auditory skills checklist was also administered and evaluated. Clinical safety was supported by monitoring of all adverse events and analysis of stability of electrode impedances, fitting parameters and auditory perceptual measures over time.

The primary measure is a single test of binomial proportions to test that the MED-El COMBI 40+ Cochlear Implant System improved performance on any measure of the speech perception battery in quiet after six (6) months of device use compared to the best-aided pre-surgical condition on age-appropriate measures. As a secondary set of analyses, group scores are compared using a Student's Paired t-Test for each audiologic measure at pre-surgical compared with the six (6) month evaluation. In addition, poolability of data across investigational sites and audiological performance over time are analyzed using repeated measures analysis of variance (RM-ANOVA) models, including terms for investigational site and time in the statistical models. Due to the multiplicity of assessments (i.e., 10 in older children, 5 in younger children), statistical significance of the primary analysis of the single test of proportions test is considered  $0.05 / 10 = 0.005$  for older children, and  $0.05 / 5 = 0.01$  for younger children. A two-sided alpha level of 0.05 is considered statistically significant for all statistical hypothesis tests in the secondary analyses. Descriptive statistics are supplied for each test according to the age group to fully characterize the outcome of all the study participants.

## 2. Adults:

Device efficacy was defined as improved scores on speech recognition materials presented at conversational speech levels (70 dB SPL) in quiet in the auditory-only condition, as measured by the Hearing In Noise Test (HINT) sentence test. Device efficacy was evaluated using a single subject repeated measures design, with the subject serving as his/her own control. This method optimizes control over inherent variability among subject and disease characteristics. No attempt was made at blinding either the patients or the clinicians. Statistical analysis was performed on each speech recognition measure for all subjects comparing the best-aided pre-surgical condition to six (6) months experience with the COMBI 40+. Trends in impedance levels and fitting parameters, in addition to the monitoring of all adverse events, were analysed to support device safety.

Sentence recognition materials presented using sound alone at normal conversational levels in quiet are considered to provide a standard clinical measure of everyday performance. It is generally agreed that an improvement as compared to the best-aided pre-surgical score of 20 percentage points on these materials represents a clinically significant increase in performance. Therefore, patients experiencing an increase of 20% or more on this measure (open set testing measure) will be classified as exhibiting *clinically significant improvement*.

Many patients with poor open-set speech understanding derive clear subjective benefit in their daily lives from cochlear implantation. Therefore, patients demonstrating an increase on sentence recognition materials of less than 20% and an improvement in any other test are defined as *some improvement*.

## G. Efficacy Results:

## 1. Younger children:

Children who entered the study as a member of this age category (ages eighteen (18) months through four (4) years eleven (11) months) continued with the same protocol throughout the study even if they exceeded the age of five (5) during the follow-up period. The mean age for this group was 2.9 years.

The following test measures were administered pre-operatively and at six (6) months device experience for the younger children. All live-voice test administration was monitored with a sound-level meter at 70 dB SPL. All recorded tests were administered at 70 dB SPL.

- IT-MAIS Parent Interview (with Infant-Toddler extension)
- Early Speech Perception (ESP) Low Verbal Version administered live-voice
- Glendonald Auditory Screening Procedure (GASP) Words administered live voice: The GASP could not be administered immediately following the ESP standard pattern perception subtest because of shared vocabulary.
- Auditory Skills Checklist was completed by the child's therapist (must have been a certified audiologist, speech language pathologist, or auditory-verbal therapist).

Of the younger children who were capable of being tested on open-set word recognition tasks (Refer to CHART 1 - Pediatric Performance Matrix):

- 70 % (16/23) demonstrated improvement on the ESP low verbal pattern perception test.
- 50 % (10/20) demonstrated improvement on the ESP low verbal spondee identification test.
- 48 % (10/21) demonstrated improvement on the ESP low verbal monosyllabic word identification test.
- 57 % (12/21) demonstrated improvement on the GASP open set word test.

IT-MAIS parental questionnaire:

- All younger children who were tested (33/33) improved on the MAIS as an overall score.
- As a group, the younger children significantly improved on all questions of the MAIS:
  - 76% (25/33) of the children frequently or always responded to their name in quiet compared with 15% (5/33) pre-operatively.

- 52% (17/33) of the children frequently or always responded to their name in noise compared with 3% (1/33) pre-operatively.
- 67% (22/33) of the children frequently or always spontaneously alerted to environmental sounds compared with 6% (2/33) pre-operatively.
- 45% (15/33) of the children frequently or always alerted to new sounds when in an unfamiliar surrounding compared with 0% (0/33) pre-operatively.
- 67% (22/33) of the children frequently or always recognized or responded appropriately to sounds in the classroom and at home compared with 3% (1/33) pre-operatively.
- 52% (17/33) of the children frequently or always were able to discriminate between two speakers using audition alone compared with 6% (2/33) pre-operatively.
- 67% (22/33) of the children frequently or always recognize speech as different than non-speech sounds compared with 6% (2/33) pre-operatively.
- 55% (18/33) of the children frequently or always were able to associate vocal tone (anger, excitement) with its meaning as compared to 12% (4/33) pre-operatively.

