RESEARCH PROTOCOL

Bilateral Cochlear Implantation Benefits in Adult Users of the HiRes® 90K Bionic Ear System
Protocol ID: NL 24990.018.08

Short title: BILATERAL COCHLEAR IMPLANTATION

Version: 5

Date: 30-06-2011
# TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE ................................................................. 11
2. OBJECTIVES ............................................................................................... 14
3. STUDY DESIGN .......................................................................................... 15
4. STUDY POPULATION ................................................................................. 16
   4.1 Population (base) .................................................................................. 16
   4.2 Inclusion criteria .................................................................................. 16
   4.3 Exclusion criteria ................................................................................ 17
   4.4 Sample size calculation ....................................................................... 17
5. TREATMENT OF SUBJECTS ..................................................................... 17
   5.1 Investigational product/treatment .......................................................... 17
   5.2 Use of co-intervention (if applicable) ..................................................... 19
6. METHODS .................................................................................................. 19
   6.1 Study parameters/endpoints .................................................................. 19
      6.1.1 Main study parameter/endpoint ..................................................... 19
      6.1.2 Secondary study parameters/endpoints (if applicable) .................. 19
   6.2 Randomisation, blinding and treatment allocation .................................. 19
   6.3 Study procedures ................................................................................. 20
   6.4 Withdrawal of individual subjects ........................................................ 23
      6.4.1 Specific criteria for withdrawal (if applicable) ............................... 23
   6.5 Replacement of individual subjects after withdrawal ............................ 23
   6.6 Follow-up of subjects withdrawn from treatment ................................. 24
   6.7 Premature termination of the study ....................................................... 24
7. SAFETY REPORTING .................................................................................. 24
   7.1 Section 10 WMO event ....................................................................... 24
   7.2 Adverse and serious adverse events ....................................................... 24
   7.3 Follow-up of adverse events ................................................................. 25
8. STATISTICAL ANALYSIS ........................................................................... 25
9. ETHICAL CONSIDERATIONS ................................................................. 26
   9.1 Regulation statement ............................................................................ 26
   9.2 Recruitment and consent ...................................................................... 26
   9.3 Benefits and risks assessment, group relatedness ................................. 26
   9.4 Compensation for injury ...................................................................... 26
   9.5 Incentives (if applicable) ...................................................................... 27
10. ADMINISTRATIVE ASPECTS AND PUBLICATION ............................. 27
   10.1 Handling and storage of data and documents ....................................... 27
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2</td>
<td>Amendments ........................................................................................................27</td>
</tr>
<tr>
<td>10.3</td>
<td>Annual progress report .....................................................................................27</td>
</tr>
<tr>
<td>10.4</td>
<td>End of study report ..........................................................................................28</td>
</tr>
<tr>
<td>10.5</td>
<td>Public disclosure and publication policy ........................................................28</td>
</tr>
<tr>
<td>11.</td>
<td>REFERENCES ...........................................................................................................28</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>CA</td>
<td>Competent Authority</td>
</tr>
<tr>
<td>CCMO</td>
<td>Central Committee on Research Involving Human Subjects</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European drug regulatory affairs Clinical Trials GCP Good Clinical Practice</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IC</td>
<td>Informed Consent</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IMPD</td>
<td>Investigational Medicinal Product Dossier</td>
</tr>
<tr>
<td>METC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
</tr>
<tr>
<td>(S)AE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics (in Dutch: officiële productinformatie)</td>
</tr>
<tr>
<td>Sponsor</td>
<td>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>Wbp</td>
<td>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)</td>
</tr>
<tr>
<td>WMO</td>
<td>Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)</td>
</tr>
</tbody>
</table>
SUMMARY

Rationale: Normal-hearing listeners gain important benefits from having two ears. Users of a Bionic Ear achieve high levels of spoken word recognition when speech is presented in quiet. However they experience difficulty in the presence of competing sounds and are poor at identifying where sounds come from. These limitations may be overcome, to some degree, by providing an implant to both ears. This study will investigate bilateral versus unilateral benefit in adults who are implanted with two Bionic Ears either simultaneously or sequentially.

Objective: The objectives are to evaluate the degree of bilateral benefit gained from having a second implant and to determine whether this benefit is stronger after simultaneous or sequential implantation.

