Research protocol

Cost-effectiveness analysis of bilateral cochlear implantation

September 1st, 2014

This document describes a cost-effectiveness study of cochlear implantation (CI). In particular, it aims at analysing the incremental cost-effectiveness of bilateral CI (BCI) with respect to unilateral CI (UCI). The study will be conducted by the Universidad Nacional de Educación a Distancia (UNED) in Madrid, Spain. This project has received financial support from the Fondo de Investigaciones Sanitarias (FIS - Health Research Fund) of the Spanish Government, and will receive a complementary grant from MED-EL.

This document shall be included as an annex of the contract signed by MED-EL and the UNED.

1. Research team

The team that will conduct this project consists of 9 researchers: 6 lecturers, 1 doctoral student and two research associates hired by this project.

1.1. Personnel of the UNED

a) Lecturers

Francisco Javier Díez, the principal investigator, is Associate Professor at UNED since 1996 and achieved the accreditation as Full Professor in 2014. He has been principal investigator in several national and international projects and supervised 5 doctoral theses about probabilistic diagnosis and medical decision analysis.

Pedro Juez has a five-year degree in Economics (1990), a six-year degree in Medicine (2006), a PhD in Economics (1997) and a PhD in Medicine (2011). He is Associate Professor at the UNED.

Emilio Letón earned a degree in Mathematics (1989) and PhD at the Universidad Complutense de Madrid (2002), with a doctoral thesis about survival analysis. He worked for 11 years as a biostatistician at Glaxo-Welcome and GlaxoSmithKline in Madrid. After being a lecturer at University Carlos III, in Getafe (Madrid), he joined the UNED in 2009.
Manuel Arias achieved a degree in Computer Science at the Technical University in Madrid and a PhD at the UNED, in 2009; in his doctoral thesis he designed and implemented the OpenMarkov tool and developed new algorithms for cost-effectiveness analysis. He was a visiting scholar at the University of East London, in the United Kingdom. He is a lecturer at the UNED.

Manuel Luque received a degree in Computer Science at the University of Malaga and a PhD at the UNED in 2009 with a thesis that applied probabilistic graphical models to the mediastinal staging of lung cancer, performing cost-effectiveness and sensitivity analyses. He has twice been a visiting scholar at the University of Aalborg, in Denmark. He is also a lecturer at the UNED.

Elena Almaraz obtained a degree in Mathematics (2005), a degree in Statistics (2007) and a PhD degree in Mathematics (2009) at the Universidad Complutense de Madrid. She has been a visiting scholar at the Health Economic Research Unit of the University of Aberdeen (United Kingdom). She has been a lecturer at the Universidad Complutense de Madrid since 2009.

b) PhD student

Íñigo Bermejo earned a Computer Engineering Degree in 2006 at the University of the Basque Country, winning the Top Student Award. After working as a programmer and software engineer in industry for several years, he joined the UNED in 2011 with a four-year predoctoral grant. The topic of his thesis is the application of probabilistic graphical models to programming cochlear implants. He is currently a research fellow at Otoconsult, in Antwerp, Belgium, supported by the European project Hearing Minds (Marie Curie grant FP7-PEOPLE-2012-IAPP, no. 324401).

c) Research fellows

We will hire two research fellows, who are called RF1 and RF2 in this report.

RF1 will be responsible for measuring the quality of life associated to BCI: reviewing the state-of-the-art, designing the vignettes and questionnaires, setting up the web site to collect the responses, sending invitations to recruit volunteers, analysing the data and publishing at least one journal paper about this research. This researcher will also be responsible for collecting data about the economic costs of CI.

The candidate we have selected for this job is Miguel Ángel Artaso, who obtained a Computer Engineer Degree at the University of Deusto (Bilbao, Spain) in 2007 and will defend his Master Thesis at the Department of Artificial Intelligence of the UNED in September 2014. He will leave his job as a programmer and analyst at a Spanish Government agency in order to work full-time on a PhD.

RF2 will be responsible for developing the Markov model and conducting the cost-effectiveness analyses, including several types of cost-effectiveness analysis. The UNED will look for a candidate for this position.

1.2. Collaboration with other groups

During this project we will be in contact with a significant number of researchers. We have met personally the following:

- Prof. Mark Sculpher, Director of the Programme on Economic Evaluation and Health Technology Assessment of the University of York. He is one of main world experts in
this field. F. J. Diez and I. Bermejo spent three months at the Centre for Health Economics of the University of York, invited by him.

- **Prof. Quentin Summerfield** is the main expert in the cost-effectiveness of CI [Barton et al., 2001, 2004; Lovett et al., 2010; Summerfield et al., 2002, 2003, 2006, 2010]. We met him at the University of York in 2012 and 2013. He agreed to participate as a member of the research team of the grant awarded by the FIS for this project.