## 2. Older Children:

Children aged five (5) years through seventeen (17) years eleven (11) months. Children in this group had a mean age at implantation of 8.8 years. All live-voice test administration was monitored with a sound-level meter at 70 dB SPL. All recorded tests were administered at 70 dB SPL. The following measures have been used to establish device efficacy:

- MAIS Parent Interview
- Early Speech Perception (ESP) Test Standard Version administered live voice
- Multisyllabic Lexical Neighborhood Test (MLNT), Level 1 recorded version
- Lexical Neighborhood Test (LNT), Level 1 recorded version
- Glendonald Auditory Screening Procedure (GASP) Words administered live voice
- Bamford-Kowal-Bench (BKB) Sentences recorded version
- Auditory Skills Checklist to be completed by the child's therapist (must be a certified audiologist, speech language pathologist, or auditory-verbal therapist).

Of the older children who were capable of being tested on open-set word recognition tasks (CHARTS 2 and 3 - Pediatric Performance Matrix):

- 68% (13/19) demonstrated improvement on the ESP standard pattern perception test.
- 79% (15/19) demonstrated improvement on the ESP standard spondee identification test.
- 68% (13/19) demonstrated improvement on the ESP standard monosyllabic word identification test.
- 79% (15/19) demonstrated improvement on the GASP open set word test.
- 63% (12/19) demonstrated improvement on the LNT word test.
- 89% (17/19) demonstrated improvement on the LNT phonemes test.
- 65% (11/17) demonstrated improvement on the MLNT words test.
- 82% (14/17) demonstrated improvement on the MLNT phonemes test.
- 53% (10/19) demonstrated improvement on the BKB sentence test.

MAIS parental questionnaire:

- All older children who were tested (20/20) improved on the MAIS as an overall score.
- As a group, the older children significantly improved on all questions of the MAIS.
  - 95% (19/20) of the children frequently or always responded to their name in quiet compared with 55% (11/20) pre-operatively.
  - 80% (16/20) of the children frequently or always responded to their name in noise compared with 25% (5/20) pre-operatively.
  - 80% (16/20) of the children frequently or always spontaneously alert to environmental sounds in the home compared with 25% (5/20) pre-operatively.
  - 70% (14/20) of the children frequently or always alerted to new sounds when in an unfamiliar surrounding compared with 25% (5/20) pre-operatively.
  - 75% (15/20) of the children frequently or always responded recognized or responded appropriately to sounds in the classroom and at home compared with 45% (9/20) pre-operatively.
  - 65% (13/20) of the children frequently or always were able to discriminate between two speakers using audition alone compared with 40% (8/20) pre-operatively.
  - 70% (14/20) of the children frequently or always recognize speech as different than non-speech sounds compared with 45% (9/20) pre-operatively.
  - 55% (11/20) of the children frequently or always were able to associate vocal tone (anger, excitement) with its meaning as compared to 25% (5/20) pre-operatively.

Communicative Skills Checklist (older and younger children) of those tested:

The terms “sometimes”, “often” and “always” refer to responses at the 25%, 50% and 75%+level, respectively.

- 84% (42/50) of the children often or always searched for the sound source compared to 34% (17/50) pre-operatively.
- 80% (40/50) of the children often or always identified a sound source compared to 34% (17/50) pre-operatively.
- 62% (31/50) of the children were able to discriminate intensity differences often or always compared to 36% (18/50) pre-operatively.
- 80% (40/50) of the children were able to discriminate durational cues often or always compared to 50% (25/50) pre-operatively.
- 68% (34/50) of the children were able to discriminate pitch differences often or always compared to 28% (14/50) pre-operatively.
- 76% (38/50) of the children were able to respond to sounds at a distance often or always compared to 22% (11/50) pre-operatively.
- 72% (36/50) of the children were often or always able to associate a familiar sound with its meaning or anticipated event compared to 26% (13/50) pre-operatively.
- 64% (32/50) of the children were often or always able to improve their speech.
- 56% (28/50) of the children were able to respond to simple directions often or always using audition alone compared to 26% (13/50) pre-operatively.
- 36% (18/50) of the children were often or always able to identify and comprehend speech in a noisy environment without lip reading compared to 8% (4/50) pre-operatively.
- 24% (12/50) of the children were able to understand a message from an electronic sound source such as radio or film compared to 6% (3/50) pre-operatively.

### 3. Adults:

Data from forty-five (45) post-linguistically deafened patients and eighteen (18) pre-linguistically deafened patients with six (6) month device experience were used to substantiate device efficacy. The performance at six (6) months device experience was compared to the pre-operative best-aided hearing condition with appropriately fitted hearing aids.

The following tests were administered pre-operatively and at six (6) months device experience. All speech recognition tests were administered from a CD recording at 70 dB SPL.

- 4-choice spondee words            CD Recording (Closed Set Test)
- Sentences in quiet                HINT sentences, CD recording

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Sentences in noise</li> <li>• Monosyllabic words</li> <li>• Sentences via telephone</li> </ul> | CUNY sentences, CD recording<br>HINT sentences at 10dB SNR, CD<br>Recording<br>CNC words, CD recording<br>CID sentences, live voice |
|---|---|

a) Post-linguistically Deafened Adults

The average age at implantation for the forty-five (45) post-linguistically deafened patients was 53.5 years. These patients had a mean duration of hearing loss of twenty-eight (28) years.

