Exploring the capabilities of modern cochlear implants : from electrophysiology to quality of life

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Chapter 2

Clinical relevance of quality of life outcome in cochlear implantation in postlingually deafened adults

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Abstract

Objectives: To evaluate the benefits of cochlear implantation in postlingually deafened adults and estimate the clinical relevance of these benefits.
Study design: Prospective intervention study.
Setting: Tertiary referral hospital.
Patients: 44 postlingually deafened adults.
Interventions: Cochlear implantation with a Clarion CII HiFocus 1 or HiRes 90K.
Main outcome measures: The Health Utility Index Mark II (HUI2) and Nijmegen Cochlear Implant Questionnaire (NCIQ) were administered to quantify health related quality of life (HRQoL); utilities were obtained from the HUI2 and time trade off (TTO) instrument. Speech perception scores were determined. Patient factors were correlated with post-implant HRQoL and speech perception scores. Clinical significant benefit was estimated using the minimal clinically significant difference (MID) and effect size (ES).
Results: The results show a significant improvement in HRQoL and speech perception ($p<0.001$). The improvement in HRQoL is mainly obtained in the first months after implantation and is largest in the categories concerning physical functioning (hearing). A shorter duration of deafness ($p=0.003$) and higher educational level ($p=0.015$) were significant predictors of better speech perception. Cochlear implantation proved to be a cost-effective procedure. By using the MID and ES, we found important clinical improvements on six health domains of the NCIQ and on the sensation domain of the HUI2 in the majority of patients; all but one of the effect sizes were large.
Conclusion: Cochlear implants have a large and significant positive impact on HRQoL and speech perception, and are cost-effective. These improvements are clinically relevant as measured by the MID.

Introduction

Cochlear implantation has proved to be a successful treatment for severely and profoundly deaf individuals.[1] A cochlear implant (CI) enhances speech perception in quiet and noise, and even allows many CI-recipients to use the telephone again.[2] Improved speech perception has been due to ongoing development in CI electrode array design, new speech processing strategies and by implanting patients with increasing amounts of residual hearing. However, not all patients benefit to the same degree. Research has shown that different factors may affect speech perception scores. For instance, previous studies verified that duration of deafness, communication mode (children) and pre-operative speech perception performance are important factors[3-5], but it remains difficult to predict how well an individual will perform after cochlear implantation.

Although speech perception scores are very important indicators, there may be other outcomes that give essential information on the benefits of a CI. In this respect, the general health status of CI-patients, often referred to as health-related quality of life (HRQoL), has more recently received increasing attention. Generic HRQoL outcomes have a number of advantages, including judgments about costs and perceived benefit.[6-9] Additionally, disease specific HRQoL relates physical, functional, psychological and social aspects to specific conditions. A common recommendation is to include both generic and disease specific measures in a study.[10]

Several generic utility measures have become available that include information on wellbeing, social and communication difficulties and that are suitable for cost-utility analysis. These include the Ontario Health Utilities Index (HUI-Mark II and III)[11] and the Australian Assessment of Quality of Life (AQoL).[12] For these instruments, the literature provides utilities from samples of the general public, which are required for cost-utility analyses from a societal perspective. It suffices to have patients fill out a questionnaire to describe their health state. A simple scoring formula then gives the utilities that the general public has assigned to these health states. In this way, the identification of health problems and assessment of outcomes in the community can be obtained. Similarly, disease specific measures, such as the Glasgow Benefit Inventory[13] and Nijmegen Cochlear Implant Questionnaire (NCIQ)[14], have been developed. These measures

assess treatment effects on hearing loss and deafness and are easy to apply. The reported outcomes of these generic and disease specific questionnaires show that cochlear implantation has a positive impact on quality of life in patients with profound sensorineural hearing loss and that it is a cost-effective procedure.[15] Unfortunately, previous studies showed weaknesses related to study design (retrospective, limited number of patients) and did not include both disease specific and generic instruments. The first aim of this study was to prospectively evaluate quality of life benefits after cochlear implantation as measured with validated generic and disease specific instruments, and to disclose the factors determining these benefits.