Study design: 48 subjects with severe sensorineural hearing loss will be included in this Randomised Controlled Trial. 28 Subjects shall receive one implant at the beginning of the study and a second implant after a period of two years (Group A). 20 Subjects shall receive two cochlear implants simultaneously during one operation (Group B). The quality of life results of the subjects included in this study will be compared to the results of a control group of 20 additional un-randomised patients who will receive a unilateral CI via regular medical treatment.

Study population: 48 subjects with an age between 18 and 70 years with severe sensorineural hearing loss who are eligible for cochlear implantation.

Intervention (if applicable): Bilateral Cochlear Implantation.

Main study parameters/endpoints: The main outcome will be the performance on the modified Plomp hearing test. Secondary outcome measures will be: performance on the Standard Dutch phoneme test (NvA-list, Bosman), the Speech intelligibility test with spatially separated sources, the Crescent of sound test (Quentin Summerfield), self-reported benefits in everyday listening situations assessed with the Speech, Spatial and Qualities Hearing Scale (SSQ), Quality-of-life questionnaire scores (Nijmegen Cochlear Implant Questionnaire (NCIQ), Health Utilities Index (HUI3), Time Trade-off (TTO), VAS scales and EuroQol-5D) and tinnitus questionnaire results (Tinnitus Handicap Inventory (THI), Tinnitus Questionnaire (TQ) and Tinnitus Burden Questionnaire).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: For group A subjects: the risks of the second surgery are considered equal to the risks of the first surgery. When worsening of the health status of a subject no longer allows a second surgery, the subject will be excluded from further implantation. For group B subjects: the duration of surgery will be prolonged with approximately 50% of the standard operation time. The evaluation consists of 5 test sessions of 4 hours each, spread over four years time.
1. INTRODUCTION AND RATIONALE

Introduction
The present study was initiated by Prof. Dr. W. Grolman (University Medical Centre Utrecht) who approached Mr. P. Boyle (Clinical Research Department, Advanced Bionics) at the beginning of 2007 for a research collaboration on adult bilateral cochlear implantation with the idea of using a randomised controlled trial to compare simultaneous and sequential bilateral implantation. After thorough discussion and with the precious participation of Prof. Q. Summerfield (Department of Psychology, University of York), the following protocol was established.

The HiResolution® Bionic Ear is an implantable prosthesis designed to provide individuals with severe or profound hearing loss, who obtain limited benefit from conventional hearing aids, access to sound and improved perception of speech via electrical stimulation of the auditory nerve. Many users of one Bionic Ear achieve high levels of spoken word recognition when speech is presented in quiet. However, even the most successful users experience difficulty in the presence of competing sounds and are poor at identifying where sounds come from. These limitations may be overcome, to some degree, by providing an implant to both ears. This study will investigate bilateral versus unilateral benefit in adults who are implanted with two Bionic Ears either simultaneously or sequentially. The objectives are to evaluate the degree of bilateral benefit gained from having a second implant and to determine whether this benefit is stronger after simultaneous or sequential implantation. Participants will be using HiRes® or HiRes Fidelity® 120 (also called HiRes 120) sound processing according to their preference, with the restriction of using the same sound processing strategy on both sides. This approach may give insights into the benefits observed with HiRes in comparison to those observed with HiRes 120 via a separate analysis.

This study will be conducted as a randomised controlled trial (RCT) to control for biases when assigning subjects to one of two study groups. RCTs are the most rigorous experimental design for establishing the effectiveness of one intervention compared with another (Wooff et al., 1990). However, the study is considered a non-significant risk evaluation of a treatment which is commonly clinically applied (unilateral cochlear implantation) with one which is increasingly commonly applied clinically in children (bilateral cochlear implantation) in numbers of European countries. The failure of bilateral implantation to also be applied to adults is largely financial; there being no compelling evidence of sufficiently large benefits of bilateral over unilateral implantation to justify the additional cost. All products in the study (i.e., HiResolution Bionic Ear System, SoundWave programming
software) have been approved for commercial distribution within the European Community. Previous research indicates that there are no significant additional safety issues when patients receive two devices instead of just one, even if performed in the same surgery. Efficacy with two devices appears to be greater than with one implant although, as stated above, the quality of study conducted to date leaves room for refusal to accept study findings through a failure to control various forms of bias. The poor standard of studies on bilateral cochlear implantation has been recently highlighted by Murphy and O’Donoghue (2007).