At six (6) months experience with the COMBI 40+ Cochlear Implant System, adults with hearing loss less than twenty-five (25) years demonstrated (refer to CHART 4 - Adult Performance Matrix):

- a mean increase in the ability to recognize words in CUNY sentences in quiet of 72% above their pre-operative score.
- a mean score of 86% on CUNY in quiet.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 70% above their pre-operative score.
- a mean score of 75% on HINT scores in quiet.
- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 61%.
- a mean score of 63% on HINT sentences in the presence of background noise.
- a mean increase in the ability to recognize CNC monosyllabic words of 40%.
- a mean score of 44% on CNC monosyllabic words.
- a mean increase in the ability to recognize CID sentences over the telephone of 68%.
- a mean score of 68% on CID sentences over the telephone.

At six (6) months experience with the COMBI 40+ Cochlear Implant System, adults with hearing loss greater than twenty-five (25) years demonstrated:

- a mean increase the ability to recognize words in CUNY sentences in quiet of 56% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 50% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 41%.
- a mean increase in the ability to recognize CNC monosyllabic words of 29%.
- a mean increase in the ability to recognize CID sentences over the telephone of 42%.

### b) Pre-linguistically Deafened Adults

The average age at implantation for the eighteen (18) pre-linguistically deafened patients was 37.4 years. These patients had a mean duration of hearing loss of 36.5 years. At six (6) months experience with the COMBI 40+, Pre-linguistically Deafened adults, ((N =18), range birth to 42<sup>note 1</sup> years, profoundly deafened prior to 6 years of age) demonstrated (refer to CHART 5 - Adult Performance Matrix):

Note 1: The upper limit of forty-two (42) years is for those cases when hearing loss was documented upon inclusion into the clinical trial. In all cases, it has been found that these patients were deafened at birth, or prior to the age of six (6) due to maternal measles, maternal meningitis, or other congenital reasons.

- a mean increase the ability to recognize words in CUNY sentences in quiet of 21% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 19% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 12%.
- a mean increase in the ability to recognize CNC monosyllabic words of 10%.
- a mean increase in the ability to recognize CID sentences over the telephone of 20%.

### c) Combined Pre and Post-linguistically Deafened Adults

As a combined group (< twenty-five (25) years deafened and > twenty-five (25) years deafened populations), eighty-five (85) percent demonstrated clinically significant improvement defined as an increase on open set sentence tests of over 20% and all but one (1) demonstrated some improvement. When both recorded sentence tests included in the audiologic battery are considered (20% improvement on HINT in quiet or CUNY sentences), 91% of subjects achieved a 20% improvement on one or both of the test scores.

Following at least six (6) months of device usage, twenty-six (26) patients had the fitting of their TEMPO+ Speech Processor optimized with the DIB. After thirty (30) days with the new program, speech understanding results on CUNY sentences in quiet and CNC words with the TEMPO+ Speech Processor were compared to the CIS PRO+ Speech Processor. Although the mean values for the TEMPO+ Speech Processor are higher than the CIS PRO+ Speech Processor, the difference was not statistically significant.

Eighty-four (84) percent of the subjects (N = 45) report that the implant has ‘quite positively’ (40%) or ‘very positively’ (44%) affected their lifestyle. Responses on the “Quality of Life” questionnaire demonstrated the following statistically



significant improvements after six (6) months device experience as compared to the pre-operative condition:

- COMBI 40+ adult recipients are less concerned about their safety or welfare because of their deafness.
- They do not change their activities as much due to concerns about their safety or welfare because of their deafness.
- They are less often upset because they are deaf.
- Their deafness does not affect enjoyment of social events as much.
- They are more comfortable attending social events.
- They feel less isolated as a result of their deafness.
- Their deafness does not affect their sense of belonging as much.
- They find it easier to visit a store or restaurant alone.
- It is easier for them to communicate.
- It is less frustrating for them to communicate.
- The quality of their closest relationship is less affected by their deafness.
- They do not feel left out of conversations with family members as much.
- Their relationships with friends are more satisfying.
- Their relationships with friends are less affected by their deafness.
- Their performance at work was less affected by their deafness.
- Deafness did not alter their hobbies or recreational activities as much.
- They more often engaged in activities that usually require hearing (watching TV, attending sporting events).
- Their lifestyle is less affected by their deafness.

Although most of the instrument items do not demonstrate statistically significant improvements in quality of life for the pre-linguistically deafened patients, probably due to limited power related to the small sample, responses to most of the items are more favorable at six (6) month post implant as compared to pre-surgical. Six (6) months after implantation of the COMBI 40+, 83% of these subjects (N = 18) reported that the device ‘very positively’ (50%) or ‘quite positively’ (33%) affected their lifestyle.

#### H. Assessment of comparability of treatment groups:

##### 1. Children:

The children were divided into younger (ages eighteen (18) months through four (4) years eleven (11) months) and older (ages five (5) years through seventeen (17) years eleven (11) months) because children express improvement in speech recognition differently due to age, maturation, language, and cognitive development. Although the speech testing battery is somewhat different, the outcomes being measured remain the same. Using age appropriate measures assures that the tests are sensitive to the improvements demonstrated by the

children in that age group. As a result, improvement for both groups was evident within the same time period (three (3) and six (6) months).