For this purpose, one needs to define or quantify "benefit": when is improvement in HRQoL meaningful? Most studies use a statistical measure, such as the *p*-value, to determine the significance of change in quality of life. However, this single value only indicates whether the results are likely to occur by chance, but does not reveal whether this particular finding has clinical significance or relevance for the individual patient. Therefore, other ways of describing HRQoL data have been proposed, including effect size (ES) and Minimal Clinically Important Difference (MID). The ES measures the magnitude of a treatment effect and is defined as the difference in score divided by the standard deviation (SD) of the baseline scores.[16] As such, it is a way of expressing the observed change in a standardized metric and called a distribution-based method. The MID is defined[17] as the smallest difference in score, in the domain of interest, which patients perceive as beneficial. Consequently, the MID would mandate, in the absence of troublesome side effects and excessive costs, a change in the patients' management. This is called an anchor-based method, the anchor being the patient's perception of change. We are not aware of any publications that have attempted to assess the MID for cochlear implantation. Different investigators have proposed a 0.5 baseline SD as a useful distribution-based proxy for the MID derived from anchor based methods.[18,19] This has received some criticism[20,21], but in the absence of further situation-specific knowledge, the 0.5 SD seems the best option to calculate a MID[22] in cochlear implantation research, at least for the time being. Therefore, the second aim of this study was to describe the clinical relevance of cochlear implantation in terms of HRQoL items, using the ES and MID.

Materials and Methods

Subjects

A series of 44 consecutive patients was followed prospectively from before until at least 12 months after their implantation date. Patients met the criteria developed at the Leiden University Medical Centre.[23] The data were collected over a period of 3.5 years (2002-2006). Intervention consisted of a cochlear implantation, either with a Clarion HiFocus with or without positioner, or with a HiRes 90K (Advanced Bionics Corp., Sylmar, CA).

Table 2.1: Demographics of 44 patients.

Characteristics	**n=44**		
Gender (no.)			
Female	29 (66%)		
Male	15 (34%)		
Educational background (no.)			
primary school	9 (20%)		
on-the-job-learning	11 (25%)		
secondary school basic	15 (34%)		
secondary school advanced	9 (20%)		
Cochlear Implant Model (no.)			
CII Hifocus 1 (with positioner)	5 (11%)		
CII Hifocus 1 (without positioner)	18 (40%)		
HiRes 90K	21 (48%)		
	Mean	**SD**	**Range**
Preoperative phoneme score (%)	22.9	20.0	0-70
Preoperative hearing thresholds (dB)	113.4	12.3	83-130
Duration of deafness (yrs.)	14.9	11.9	1-43
Age at implantation (yrs.)	54.7	15.7	25-86

Table 2.1 shows the demographic profile of the forty-four Dutch adult participants. Causes of deafness are shown in table 2.2. Subjects were implanted between 2002 and 2005; standard procedures were adhered to.[24] There was no significant side

predominance, with 25 receiving implants on the right side and 19 on the left. Initial fitting was performed at approximately 4-6 weeks after surgery.[25] The rehabilitation program commenced immediately after the fitting. All patients reported daily use of the device (= minimum of 6 hours).

Table 2.2: Causes of deafness in the study group.

Causes of deafness	**n**
Hereditary (progressive)	13 (22%)
Otosclerosis	1 (2%)
Congenital (unknown)	3 (7%)
Usher	1 (2%)
COCH gene	1 (2%)
Trauma	2 (5%)
Meniere	2 (5%)
Meningitis	5 (11%)
Rh immunization	1 (2%)
Mumps	1 (2%)
Chronic otitis	1 (2)%
Unknown Progressive	12 (27%)
Unknown Sudden Deafness	1 (2%)
Total	**44**

Speech Perception

Speech perception scores were obtained in a free-field condition using the Dutch Society of Audiology CVC (monosyllabic) word lists[26], preoperatively with adequately fitted hearing aids (when in use by the patient), and post-operatively with the CI. Although these tests are typically scored with phonemes ($CVC_{phoneme}$) in the Netherlands and Flanders, the data are also shown as word (CVC_{word}) scores. The average of the 65 and 75 dB SPL scores was used (in total 8 lists of 11 words per data-point).

Preoperative CVC scores were available for all but one patient. Because of patient (poor health, vacation) and administrational (understaffed audiological services) factors, no audiological follow-up data were available for 3, 1 and 6 patients at 2, 12 and 24 months, respectively.