**Rationale**

Normal-hearing listeners gain important everyday benefits from having two ears. One advantage is the ability to determine where sounds are coming from (e.g., Middlebrooks and Green, 1991). The other important advantage is the ability to hear sounds and understand speech in noisy environments, especially if the sound sources come from different directions (e.g., Bronkhorst and Plomp, 1988; Dirks and Wilson, 1969; MacKeith and Coles, 1971). More specifically, normal listeners have the following capabilities.

1. **Localisation.**

   Normal listeners are able to localise sound in the horizontal plane (at ear level) with an accuracy of +/-14 degrees (Stevens and Newman, 1936). The brain uses interaural differences in intensity and time between the two ears to determine the location of a sound source in the horizontal plane (Akeroyd, 2006). To localise sound in the vertical plane, or when interaural time and intensity cues are ambiguous, spectral information is important. The external ear alters the relative intensities of the many frequencies entering the ear canal. The direct path to the tympanic membrane and the delayed path caused by reflection of sound around the pinna and off the concha add together to produce a filtered spectrum containing a characteristic pattern of peaks and valleys across frequencies. The amplitude spectrum of a complex sound reaching the tympanic membrane differs depending upon the location of the sound relative to the body (see Middlebrooks et al., 1989).

2. **Head shadow.**

   When listening to speech in noise, the head acts as a sound barrier that attenuates noise on the side contralateral to the signal. Therefore, when one ear is closer to the noise source, adding a second ear contralateral to the noise provides an ear with a better signal-to-noise ratio (SNR). The head shadow effect is purely geometric and does not require binaural processing by the brain.
3. **Binaural squelch.**

When signals and noise come from different directions, the brain is able to separate them by comparing time, intensity, and spectral differences between the two ears. The practical effect is that the brain is able to suppress signals that the listener does not wish to hear.

4. **Binaural summation.**

When identical signals are presented to the two ears, there is an advantage when hearing with both ears instead of just one alone. The brain uses binaural redundancy and binaural loudness summation to produce this advantage.

Based upon the advantages normal-hearing listeners derive from hearing with two ears, several research centres have studied the benefits of bilateral cochlear implantation with the Nucleus and MED-EL devices (e.g., Gantz et al., 2002; Litovksy et al., 2004; Müller et al., 2002; Nopp et al., 2004; Schleich et al., 2004; Tyler et al., 2002). Taken together, these studies indicate that most, if not all, bilateral implantees experience near-normal head shadow effects. They are also able to localise sound with two implants significantly better than with one implant alone. Fewer bilateral implant users exhibit binaural summation and binaural squelch effects. Notably, there have been no reports of decrements in speech perception or localisation for bilateral vs. unilateral implant use. Moreover, in cases where preference was assessed, all patients strongly preferred two implants to using one implant with the better ear alone.

A recent review (Murphy & O'Donoghue, 2007) highlighted the lack of high quality studies of bilateral implantation which would be capable of controlling for bias and hence accepted by commissioners of healthcare. Such findings demonstrate the need for studies capable of quantifying the benefits of bilateral implantation in both clinical and health-economic frameworks.

Another important aspect which concerns the benefits provided by bilateral implantation is the need for fine frequency information; it is of indisputable importance to convey fine structure, particularly for speech recognition in noise and for melody recognition (Wilson et al., 2005). Previously, the University of Iowa has reported bilateral results from four subjects who were implanted simultaneously with two Bionic Ears and were initially programmed with the Continuous Interleaved Sampler (CIS) conventional strategy (Tyler et al., 2004). After 24 months of CIS use, the subjects were switched over to HiRes sound processing. Sentence recognition was assessed in the most difficult listening situation, where both speech and noise were presented directly in front of the listener. This test condition is very difficult
because there is no spatial separation of signal and noise. The results showed substantial improvement in performance with HiRes after only one month of use. Notably, the improvement in sentence-in-noise scores after switching to HiRes was much greater for users of two Bionic Ears than the mean improvement in scores for subjects using only one Bionic Ear (Koch et al., 2004). Within this study, the term HiRes processing shall include HiRes Fidelity® 120 processing, the more individually beneficial processing approach between “standard” HiRes and HiRes 120 being applied to any particular subject.