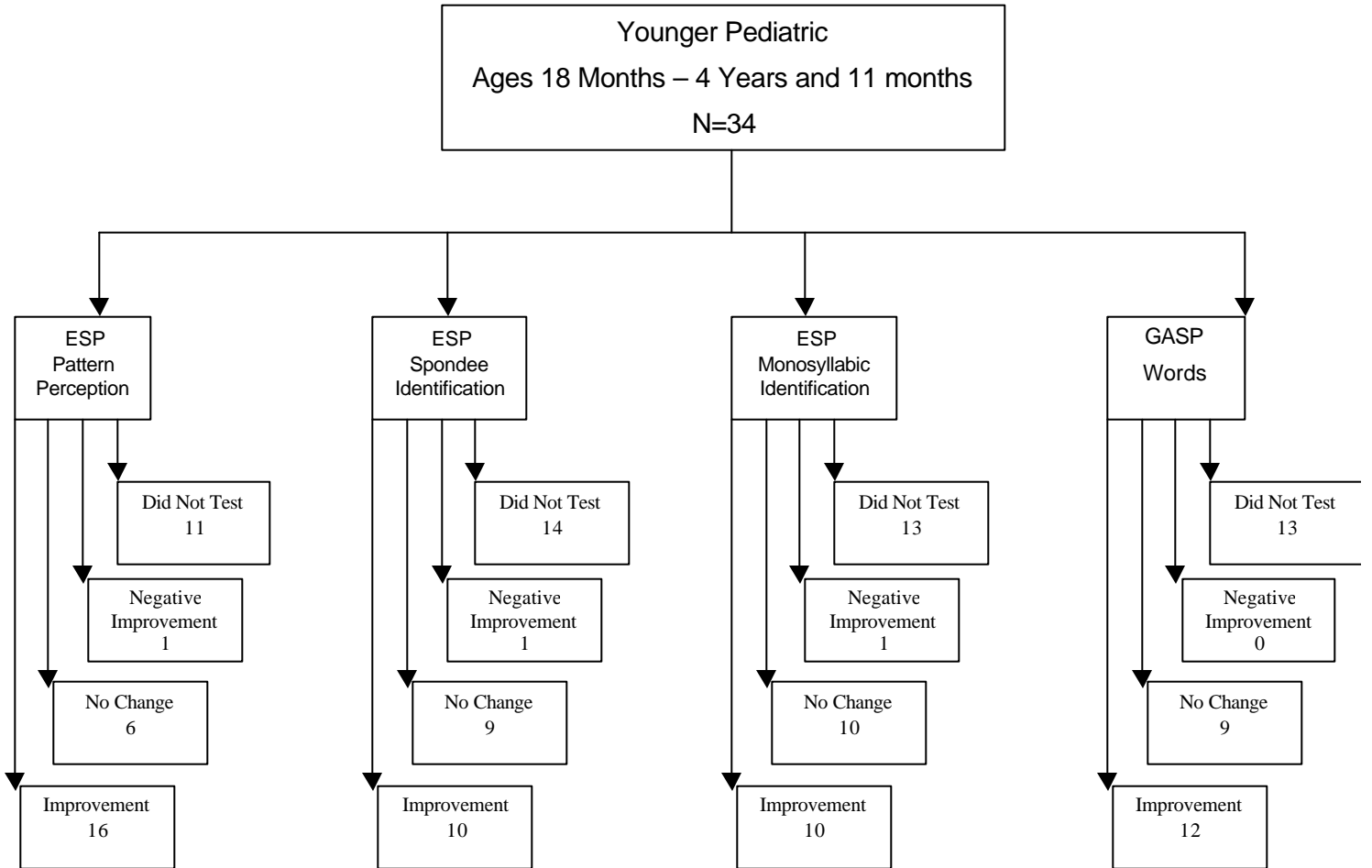
## 2. Adults:

Within the primary study sample, i.e. forty-five (45) post-linguistically deafened subjects, three (3) secondary analyses to compare audiologic benefit in subsets of subjects were conducted.

- a) In a comparison of subjects implanted at less than fifty (50) years of age (N = 20) versus those fifty (50) years of age or older (N = 25), the data suggest that the audiologic benefit demonstrated at six (6) months was similar between the two (2) age groups.
- b) A comparison of audiologic benefit between those deafened for less than twenty-five (25) years versus twenty-five (25) years or greater suggested that a shorter length of deafness was associated with greater levels of audiologic improvement at six (6) months. Of note, however, even those who had been deafened for longer periods of time (>twenty-five (25) years) experienced an average improvement in audiologic test scores of 25% to 56% compared to pre-implant scores.
- c) A final comparison of the forty-five (45) post-linguistically deafened subjects addressed the poolability of subjects across participating centers. Although the power for this analysis was low, there was no evidence to suggest that any single institution differed from the others related to audiologic benefit achieved by the respective subjects.

An analysis was also conducted to examine the comparability of the post-linguistically deafened sample (N = 45) and the pre-linguistically deafened sample (N = 18). Although the pre-linguistically deafened subjects did demonstrate statistically significant improvements in audiologic performance at six (6) months, the level of improvement for all open-set tests was significantly greater among the post-linguistically deafened sample.