Quality of Life

Quality of Life was evaluated in all patients, at three test moments: pre-operatively, and postoperatively at 4 months (shortly after completion of the initial training) and at 12 months. Quality of life was measured by means of the HUI-Mark II[27] and the NCIQ.[14] Utilities, reflecting both the quality of life *and* the value of that quality of life relative to death and optimal health, were measured by means of a time trade-off measure[27] and through the Health Utility Index.

The HUI-Mark II is a generic, multi-attribute, preference based classification system, and is administered as a measure of general health status. It focuses on the more functional concepts of HRQoL, such as disabilities (dysfunction) and resulting dependencies. The HUI-Mark II encompasses seven domains or attributes (sensation, mobility, emotion, cognition, self-care, pain and fertility). Three to five levels of functioning are defined in each domain. Any specific combination of functioning on the applicable domain levels constitutes a unique health state, which has an associated weight or utility, indicating the subjective assessment of the state in question. This utility (HUI_{mean}), on a scale from 0 (=death) to 1.0 (=perfect health), is obtained by applying a multi-attribute utility function, based on data obtained from a sample of the Canadian public. Utilities express the overall valuation of a health state, and can be multiplied by expected life years to compute quality adjusted life years (QALYs).

The NCIQ is a validated, disease specific instrument that measures hearing-related quality of life. The questionnaire comprises three general domains: physical, psychological, and social functioning. Each domain can be divided in sub-domains. The sub-domains consist of 10 items, with a five-point response scale. There is also a sixth response category if the item is not considered relevant. The answer categories (1-5) were transformed to a 0 (poor) to 100 (optimal) scale. A minimum of seven completed items was required for a specific sub-domain. The sum of the scores of each sub-domain was divided by the number of completed items. $NCIQ_{total}$ scores were calculated by dividing the sum of all sub-domain scores by the total of 6 (sub-domains).

To measure subjects' valuation of their current health, we used the time trade-off instrument (TTO). The respondent was asked whether she was willing to trade years of life expectancy (LE) with her present hearing, to reach perfect hearing. The less a patient values her present state of hearing, the more willing she may be

to give up years of life. The utility is calculated as: U= (LE- #yrs traded)/LE. The number of subjects who failed to complete the questionnaires at one of the test moments is summarized in table 2.3. All patients completed at least one quality of life test protocol post-operatively. The missing questionnaires were due to patients moving home (2), declining to attend (2), poor health (1), vacation (1) and administrational (3). The additional missing TTO's were due to the fact that patients did not understand the test. The missing sub-domains were "forgotten" questions of the HUI2 questionnaire.

Table 2.3: Missing data and reasons why subjects failed to complete the quality of life protocol. *QoL*: Quality of Life; *HUI2*: Health Utility Index Mark II; *NCIQ*: Nijmegen Cochlear Implant Questionnaire; *TTO*: time trade-off.

QoL				
Recruited		**44**		
preoperative		HUI2	NCIQ	TTO
major	Missing entire questionnaire	0	0	1
minor	Missing dimension	5	0	0
2months				
major	Missing entire questionnaire	4	3	6
minor	Missing dimension	1	0	0
12 months				
major	Missing entire questionnaire	6	6	6
minor	Missing dimension	4	0	0

Cost-utility

Individual lifelong incremental costs and QALY gains were calculated, based on the patients own life expectancy (28) at the date of surgery. Incremental costs of providing a CI were estimated at € 40.768 initial costs (including counselling, surgery and rehabilitation), plus € 2.007 per follow-up year (calculated as the difference between costs for maintaining implants and costs for hearing aids).[29] Follow-up costs and utility improvement were assumed to last for the patient's entire remaining life time, both discounted at a rate of 3% per annum. The

individual QALY gain was therefore calculated as the difference between the pre-implant utility and the 12-month post-implant utility, times the patient's discounted life expectancy. The cost-utility ratio was then calculated as the average discounted incremental costs, divided by the average discounted QALY gain. Confidence intervals for cost-utility ratios were calculated as those willingness-to-pay (WTP) values for which the net benefit (WTP × QALY costs) was not statistically significantly different from 0.[30]

Patient factors

The influence of eight preoperative factors on post-implant quality of life and speech perception scores, as assigned by team members, was examined after 12-months follow-up. Categorical variables comprised gender, aetiology, cochlear implant model, and educational background. Continuous variables comprised preoperative hearing thresholds, preoperative CVC (preopCVC) scores, duration of deafness and age at implant.