2. OBJECTIVES

Based upon the fact that users of two implants demonstrate quantifiable improved benefit over single-implant use, upon the need for studies in which the methodology strongly controls for biases such as in RCTs, and upon preliminary data indicating that HiRes sound processing may provide enhanced binaural benefit, this study will:

(1) Evaluate the efficacy of bilateral implant use with HiRes after simultaneous implantation compared to a unilateral control group in a between-subjects design;

(2) Compare the benefits of HiRes applied unilaterally to bilateral use after sequential implantation using a within-subject design;

(3) Compare the efficacy of HiRes from simultaneous bilateral implantation with sequential bilateral implantation where there is a two-year gap between implantations using a between-subject design.

The results should document the benefits of using two implants versus one. We would like to determine whether simultaneous bilateral implantation holds any advantages over a modest delay in implanting the second ear. The study will also document the duration of each operation, medical or surgical complications, as well as any adverse events associated with bilateral implantation. Given that this is an RCT, various forms of selection bias will be avoided. Since all subjects ultimately receive bilateral implantation, there shall be no withholding of treatment; addressing an important ethical dimension to this work.
3. STUDY DESIGN

Subject selection shall take account of differences in hearing thresholds between ears, duration of deafness, anatomical and aetiological issues as well as psychological and motivational attributes. Subjects assigned to simultaneous bilateral implantation shall receive two implants at the beginning of the study and be evaluated before surgery and after one, two, three and four years of bilateral implant use (Group B). The group assigned to sequential implantation shall receive one implant at the beginning of the study and be evaluated before this first surgery and one and two years thereafter. After two years they shall receive a second implant. Evaluation will take place after one and two years of bilateral use (Group A).

Those subjects randomised for simultaneous implantation will be implanted with two Bionic Ears at the same surgery (or within one month of each other, should medical opinion require a delay). The devices will be programmed at the same time 4-6 weeks after surgery (or after the second surgery). The same processing strategy (HiRes or HiRes 120), shall be applied to both implants and parameters shall be controlled to minimise differences between ears. Subjects randomised for sequential implantation shall receive the first Bionic Ear implant in one ear to be chosen according to the following guidelines: for subjects wearing a hearing aid, the ear without hearing aid will be the first ear to be implanted; for subjects wearing two or no hearing aids, an attempt to randomise between the “better” or “worse” ear will be carried out. Since the goal of the study is to compare bilateral cochlear implantation with the next best alternative, the use of a contralateral hearing aid shall be encouraged for the unilateral users.

Forty subjects will each be assigned to one of the two study groups described above. A sample size of 20 subjects in each group is required to allow valid statistical assessment of bilateral benefit (see power calculations). In order to compensate for potential subject attrition, a total of 48 subjects will be recruited. The additional eight subjects shall be “randomised” to sequential implantation since it is from this group that attrition is anticipated with failure to take up their second implant after the initial “unilateral” phase.

Subjects shall be randomised into one of the two groups using a strict randomisation process. Subjects willing to participate must be informed that they can be assigned to either condition or accept to submit to this randomisation. It is only after the subject has signed their consent form that he/she is informed of the assigned group.
A further concern regarding the sequential group is that the knowledge that a subject is going to receive a second implant might change, or bias, their judgment of their quality-of-life. Accordingly, a third group will be recruited (un-randomised) to control for this. Following the recruitment of the initial 48 subjects, the next 20 subjects who fit within the inclusion criteria will be recruited into this third group. The members of this un-randomised group will not receive a second implant. They will complete the same self-report measures of quality-of-life as other subjects before surgery and after one and two years of unilateral implant use since those are the time points at which the sequential group would complete assessments as unilateral users before receiving their second implant. The third arm’s auditory skills and speech understanding will not be tested during the study since only the expectations on quality of life need to be controlled.

4. STUDY POPULATION

4.1 Population (base)
Subjects eligible for participation in the study must be adults who will be implanted bilaterally, either immediately or after a two year period of unilateral implantation, with two HiResolution Bionic Ears (HiRes 90K implants).