CHART 1 - Pediatric Performance Matrix  
Younger Group: Ages 18 Months – 4 Years and 11 months  
Pre-operative vs. 6 month data



**CHART 2 - Pediatric Performance Matrix**  
**Older Group: Ages 5 Years to 17 years and 11 months**  
**Pre-operative vs. 6 month data**

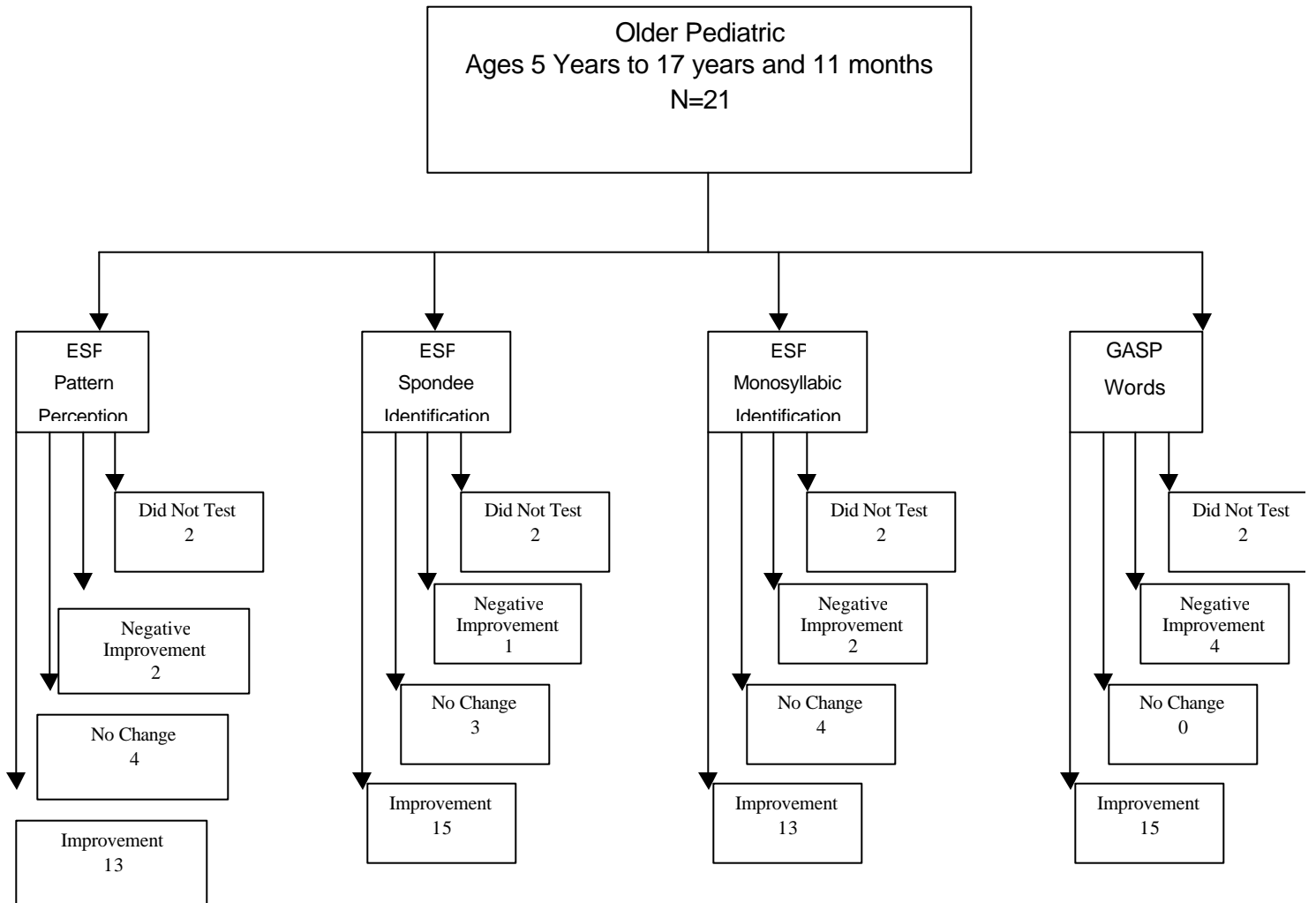


CHART 3 - Pediatric Performance Matrix  
Older Group: Ages 5 Years to 17 years and 11 months  
Pre-operative vs. 6 month data