Determination of clinically important effect

The first estimator of important change for continuous variables was the effect size.[16] The ES was calculated as the average change divided by the baseline SD, and classified according to Cohen (1988): less than 0.2="none", between 0.2 and 0.5="small", between 0.5 and 0.8="medium" and greater than 0.8="large". The second estimator of important change for continuous variables was the MID. The MID was defined as 0.5 SD of the baseline and was interpreted as a difference likely to be recognized as meaningful, all else being equal. The percentage of patients who improved in terms of the MID in either a specific domain or summated score were then calculated.[18]

Data analysis

Data were analysed using SPSS version 12.0. The comparison of pre- and postoperative data was performed using the paired *t*-test. A multivariate linear regression analysis using a forward stepwise selection procedure was performed to find factors contributing to 12-months postimplant $CVC_{phoneme}$, CVC_{word}, $HUI2_{mean}$,

$NCIQ_{total}$, and TTO score. P-values less than 0.05 were considered significant.
The Institutional Review Board of the Leiden University Medical Centre granted approval under CME number P02.106

Results

Speech perception performance

Compared to pre-implant scores, patients had a statistically significant increase in phoneme and word scores at 2 months, 1 year and 2 years post-implant ($p<0.001$) (figure 2.1).

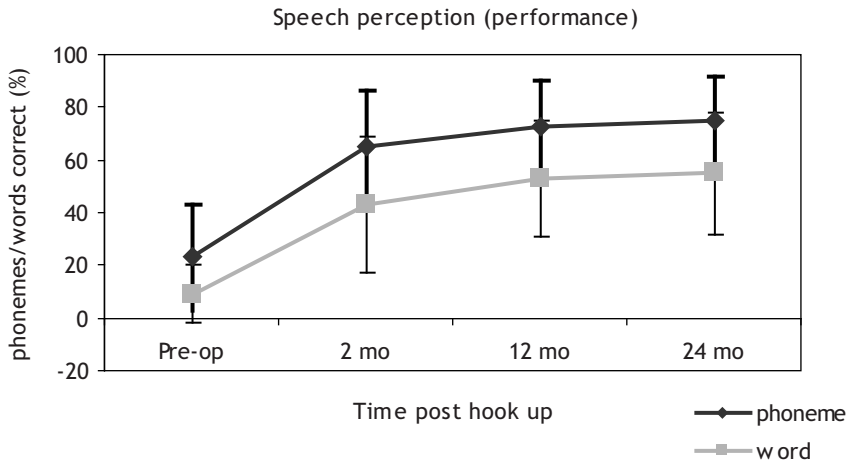

Figure 2.1: Average phoneme and word scores on a CVC word test in quiet (free field sound only, average 65/75 dB SPL) as measured pre-operatively with hearing aids (if applicable), and 2, 12 and 24 months post-operatively for the 44 patients in this study (error bar=1 SE).

Quality of life

The HUI2 showed significant improvement for the sub-domain "sensation" (comprising hearing function) 4- and 12-months post-implant (Table 2.4). At the 4-months evaluation, the sub-domain "pain" revealed a small, but significant

increase, which was no longer present after 12 months. The other domains did not reveal any significant change. The latter is likely because these specific domains were already near the top of the scale preoperatively.

Table 2.4: Means and standard deviations (between parentheses) on the domains of HUI2 and NCIQ. Significant changes (student's t-test) after 4 and 12 months are indicated. *NA*: not avalaible; *HUI2*: Health Utility Index Mark II; *NCIQ*: Nijmegen Cochlear Implant Questionnaire