4.2 Inclusion criteria

1. Postlingual onset of hearing loss, defined as: the patient did not attend education for hearing impaired, but went to a regular primary school.
2. Sensory hearing loss of a severe or greater degree in both ears, defined as pure tone average (500, 1000, 2000 Hz) ≥ 70 dB HL.
3. A comparable duration of severe-to-profound hearing loss between the two ears (difference between the ears: <10 years).
4. Subject was able to use hearing aids until at least 10 years ago.
5. Marginal hearing aid benefit with hearing aids, defined as an aided phoneme score ≤ 50% at 65 dB SPL in patients with onset of hearing loss in adulthood.
6. Dutch language proficiency.
7. Willingness and ability to participate in all scheduled procedures outlined in the protocol.
8. General health allowing general anaesthesia for the potential implantation of two cochlear implants during a single surgery.
9. Patients covered by the Dutch health insurance.
10. Patients should agree to be implanted with cochlear implants from Advanced Bionics.
4.3 Exclusion criteria
1. Previous implant experience.
2. Disability which could interfere with the completion of the tests.
3. Abnormal cochlear anatomy in one or both ears.
4. Chronic ear infection in one or both ears.

4.4 Sample size calculation
To detect a clinically relevant difference of 5 dB SNR (SD 5 dB) between the groups on the Hearing in Noise test (modified Plomp test), with an alpha of 0.05 and a power of 80%, 16 subjects per group are needed. In order to compensate for any data lost through drop out of subjects during the study or failure to perform a required test within the limits of the protocol 4 extra subjects will be added to the 16 subjects needed in each group. Thus, adequate statistical power will be achieved with 20 patients per group, i.e. 40 in total. An additional modest increase of eight subjects in the "sequential implantation" group is proposed, since it is from this group that attrition is anticipated with failure to take up their second implant after the initial unilateral phase. Leaving a total randomised study population of 48 subjects.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment
Preoperative medical evaluation will be carried out locally by the centre’s Cochlear Implant Team, the anaesthesiologist and the patient's ENT surgeon and includes a clinical history and interview, determination of general health status and suitability for surgery, an otologic examination and radiographic evaluation of each ear, preferably using CT scans. Routine audiological testing will be performed to determine the degree and type of hearing loss. Clinical routine speech recognition testing will be performed to establish candidacy.

Before (the first) surgery, subjects will be asked to read and sign the Information and Consent Form presented by the patient's ENT surgeon. This physician will fill in a Demographics Form to gather subject information such as the date of birth and audiological information.
Baseline evaluation for gathering study-related data will take place locally, before (the first) surgery:

1. Pure tone audiometry

2. Speech audiometry with use of the most appropriate hearing aids (CVC score in quiet)


The standard surgical procedures developed for placement of the internal components of the HiRes 90K will be followed. It is anticipated that most of the bilateral implants for the group with simultaneous implantation will be placed during the same surgery. Specific procedures for implanting the two devices will be left to the discretion of the surgeon.

The patients will be asked to fill in a weekly costs diary starting on the day of (the first) surgery until the end of the study. The participants are only required to fill in the diary if they have physical complaints regarding the CI or if they generate costs.

The first follow-up visit will occur approximately four to six weeks after surgery (or the second delayed surgery of a “simultaneous” bilateral implantation) to custom fit the processor(s) using the SoundWave™ Professional Suite software. Routine clinical procedures will be used to fit either the HiRes or HiRes 120 sound processing algorithm according to subject preference, whenever possible to determine. All subjects will be fitted with the Harmony® sound processor. For the simultaneously implanted group, both devices will be fitted on the same day, even if the devices were placed in separate operations. The two processors will be fitted independently and sequentially during the same fitting session.

An electronic copy of the SoundWave program for each ear will be submitted to Advanced Bionics.

Post-implantation evaluation sessions for collecting data will take place at one, two, three and four years after first fitting. For the sequential subjects who will be receiving their second implant after two years of unilateral use, two session will occur one and two years after the first fitting, the last two sessions will occur one and two years after the second fitting (i.e. one and two years after bilateral use). All objective evaluation measurements will take place at the UMC Utrecht to ensure that the data are gathered in an identical way.