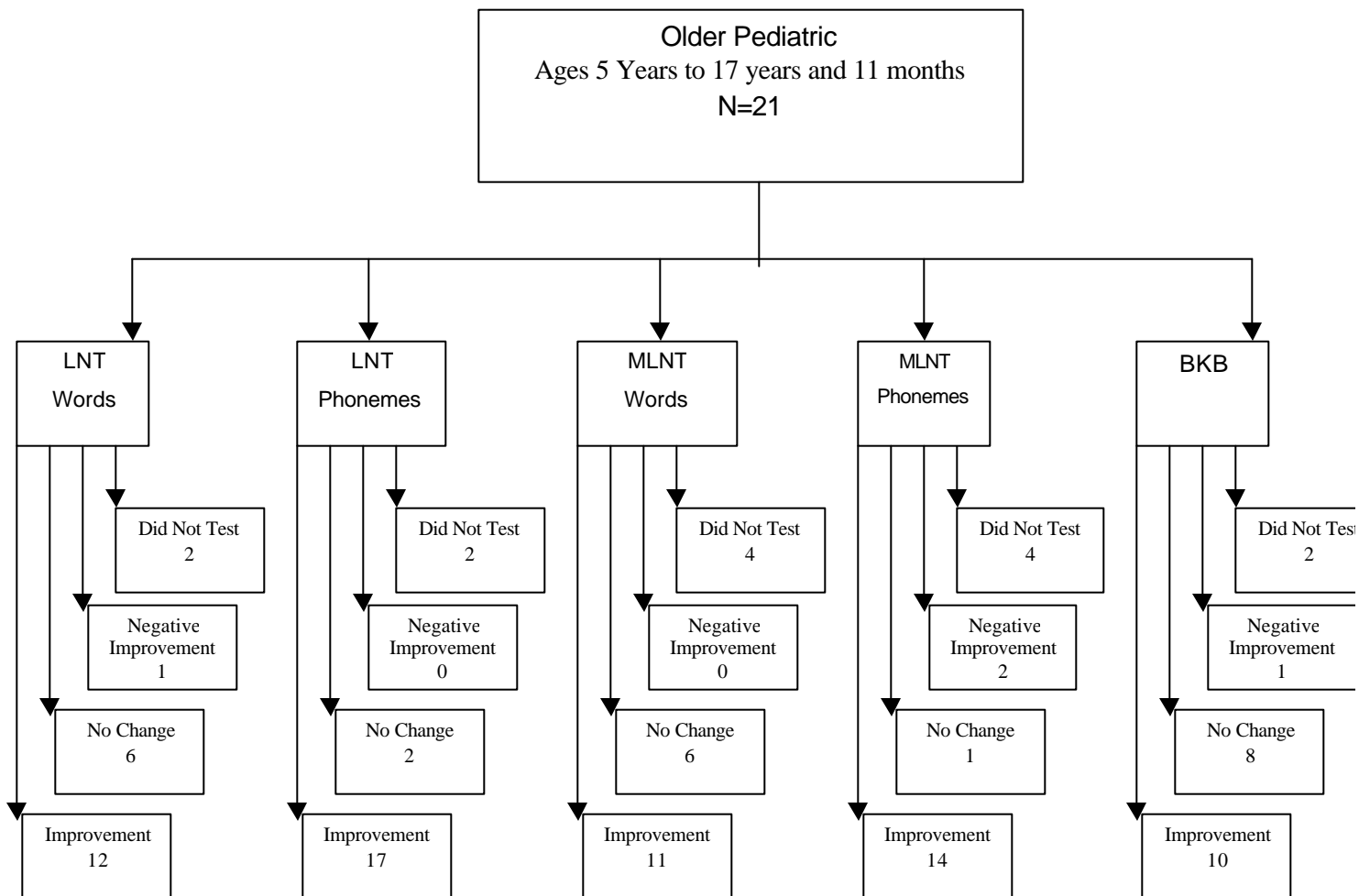


CHART 4 - Adult Performance Matrix  
Post-Linguistically Deafened  
Pre-operative vs. 6 month data