HUI2	**Preop (SD)**	**4-months postop (SD)**	***p* value (change to baseline)**	**12-months postop (SD)**	***p* value (change to 4-months)**
Sensation	0.76 (0.12)	0.89 (0.10)	<0.0001	0.92 (0.07)	0.05
Mobility	1.00 (0.00)	1.00 (0.01)	0.32	1.00 (0.01)	NA
Emotion	0.96 (0.05)	0.96 (0.04)	0.25	0.96 (0.04)	0.96
Cognition	0.98 (0.03)	0.99 (0.02)	0.16	0.99 (0.02)	1.00
Self-Care	1.00 (0.00)	1.00 (0.00)	NA	1.00 (0.00)	NA
Pain	0.97 (0.04)	0.99 (0.01)	0.027	0.98 (0.05)	0.07
NCIQ					
Sound perception basic	21.3 (18.9)	68.4 (15.3)	<0.0001	71.3 (16.2)	0.4
Sound perception advanced	23.8 (13.1)	54.2 (13.5)	<0.0001	61.3 (16.8)	0.002
Speech production	71.4 (21.0)	85.5 (11.9)	<0.0001	85.6 (12.1)	0.92
Self-esteem	52.4 (20.7)	68.9 (15.8)	<0.0001	70.2 (16.9)	0.57
Activity	47.9 (21.2)	73.2 (16.8)	<0.0001	75.7 (19.4)	0.25
Social interactions	50.3 (19.8)	71.7 (13.4)	<0.0001	74.6 (16.0)	0.17
Total	44.5 (12.7)	70.3 (10.0)	<0.0001	73.1 (12.5)	0.11

Table 2.4 also shows the scores on the six NCIQ sub-domains. Differences between pre- and 4-months post-implant scores for all sub-domains were statistically significant. Only the sub-domain "speech perception advanced" revealed significant additional improvement after 12 months.

Utilities and cost-Utility

Cochlear implantation is associated with a significant increase in utility as measured by HUI2 and TTO. The increase in utility was mainly achieved in the first months after implantation (Table 2.5). The average individual estimated gain in utility was 0.18 (95% confidence interval 0.13 to 0.23) for the HUI2 and 0.24 (95% confidence interval 0.14 to 0.34) for the TTO.

Table 2.5: Means and standard deviation (between parentheses) of utility (HUI2, TTO). Significant changes (student's t-test) after 4 and 12 months are indicated. *HUI2*: Health Utility Index Mark II; *TTO*: time trade-off.

Utility	Preop (SD)	4-months postop (SD)	*p* value (change to baseline)	12-months postop (SD)	*p* value (change to 4-months)
HUI_{mean}	0.68 (0.14)	0.83 (0.12)	<0.0001	0.84 (0.10)	0.35
TTO	0.63 (0.25)	0.85 (0.18)	<0.0001	0.87 (0.19)	0.83

With an average age of 54.7 at implantation, the average undiscounted and discounted life expectancies were 28.8 and 17.5 years, respectively. Average lifelong CI costs were estimated at € 73,884 (95% confidence interval € 70,400 to € 77,200). The lifelong discounted QALY gain was estimated at 3.3 QALY (95% confidence interval 2.4 to 4.1) according to the HUI2 and 4.3 QALY (95% confidence interval 2.8 to 5.8) according to the TTO, yielding cost-utility ratios of € 22,500 (95% confidence interval € 18,400 to € 30,300) and € 17,100 (95% confidence interval € 12,600 to € 25,900) per QALY, respectively.

Predicting factors

Multivariate analysis (Table 2.6) revealed that both shorter duration of deafness and better education were significantly associated with better 12-months hearing performance, accounting for 30% ($CVC_{phoneme}$) and 33% (CVC_{word}) of the variability. Univariate analysis indicated that duration of deafness was the most important factor, accounting for 18% ($CVC_{phoneme}$) and 19% (CVC_{word}) of the variability.

Table 2.6: Results of a multivariate linear regression analysis using a forward stepwise selection procedure of variables associated with hearing performance and quality of life outcome. CVC: Consonant-Vocal-Consonant; *TTO*: time trade-off; *HUI2*: Health Utility Index Mark II; *NCIQ*: Nijmegen Cochlear Implant Questionnaire.

Variable	Factor	Beta	SE	p-value	R^2
$CVC_{phoneme}$	Duration of deafness	-0.618	0.192	0.003	
	Education	5.567	2.185	0.015	0.298
CVC_{word}	Duration of deafness	-0.865	0.251	0.001	
	Education	7.98	2.867	0.008	0.329
HUI2	PreoperativeCVC	0.003	0.001	0.02	
	Duration of deafness	0.003	0.001	0.033	0.324
NCIQ	Age at Implantation	-0.476	0.1	<0.0001	
	Duration of deafness	0.3	0.13	0.027	0.494
TTO	Age at Implantation	-0.006	0.002	0.001	0.282

Both higher preopCVC scores and longer duration of deafness were significant predictors of better 12-month HUI_{mean} scores, accounting for 32% of its variability. Multiple linear regression modelling indicated that younger age and longer duration of deafness were significantly associated with better 12 months scores of the $NCIQ_{total.}$ These factors accounted for 49% of the variability. Younger age at implantation was also shown to be a significant positive predictor for the 12-months TTO score (accounting for 28% of the variability).