- Dr. **Paul Govaerts**, CEO of Otoconsult in Antwerp, Belgium, is has done research of several aspects of CI, which has earned him a solid international reputation. He is also a member of the research team of the FIS grant. He claims that medical decisions should not be based on cost-effectiveness analysis, but on expert assessment. He is especially severe about previous studies on the cost-effectiveness of BCI. His critical attitude will help us refine the quality of life questionnaires and anticipate the criticism of other medical doctors who share the same attitude.

- Dr. **Blake Papsin**, of the University of Toronto, is one of the most prestigious researchers on BCI, especially on its neurological aspects, and one of the strongest advocates for BCI [Papsin and Gordon, 2008].

- Dr. **Richard Miyamoto**, of Indiana University, was President of the American Academy of Otolaryngology—Head and Neck Surgery. He co-authored a study that concluded that BCI is cost-effective for both children and adults [Bichey and Miyamoto, 2008].

- Mr. **Koonal Shah**, Senior Economist at the Office of Health Economics, in London, is conducting a NICE study with a large number of respondents to assess the quality of life of terminal patients.

We have exchanged information via e-mail with all of them and also with several other researchers in different countries, including the following:

- Ms. **Mary Bond**, of the University of Exeter, led the PenTAG study commissioned by NICE [Bond et al., 2007, 2009]. This study, consisting of a systematic review, a Markov model and a cost-effectiveness analysis, was the basis for the coverage of paediatric BCI in the United Kingdom.

- Dr. **Rosemary Lovett** did a PhD thesis at the University of York supervised by Prof. Summerfield. She has collaborated with him in several studies aimed at measuring the quality of life related with BCI [Lovett et al., 2010; Summerfield et al., 2010]. After working for two years at the UCL Ear Institute, she was hired by NICE in 2013 to perform health technology assessments.

- Dr. **Yaling Yang** was a member of the **NICEQoL**, which extended the EQ-5D questionnaire with new dimensions specific for hearing loss. Since 2013 she is a Senior Researcher at the University of Oxford. This new project would be an opportunity to apply their questionnaires to BCI, a topic that her research group has not studied yet.

- Ms. **Helen Cullington** is Principal Clinical Scientist and Associate Professor at the University of Southampton Auditory Implant Service, where she leads the **National Audit of Bilateral Cochlear Implants** and the project 2 ears are better than 1.

- Drs. **Marc Lammers** and **Wilko Grolman**, of the University of Utrecht, and Dr. **Marloes Sparreboom**, of the Radbout University Nijmegen, conducted several research studies that convinced the Dutch authorities to reimburse BCI for children under 5.
2. Work plan

The agreement between MED-EL and the UNED will last for twelve months, denoted as M1-M12 in this report, from the 1st October 2014 to the 30th September 2015.

The research plan consists of three main tasks: measuring effectiveness, measuring costs and performing the analyses, with a Markov model.

2.1. Measuring effectiveness

The most time-consuming task in this project will be the measurement of the gain in quality of life due to BCI with respect to UCI. As mentioned above, the main researcher in this task will be RF1.

a) Review of the state of the art

We have already done a review of the main studies related with the quality of life (QoL) of BCI, most of which have been led by Prof. Summerfield. Now we will conduct a wider analysis of the literature on the elicitation of health related QoL, paying special attention to the studies on children [Griebsch et al., 2005; De Civita et al., 2005] and those related with hearing loss [Lin and Niparko, 2006; Connelly, 2008; etc.].

Time schedule: M1-M3.

Deliverable 1.A.1: A technical report about the state of the art (M3).

b) Preparation of the questionnaires and the web site

Based on the above-mentioned studies, we will prepare some vignettes describing the quality of life related with cochlear implantation for those who do not use it, as in [Summerfield et al., 2010]. The questionnaires will have a common part, consisting of a direct comparison of quality of life for both UCI and BCI using the time trade-off method.

We will also design specific questionnaires for users of CIs or hearing aids, which will include all the dimensions of the HUI-3, EQ-5D and the SF-6D, as well as other specific questions, such failure rates of their CIs.

A draft of the questionnaires will be sent to MED-EL and to other experts, including all the scientist mentioned in Section 1.2, to receive their feedback.

We will consider the possibility of asking also about willingness to pay (WTP), which might be used to perform a cost-benefit analysis.1 There are analyses of this type for paediatric cochlear implantation [Schulze-Gattermann et al., 2002; Sach et al., 2004; Whynes and Sach, 2007], but none of them has dealt with BCI. However, this task is not a priority in our project.

These questionnaires will be encoded into a web site where the volunteers recruited will be able to enter their responses, which will be stored in a database.