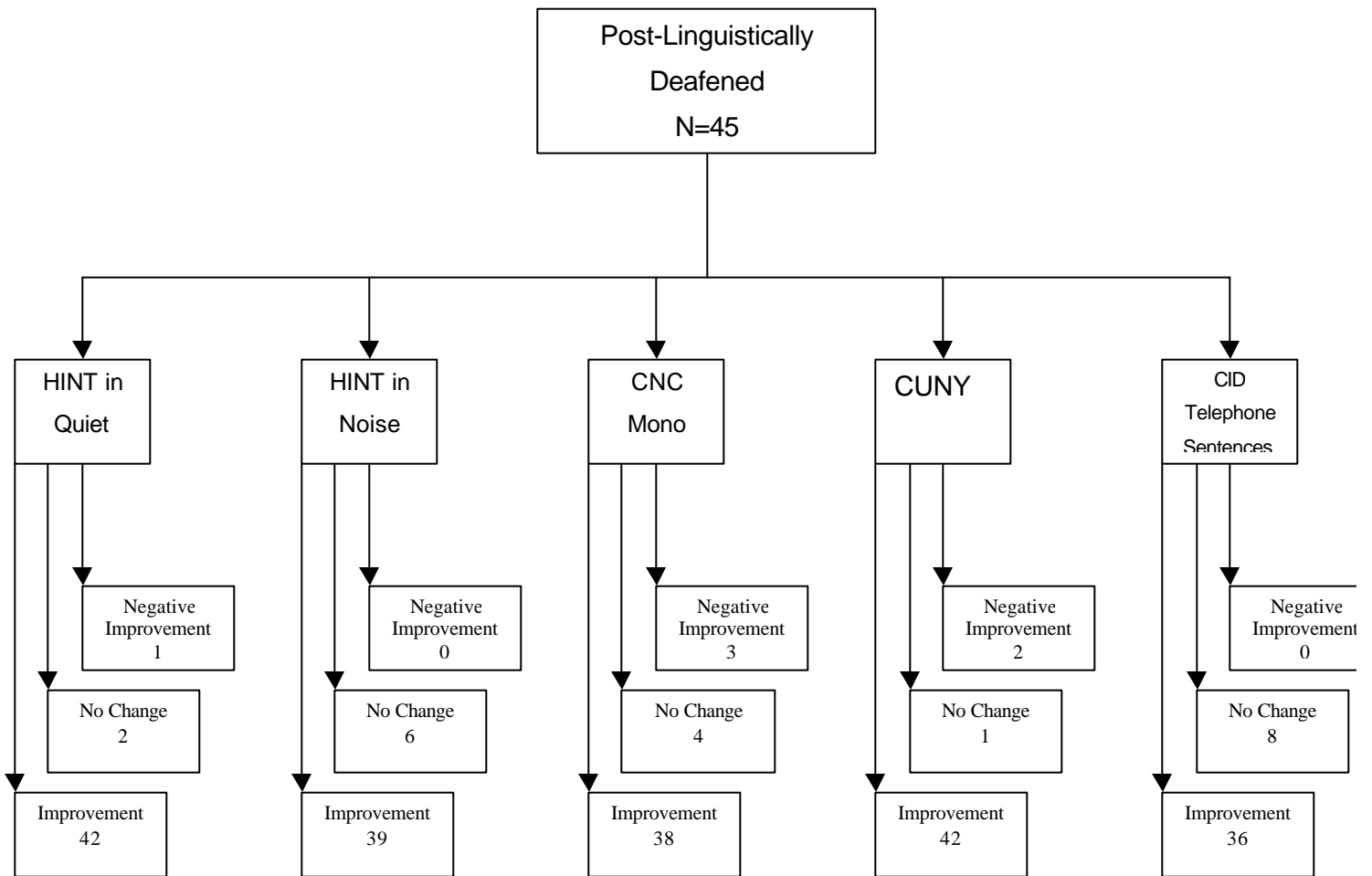
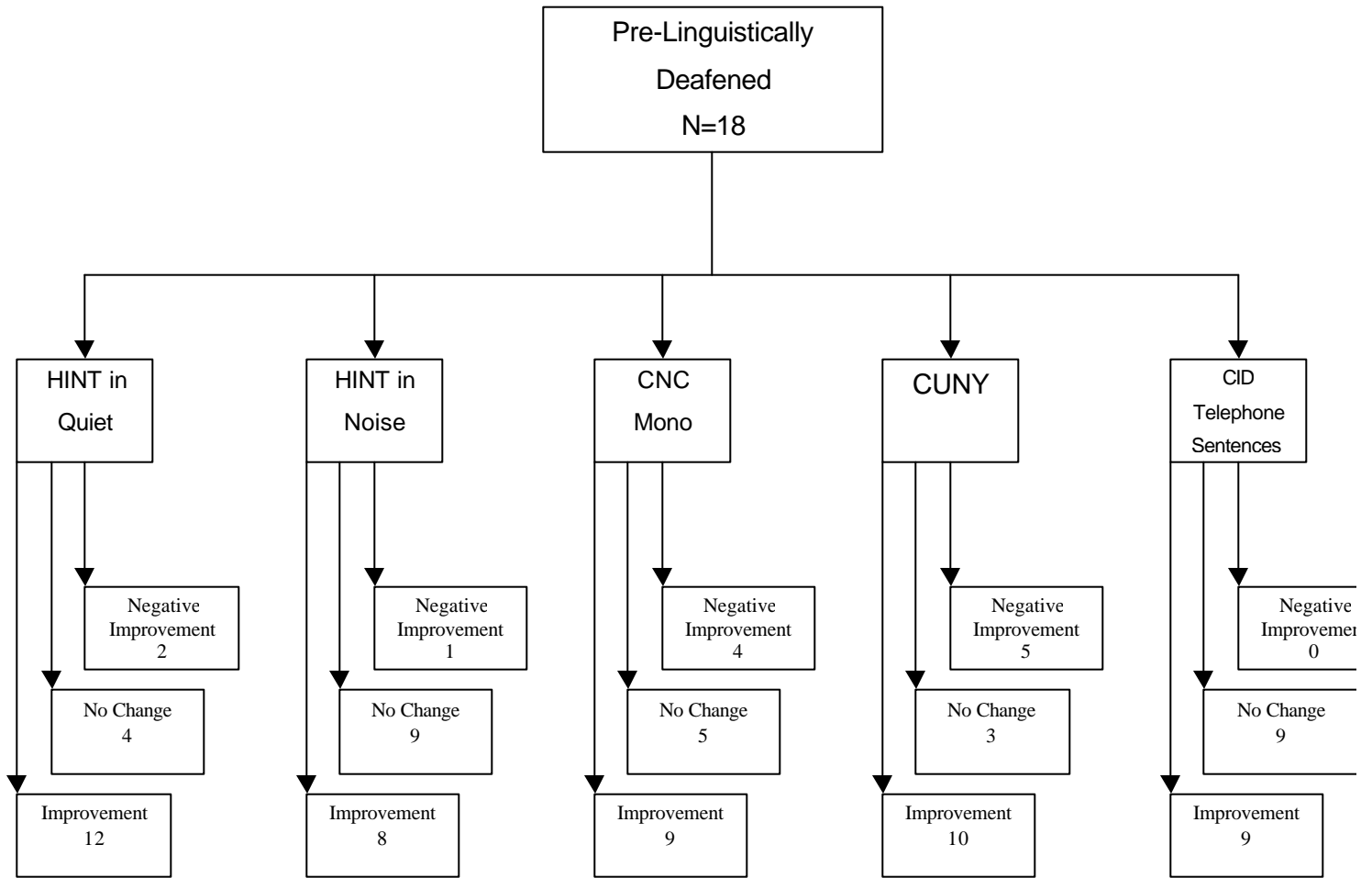