If considered necessary, extra sessions can exceptionally be added, during which subjects will do no more than what they would do at the regular sessions.
5.2 Use of co-intervention (if applicable)
Since the goal of the study is to compare bilateral cochlear implantation with the next best alternative, the use of a contralateral hearing aid shall be encouraged for the unilateral users.

6. METHODS
6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint
- Performance on modified Plomp test with sentences in Dutch (Objective) in the individual patient’s best aided condition.

6.1.2 Secondary study parameters/endpoints (if applicable)
Objective:
- Performance on Standard Dutch phoneme perception test (NvA-list)
- Performance on Speech intelligibility with spatially separated sources
- Performance on Crescent of sound tests (Quentin Summerfield)
Subjective:
- Self-reported benefits in everyday listening situations assessed with the Speech, Spatial and Qualities Hearing Scale (SSQ)
- Quality-of-life questionnaire score:
  - General QOL: Health Utilities Index (HUI3)
  - QOL specified to hearing / cochlear implantation: Nijmegen Cochlear Implant Questionnaire (NCIQ)
  - TTO (time trade-off): 1 question
  - Visual Analogue scale: 2 questions
  - EuroQol-5D: 6 questions
- Tinnitus questionnaires:
  - Tinnitus Handicap Inventory (THI)
  - Tinnitus Questionnaire (TQ)
  - Tinnitus Burden Questionnaire
- Cost utility analysis: Direct and indirect costs vs QoL
  - Costs diary
6.2 Randomisation, blinding and treatment allocation

40 subjects will each be assigned to one of the two study groups, 20 in each group. Eight additional subjects will be randomised to sequential implantation in order to compensate for potential subject attrition.

A website randomisation program shall be used to divide the subjects randomly into two groups: the sequential group (n=28) or the simultaneous group (n=20). The randomisation chart is established before the start of the study by an independent data manager. When a local executor recruits a subject, the physician can log on to the program and enter the subject's characteristics. A minimisation model will be used to make sure that the ratio simultaneous / sequential subjects in each hospital will be about equal (20:28 = 5:7). The physician will receive an allocation group number on his/her screen within a few seconds. It is only after the subject has signed their consent form that he/she is informed of the assigned group.

A further concern regarding the sequential group is that the knowledge that a subject is going to receive a second implant might change, or bias, their judgment of their quality-of-life. Accordingly, a third group will be recruited (un-randomised) to control for this. Following the recruitment of the initial 48 subjects, the next 20 subjects who fit within the inclusion criteria will be recruited into this third group. The members of this un-randomised group will not receive a second implant. Blinding is not possible since both patients and doctors will be able to see from the outside whether a subject has one cochlear implant or two.

6.3 Study procedures

Modified Plomp test with sentences in Dutch
The Plomp sentence test is designed to determine a patient's ability to understand speech in a noisy environment. This provides a more comprehensive understanding of a person's listening capabilities in daily life than a speech intelligibility test in quiet only. The Plomp test outcome is the critical signal-to-noise-ratio (SNR) at which 50% of sentences is understood correctly. This level is called the Speech Reception Threshold in noise (SRTn). Both sentences and noise are presented from the front at 70cm distance from the patient.
In the conventional Plomp test a response is considered correct when the presented sentence is repeated without any mistakes. A patient is tested in quiet first to check if the patient is able to perform the task. Although the Plomp test is commonly used in the clinic for patients with mild-moderate hearing loss, it has not been used routinely for cochlear implant users. A speech perception in noise test which is routinely used by a CI-team is a word perception in noise test.

The reason for this is that a number of cochlear implant users will not be able to repeat sentences 100% correctly even if presented in quiet. However, in a word test patients cannot use their language ability, as they commonly do in understanding sentences. Therefore we have modified the scoring system of the Plomp test slightly.

In the “modified Plomp test” we will be scoring the number of words repeated back correctly instead of complete sentences. A sentence is considered to be repeated correctly when a subject repeats ≤ 2 words of the sentence incorrectly.