Estimations of clinically important changes

Effect sizes for HRQoL and utility measures are shown in table 2.7. The only sub-domain of the HUI2 with a large ES was “sensation” (d>0.8). Effect sizes for all other HUI2 domains were small. All domains of the NCIQ, except speech production, showed a large ES (d>0.8). Effect sizes were large for the HUI_{mean} and TTO utilities.

The MID and percentage of patients that improved in terms of the MID are also shown in table 2.7. Over eighty percent of our patients experienced a clinically important change for the $HUI\text{-}_{Sensation}$ sub-domain, while the other five sub-

domains of the HUI2 showed an improvement in the minority of the patients. In all sub-domains of the NCIQ, as well as the summated $NCIQ_{total}$, the majority of the patients improved in terms of the MID. The percentage of patients improving in terms of the MID for the HUI2 and TTO utilities were 78.1% and 71.4%.

Table 2.7: Estimations of clinical relevance. Q*oL*: Quality of Life; *HUI2*: Health Utility Index Mark II; *NCIQ:* Nijmegen Cochlear Implant Questionnaire; *TTO*: time trade-off; *ES:* effect size; *MID*: Minimal Clinically Important Difference (in % of patients).

Instrument	Domain	ES[a]	MID[b]	(%)>MID
HUI2	$HUI-_{Sensation}$	1.3	0.06	80.6%
	$HUI-_{Mobility}$	-	0	-
	$HUI-_{Emotion}$	0.3	0.03	18.9%
	$HUI-_{Cognition}$	0.2	0.01	16.7%
	$HUI-_{Self\ care}$	-	0	-
	$HUI-_{Pain}$	0.1	0.02	22.2%
NCIQ	$NCIQ-_{Basic\ sound\ perception}$	2.6	9.47	97.4%
	$NCIQ-_{Advanced\ sound\ perception}$	2.9	6.55	94.7%
	$NCIQ-_{Speech\ Production}$	0.6	10.51	55.3%
	$NCIQ-_{Self\text{-}esteem}$	0.9	10.33	65.8%
	$NCIQ-_{Activity}$	1.4	10.62	89.5%
	$NCIQ-_{Social\ functioning}$	1.3	9.89	86.8%
	$NCIQ-_{Total}$	2.3	6.36	100.0%
Utility	$HUI2_{Mean}$	1.3	0.07	78.1%
	TTO	1	0.12	71.4%

[a] Effect size: d < 0.2 indicates no effect, d between 0.2 and 0.5, a small effect; d between 0.5 and 0.8, a medium effect; and d >0.8, a large effect.
[b] Minimal Clinically Important Difference (MID): 0.5 SD of baseline

Discussion

This paper reports the results of a prospective clinical study using a comprehensive data set of HRQoL and speech perception scores to measure benefits associated with cochlear implantation. Our results show that patients achieve significant improvements in the ability to communicate, self esteem, activities and social functioning. To our knowledge, this is the first study that applies both the MID and ES to show that these significant improvements are clinically relevant.

The present study used the NCIQ as a disease specific instrument. To our knowledge, only a few studies reported on the NCIQ. Hinderink and colleagues[14] showed a significant (p<0.01) increase in all NCIQ sub-domains during CI use. The effect size was large (d>0.8) for all domains. These results were confirmed by Cohen et al.[31], who reported retrospectively on 26 implantees, and measured benefits in all domains. Our data reflected significant changes on all six sub-domains, with the largest increase in the sound perception related sub-domains. However, significant changes were also obtained in the psychological ("self-esteem") and social sub-domains ("activity" and "social interaction"). Hawthorne et al.[32] reported a significant improvement in social participation as measured by the shortened form of the Glasgow Health Status Inventory, comprised of three subscales (self esteem related to hearing, level of social interaction related to hearing and hearing handicap). Mo et al.[33], using the Patient Quality of Life form, reported that CI users improved significantly in the ability to communicate, were less isolated, felt less like a burden (to others) and had better relations with their relatives.