Time schedule: M3-M5.

Deliverable 1.B.1: A draft of the questionnaires (M3).

Deliverable 1.B.2: Questionnaires modified in accordance with the feedback received, to be used in the pilot study (M5)

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1 The difference between cost-benefit and cost-effectiveness analysis is that the former assigns a monetary value to each health state, and therefore it uses a single criterion—the economic benefit—while the latter counts separately two criteria: the medical benefits and the economic cost.
Deliverable 1.B.3: The URL of the web site for the questionnaire (M5).

c) **Pilot study**

We will conduct a pilot study in which the students of the Computer Science School of the UNED—around 4,000 people—will be invited to take part. One of the goals of this study is to check that the web site is ready for the main study, in which over 500,000 people will be invited to participate.

The second goal is to estimate the response rate and find out the optimal incentives.

The third and most important goal is to know how the framing of the questions and the personal features affects the responses. This information will help us fine-tune the questionnaires and decide the type of analyses to be performed on data of the main study.

Time schedule: M4-M6.

Deliverable 1.C.1: a report including a statistical analysis of the results (M6).

d) **Revision of the questionnaires**

The questionnaires will be revised in the light of the results of the pilot study. A new draft of the questionnaires, together with a brief report explaining the changes made, will be sent to the experts, including MED-EL, to receive additional feedback.

Time schedule: M7-M8.

Deliverable 1.D.1: a draft of the new questionnaires and a report explaining the changes (M7).

Deliverable 1.D.2: final version of the questionnaires (M8).

e) **Recruitment of volunteers**

We intend to recruit six groups of informants:

1. Users of BCI
2. Users of UCI
3. Users of hearing aids
4. Experts: otolaryngologists, audiologists, audioprosthesists, speech therapists…
5. Handicapped people
6. Other volunteers

The smallest group in the general population—and consequently the most difficult to recruit volunteers from—is the first one. Fortunately, both Mr. Joan Zamora, President of the Spanish Federation of Cochlear Implant Users (AICE), and Ms. Carmen Jáudenes, Director of the Spanish Confederation of Families of Deaf People (FIAPAS), have expressed their willingness to collaborate in this study, which is of great interest for their members. In total they can contact around 600 BCI users, thousands of UCI users, and several thousand hearing aid users. The foundation “Oír es Clave” and the association toigo have also offered us their support.

The experts for the fourth group can be recruited through their professional associations, such as the Spanish Society of Otorhinolaryngology, the Spanish Society of Audiology, the National Association of Audioprosthesists, the Official Association of Speech Therapists, etc.

Handicapped people can be contacted through the Unit for Disabled Students (UNIDIS) of the UNED, which gives service to around 5,000 people.
Finally, general-population volunteers will be recruited among the students of this university, which enrolls around 260,000 people of very different ages and personal situations, and among the 270,000 Facebook followers of the private company Nonabox. It is very difficult to estimate now the response rate in this group, but even with a rate as low as 0’2% we would recruit around 1,000 volunteers.

Those who agree to take part in this study will receive by email the URL of the website mentioned above, where they will be able to answer the questionnaires anonymously. The questionnaire for CI users will include additional questions, as mentioned above.

Time schedule: M7-M8.
Deliverable 1.E.1: a report describing the number and profiles of the volunteers recruited (M8).

f) Data collection, analysis and publication

The data collected at the website will be analysed with several statistical techniques to detect statistical differences due to the framing of questions and to personal features.

The results will be submitted to a high impact journal on the psychology of decision making.

Time schedule: M9-M12.
Deliverable 1.F.1: a report containing a preliminary analysis of the data (M9).
Deliverable 1.F.2: a draft of the journal paper, including an exhaustive analysis of the data (M10).
Deliverable 1.F.3: the version of the paper submitted to a journal (M12).

2.2. Measuring costs

The researcher devoted full-time to this task will be RFI, assisted by the principal investigator and Prof. Pedro Juez.

a) Review of the state of the art

We will review of the literature on the estimation of costs in economic evaluation, with special attention to those devoted to CI. There are several paper studies carried out in the United Kingdom [Barton et al., 2001, 2004; Bond et al., 2007, 2009; Summerfield et al., 2010], two in Spain [Manrique et al., 2006; L-Pedraza et al., 2007] and a recent systematic review by Nadège et al. [2011].

Time schedule: M3-M4.
Deliverable 2.A.1: a technical report (M4).

b) Cost of CI in Spain

We will then send questionnaires to the manufacturers of cochlear implants, to several public and private hospitals and to the associations of CI users, especially to the AICE, who performed in 2002 a study of the cost of cochlear implantation in Spain, including educational costs.