Test procedure:
- The sound level that corresponds to the patient’s maximum CVC score in quiet (standard procedure) is the individual stimulus level that will be used for the modified Plomp test.
- The starting speech to noise level ratio (SNR) is set to +20 dB (noise 20dB less than individual sound level), at which, in most cases, less than two words per sentence should be repeated back incorrectly.
- The presentation of the noise starts 500 ms before the sentence and stops 500 ms after the sentence.
- If two or less words in a sentence are repeated back incorrectly, the SNR for the next sentence will be decreased by increasing the level of the noise, i.e., the task will be made more difficult. If more than two words are repeated back incorrectly, the SNR will be increased, i.e., the task will be made easier.
- Initially, the SNR will be changed in 10-dB steps. The step size will be reduced to 5 dB after one reversal and to 2.5 dB after the next reversal.
- This step size is used for the remainder of the sentences in the list. The average SNR used for the final ten sentences in the list is calculated and used as an estimate of the Speech Reception Threshold (SRT) in noise.

Speech intelligibility with spatially separated sources
This is a Speech Reception Threshold (SRT) test with spatially separated sources consisting of a target speech signal masked by an interfering signal. The speech material was taken from the sentences VU ‘98 CD (Versfeld et al., 2000), recorded
from a male and a female speaker. The spatial separation between the speech and the noise is introduced by positioning two loudspeakers at −45 and +45 degrees.

Crescent of sound (Quentin Summerfield)
This set of tests includes spatial and presentation level roving tests and will assess localisation, lateralisation, head shadow and squelch effect. A set of seven loudspeakers are controlled by a cluster of eight computers, creating situations representing real-life listening conditions and which may help to differentiate the abilities of bilaterally implanted subjects from either unilateral implant users of bimodal implant and contralateral hearing aid users.

Self-reported benefits
Self-reported benefits in everyday listening situations will be assessed with the Speech, Spatial and Qualities Hearing Scale (SSQ) (Gatehouse and Noble, 2004). The SSQ consists of three scales that assess different domains of hearing.

- The Speech Hearing Scale consists of 15 questions that assess the ability to separate speech from competing noise in a wide range of listening contexts.
- The Spatial Scale consists of 17 questions that assess the ability to locate sound sources and their direction of movement.
- The Sound Qualities Scale consists of 19 questions that assess naturalness and clarity of sound sources.

The subject responds to each question using a rating scale that ranges from zero (Not at all) to 10 (Perfectly).

Quality-of-life questionnaires
- The Ontario Health Utilities Index 3 is a measure of general health status. It contains questions on: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain.
- The Nijmegen Cochlear Implant Questionnaire (NCIQ) measures hearing-related quality of life and is therefore more sensitive to the differences between unilateral and bilateral implant use.
- Time Trade-off (TTO): comprises one question about how many years of the life patients are living at the moment, they would sacrifice for living with perfect hearing for the rest of their days.
- Visual Analogue Scale (VAS): comprises two 10cm scales on which patients can rate their hearing and health.
• **EuroQol-5D**: is a measure of general health status. It contains questions on: mobility, self-care, daily activities, pain/complaints, anxiety/depression.

**Tinnitus Questionnaires**

• The **Tinnitus Questionnaire (TQ)** encompasses 52 questions on tinnitus related to: emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints.

• The **Tinnitus Handicap Questionnaire (THQ)** has 3 subscales: a functional subscale (11 items), an emotional subscale (9 items) and a catastrophic subscale (5 items).

• The **Utrecht Tinnitus Burden Questionnaire**: This questionnaire contains questions on the severity and character of tinnitus described by subjects.

**Costs diary:**

• Subjects are asked to keep a weekly diary involving physical complaints and costs regarding their CI(s), starting on the day of (the first) surgery. In case they do not experience any complaints or generate costs, they do not need to fill in the diary. In case they do, we ask them to specify complaints and/or costs in the diary. All subjects will be reminded on regular basis by email to keep filling in the diary.

**6.4 Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

**6.4.1 Specific criteria for withdrawal (if applicable)**

As before every surgery, the anaesthesiologist will evaluate the patient’s health status. In case the health status has worsened between the first and second surgery and the anaesthesiologist advises not to continue, the patient will be excluded from further implantation.

**6.5 Replacement of individual subjects after withdrawal**

To anticipate on possible withdrawal 8 more subjects than needed will be recruited for group A. Therefore there will be no reason to replace subjects after withdrawal unless more subjects will withdraw than 8.
6.6 Follow-up of subjects withdrawn from treatment
During the study, each patient will stay in care of their CI-team. In case a subject is withdrawn from the study he/she will continue with the standard medical treatment provided by the CI-team.