Previous studies have used either the Mark II[7,23,34] or Mark III version[35,36] of the HUI as a generic HRQoL instrument. Although the HUI3 is preferred by its developers[11], not least because it distinguishes deficits in auditory function from visual function, the HUI2 was preferred in the present study to allow us specific comparison with a corresponding Dutch study.[34] In this retrospective study conducted in the Netherlands, Krabbe et al. measured a larger gain in utility (0.28) compared to our group. Interestingly, the difference between both groups in HUI2 utility gain can solely be attributed to the preoperative values (0.55 vs. 0.68), which -contrary to the present study-, were collected retrospectively. However, our findings compare well with those reported by Palmer et al.[7] and the UK Cochlear Implant Study

group[9] using the HUI3. The observed positive effect of CI on HUI utility in the above mentioned studies is mainly due to the sensation domain. Thus, the HUI is a sensitive instrument for hearing-specific quality of life, but rehabilitation of hearing does not strongly influence the other domains (or the questionnaire is not responsive to the changes in these domains). However, we feel that the benefit of the sensation domain of the HUI outweighs a potential benefit of e.g. an EQ-5D[37], which has more generic scales such as daily activities, but which lacks sensation.

The calculated cost-utility was € 22,500 per QALY for the HUI2 instrument and € 17,100 per QALY for the TTO instrument. Costs are commonly classified as definitely acceptable up to €16,000 per QALY, as acceptable up to €40,000 per QALY, and as possibly acceptable up to €80,000 per QALY.[38] According to this rule of thumb, it is appropriate to state that in our study cochlear implantation is cost-effective.

Older age at implantation had a significant negative effect on the TTO utility and $NCIQ_{total}$ score, but there was no association with *gain* in TTO utility and $NCIQ_{total}$ (data not shown). These findings are in line with the ones of the UK Cochlear Implant study group[8] who reported that baseline and outcome measures for the HUI3 both declined with age at implantation, but the measure of effectiveness (gain) did not vary with age at implantation. A possible explanation is given by Piette et al.[39] who found that increasing age in itself has a deteriorating effect on the overall quality of life outcome.
Longer duration of deafness, as well as higher preoperative CVC scores predicted better HUI2 and $NCIQ_{total}$ scores. These results are in contrast with previous studies. Maillet et al.[40] found that, in general, the longer an individual has been deaf, the less the improvement in HRQoL that is perceived. Hawthorne et al.[32] described a suggestive but not significant relationship between the AQoL instrument and hearing loss (e.g., pre-implant profound hearing loss obtained better AQoL change scores than severe to moderate hearing loss). However, the sparse but conflicting evidence may imply that the complicated nature of HRQoL as an outcome measure needs further study of a larger sample size to elucidate the relative importance of different factors.

Our findings reconfirmed shorter duration of deafness[41] as an important predictor for post-implant hearing performance and identified educational level as a new one. Educational level may serve as a surrogate for higher verbal learning scores and better verbal working memory that have recently be identified as predictors for improvement in spoken word recognition.[42,43]

Our results support previous findings that cochlear implantation significantly improves quality of life and hearing capacity. However, the key issue for the clinician and patient is whether the detected difference may be regarded as clinically relevant. Like the present study, several others[8,33] have shown with the ES as a measure of effectiveness, that cochlear implantation is an effective intervention. Moreover, this study is the first to show that improvements as measured by the MID were clinically relevant. The MID was estimated by the 0.5SD method as a pragmatic estimate, which is supported by sufficient consensus in literature.[18,19] However, we suspect that the 0.5 SD estimate of MID is a rather crude measure in cochlear implantation as it was first proposed for QoL measures in oncology and pulmonology. Because the effectiveness of CI in post-lingually deafened adults appears to be overly large, a positive outcome in terms of clinical relevance could be anticipated in this patient group. However, it remains to be seen whether similar results will be obtained, for instance, in patients with larger amounts of residual hearing. Together, these observations indicate that our understanding of the *minimal* clinical important difference in CI is incomplete. Therefore, further investigations, using an anchor based method, are necessary.

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