Time schedule: M5-M6.
2.3. Cost-effectiveness analysis

a) State of the art

On the one hand, RF2 should receive some training about cost-effectiveness analysis, beginning with the classical references [Drummond et al., 2005; Gold et al., 1996] and continuing with other books that describe Markov models in greater detail [Briggs et al., 2006; Gray et al., 2010; etc.]. Then he/she should analyse in detail the Markov models built for BCI [Bond et al., 2007; Summerfield et al., 2010].

On the other hand, this researcher should get familiar with the models and tools used at our research group. The model that we use for our cost-effectiveness analysis will be a Markov process with atemporal decisions (MPAD), a new type of probabilistic graphical model developed by our group. He/she should study in detail the MAPDs that we have built for performing cost-effectiveness analysis on different medical problems. We have built them using OpenMarkov, a software tool developed by our group. It is implemented in Java and uses modern software engineering technologies, such as UML, JUnit, maven, mercurial, etc. It this researcher has not used these tools previously, he/she will have to devote some time to getting acquainted with them.

Time schedule: M1-M3.

Deliverable 3.A.1: a technical report about the state of the art (M3).

b) Construction of a Markov model

The structure of the new model will be similar to that of Bond et al. [2007] and Summerfield et al. [2010], but all the hypotheses explicit or implicit in those models will be carefully revised. Then the model will be populated with our own estimates of costs and effectiveness. From the point of view of the implementation, the main difference is that our model will be an MPAD, built with OpenMarkov and encoded in the ProbModelXML format, while previous models where built with Excel.

Time schedule: M4-M9.

Deliverable 3.B.1: first version of the Markov model format; the quality of life will be that obtained at the pilot study (M6).

Deliverable 3.B.2: new version of the Markov model format; the quality of life will be that obtained at the pilot study (M9).

c) Cost-effectiveness analysis and sensitivity analyses

Using OpenMarkov facilities, we will perform a cost-effectiveness analysis to determine the cost-effectiveness of BCI for the reference case. We will introduce several variations in the Markov model to estimate the cost and the effectiveness of UCI alone, UCI plus contralateral hearing aids, and BCI, both in prelingually and postlingually deafened people of different ages. The goal is to determine for what groups BCI is cost-effective.

Then we will perform several sensitivity analyses to find out whether the uncertainty about the parameters of the model affects the estimates of cost, effectiveness and net benefit. In particular, we will compute the acceptability curve for each age of implantation.

Time schedule: M7-M9.

Deliverable 3.C.1: a report containing the preliminary analyses (M9).

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d) Publication of the results

We will submit abstracts and posters to different forums, such as the International Conference on Cochlear Implants and Other Implantable Auditory Technologies or the Symposium on Cochlear Implants in Children. Finally, we will write a comprehensive report that may be submitted to Health Technology Assessment, the journal that published the PenTAG study [Bond et al., 2009], or to another high-impact journal.

- Deliverable 1.D.2: a draft of the journal paper (M10).
- Deliverable 1.D.2: the version of the paper submitted to a journal (M12).

3. Ethical code

Given that this study will perform no clinical experiment, either in human beings or in animals, it does not require the approval of any ethics committee. In fact, the FIS did not require any ethics report when assigning a grant to this project.

However, the researchers and MED-EL agree that the project will be conducted in accordance with the following ethical code, whose main purpose is to increase the transparency and, consequently, the credibility of the study. This code will be published on the web page of the project in English and Spanish.

1. The project will be carried out following the highest standards of scientific rigour, objectivity and transparency.
2. The results of the study will be published even if they contradict the initial hypotheses that motivated it.
3. This study will not collect any information that might benefit or harm one particular company with respect to its competitors. In particular, it will not ask CI users about the brand of their implant(s).
4. All the responses to the questionnaires will be collected anonymously. They will be published at the web page of the project, except for the data that might identify individual respondents (for example, the age at which a person received the first and second implants). At the end of the on-line interview, the user will receive a random code that will allow him/her to check that his/her responses have not been altered.

This database will be published under a licence that will allow other researchers to perform further analyses for non-commercial purposes.

5. If a respondent decides to introduce their e-mail address in order to participate at a raffle (as an incentive to increase the response rate) and/or to be invited to take part at future research projects, this information will be stored independently of his/her responses to the questionnaires and protected in accordance with national and international law. The UNED will not share this information with other parties nor use it for other purposes than those authorised by the respondent. Every respondent will have the possibility to ask that his/her e-mail be removed from this database at any moment.

6. The decision models used to obtain the results of the study will be published at the web page under a Creative Commons BY-NC-SA licence, which will allow other researchers to modify and redistribute them.
7. Any potential conflict of interest, including all kinds of financial support, will be disclosed.

4. Budget

References