CHART 5 - Adult Performance Matrix  
Pre-Linguistically Deafened  
Pre-operative vs. 6 month data



## XI. CONCLUSIONS DRAWN FROM STUDY:

### A. Safety:

Safety data were collected on 188 US patients followed for a total experience of 1266 months. There were a total of forty-one (41) adverse events, twenty-two (22) occurring in adults and nineteen (19) occurring in children. Of these, three (3) were classified as major and required surgical intervention. All complications have been resolved and the patients continue to use the device except for one (1) device explantation. The patient has subsequently been re-implanted.

There have been no life-threatening or hazardous, permanent side effects. There were no internal device failures in children or adults during the study period. Although the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for this device.

### B. Stability of MCL, THR, and Dynamic Range:

Electrode instability or neural damage was considered to exist if the threshold (THR) charge (THR\* pulse duration) increased by more than 50% from one programming session to the next, or if the dynamic range decreased by more than 30%. There was no evidence of electrode instability or neural damage. Safety of the COMBI 40+ is substantiated by the stability or increase of speech recognition results over time, stability of fitting parameters over time, and the incidence of major side effects of less than 0.25 % per month.

### C. Efficacy:

Data from forty-five (45) post-linguistically deafened adults, eighteen (18) pre-linguistically deafened adults, and fifty-five (55) children with six (6) months of device experience were used to substantiate device efficacy.

The majority of the post-linguistically adult subjects demonstrated significant improvement on recorded measures of speech recognition and on the subjective questionnaire at six (6) months device experience as compared to the best-aided pre-operative condition. For each audiologic test, the data demonstrate a highly statistically significant audiologic ( $p < 0.001$ ), improvement at six (6) months as compared to pre-operatively. Mean improvement scores range from 32% to 62% depending on the specific test. Further improvement in audiological performance from six (6) months to one (1) year was demonstrated for HINT sentences in quiet and CUNY sentences. Except for the four-choice spondee test, each audiological test demonstrated higher scores among those deafened for a shorter length of time (< twenty-five (25) years) than those deafened for longer lengths of time (> twenty-five (25) years). Overall, 84% of the subjects subjectively report that the implant has positively or very positively affected their lifestyle.



For the pre-linguistically deafened adults, changes in HINT in quiet scores from pre-implant to six (6) months post-implant demonstrated a highly significant audiological improvement ( $p < 0.001$ ), and all other audiologic tests in the battery demonstrated similar levels of improvement in performance. 20% or more improvement was detected in 18% to 55% of the subjects, depending on the specific test. Overall, 83% of the subjects subjectively report that the implant has very positively or quite positively affected their lifestyle.

Device efficacy was demonstrated on the MAIS questionnaire at three (3) and six (6) months as compared to the pre-surgical condition for both younger and older children. Significant improvement was seen on all questions of the MAIS in both age groups at six (6) months. All children demonstrated some improvement on the MAIS.

Statistically significant improvement was seen on the ESP low verbal test (pattern perception, spondee, and monosyllabic words) and on the GASP at both three (3) months and six (6) months device experience as compared to the best-aided pre-surgical condition for the younger children. For the older children, significant improvement was seen on the standard ESP (pattern perception, spondee, and monosyllabic words), GASP, LNT (words and phonemes), and MLNT (words and phonemes) at both three (3) and six (6) months. Improvement on the BKB sentences was significant at six (6) months as compared to best-aided pre-surgical condition.

#### D. Risk/Benefit:

Data from this clinical trial indicate that the incidence of medical/surgical and device related adverse events with the COMBI 40+ Cochlear Implant System is low. The incidence of major complications was less than 3%, and there were no life-threatening or permanent adverse effects. The overall incidence of complications was less than 1.9 % per month of device usage. The efficacy data demonstrate highly significant benefits at six (6) months device experience as compared to the best-aided pre-surgical condition for longer (> twenty-five (25) years) and shorter term (< twenty-five (25) years) deafened adults, implantation at younger than fifty (50) years of age, implantation at older than fifty (50) years of age, pre-linguistically deafened adults, and for younger and older children. Several of the younger children lacked the cognitive ability and linguistic skills to be tested with standardized speech recognition measures. For these children, efficacy is more appropriately measured by the MAIS questionnaire.

There is no evidence that the benefits provided by the system degrade over time, and the complication rate was found to be acceptable. The data provide reasonable assurance that the COMBI 40+ Cochlear Implant System is safe and effective for its intended use in the intended population.

## XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear, Nose and Throat Devices Panel, an FDA advisory committee, for review and recommendation because the

information in the PMA substantially duplicates information previously reviewed by this panel.

### XIII. CDRH DECISION

The applicant's manufacturing facilities were inspected on May 29<sup>th</sup> and June 22<sup>nd</sup> and 28<sup>th</sup>, 2001 and were found to be in compliance with the device Quality System Regulations.

FDA issued an approval order on August 20, 2001.

### XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling

Hazards to Health from Use of the Device: See the Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.