6.7 Premature termination of the study
Serious adverse events are not expected, but in case they do occur, each member of the research group has the right to terminate the study prematurely.

7. SAFETY REPORTING

7.1 Section 10 WMO event
In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

7.2 Adverse and serious adverse events
Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.
Adverse events could be: implant failure, infection, explantation.

A serious adverse event is any untoward medical occurrence or effect that at any dose results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.
All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

7.3 Follow-up of adverse events
In the case of implant failure, infection, explantation or any other event resulting in the temporary non use of the implant system, subjects will not be permanently excluded from the study, under the intention to treat. Once the problem is solved, the subject will re-enter and continue the study for the amount of time left since he/she had not been operational with the device. This ensures that subjects from the simultaneous group experience two years of bilateral use while those from the sequential group experience two years of unilateral use followed by two years of bilateral use within the study duration. A separate analysis for such a subject may be further conducted to control for possible biases.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8. STATISTICAL ANALYSIS
The aim of the study is to measure changes in auditory performance, speech understanding and quality of life that accompany the receipt of a second cochlear implant by subjects who receive two implants at virtually the same time, ideally simultaneously and those who have had one implant for a reasonable time period. Three types of measures will be obtained: measures of the ability to localise the source of sounds in space, measures of the ability to understand speech in a background of noise, and measures of quality of life, including both health related and non-health-related measures. Overall, the study is an RCT, but has a repeated measures design, in which subjects who are implanted sequentially are tested with a second cochlear implant in the same manner as with one cochlear implant (or one implant and a contralateral hearing aid). Both groups will be equally tested thus providing between-group measures comparing unilateral and bilateral use as well as simultaneous and sequential bilateral benefit. The sequential group subjects will be tested again following 12 and 24 months of bilateral experience, thus providing a within subject control group for unilateral and bilateral conditions. Major test intervals are at one and two years post implantation. First, the effect of bilateral cochlear implantation between the randomised groups will be calculated as mean differences, rate differences, and rate ratios with 95% confidence
intervals. Differences in percentages and mean values between the groups will be analyzed by Chi-square tests and Student T-tests, respectively. All trial analyses will be performed on an intention-to-treat basis.

Second, each subject from the sequential group will act as his or her own control with sufficient data being collected to make within-subject comparisons. Differences in percentages and mean values before and after implantation will be calculated using paired t-tests for continuous measures and the McNemar test for percentages.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement
The study will be conducted according to the principles of the Declaration of Helsinki (version 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent
When a patient meets the criteria for cochlear implantation and the inclusion criteria for this study, he/she will be asked to participate by a member of the Cochlear Implant team. Like all patients eligible for cochlear implantation, the patients in this study will have several appointments with the ENT specialist, audiologist, social worker etc. There will be ample opportunity for the patient and his/her partner to consider participation and discuss their questions. The content of the study will be explained by the patient’s otolaryngologist who will give the subject written patient information and the informed consent form.

9.3 Benefits and risks assessment, group relatedness
Compared to routine clinical practice, the study requires that the subjects undergo a second cochlear implantation either in an extended surgery or in an additional separate surgery. This carries the usual risks associated with surgery and a slightly longer anaesthetic exposure. The clinical management will otherwise be unaffected besides appointment times being longer to ensure that both implants are optimally working.

Efficacy with two devices seems to be greater than with one implant although the quality of studies conducted to date leaves room for refusal to accept study findings through a failure to control various forms of bias.
9.4 Compensation for injury
The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

9.5 Incentives (if applicable)
All participants will receive compensation for travel expenses.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents
All data will be treated confidentially. The data will be analysed anonymously by using a unique patient identification number. The key code will be safeguarded by the investigators. The paper data files will be stored in a locked room. The data will be stored on the investigator’s computer as well which is secured by a password and situated in a locked room. The subjects’ general practitioner will be informed about the participation of the subject.

10.2 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 Annual progress report
The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/spONSOR will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.5 Public disclosure and publication policy
The data from this study will be used for publication in peer-reviewed international journals. It will be part of a thesis on the benefits of bilateral cochlear implantation.

11. REFERENCES


Tyler, RS. (2004). Personal communication.

