Washington State Health Care Authority

Health Technology Assessment

Cochlear Implants: Bilateral versus Unilateral

Final Evidence Report

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Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
hta.hca.wa.gov

shtap@hca.wa.gov

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A Health Technology Assessment

Prepared for Washington State Health Care Authority

FINAL REPORT– April 17, 2013

Acknowledgement

This report was prepared by:

Hayes, Inc.
157 S. Broad Street Suite 200
Lansdale, PA 19446
P: 215.855.0615 F: 215.855.5218

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LIST OF KEY ABBREVIATIONS

CI, cochlear implant(s/ation)
dB, decibel
dB HL, decibel hearing loss
HA, hearing aid
ICER, incremental cost-effectiveness ratio
PICO, population(s)-intervention(s)-comparator(s)-outcome(s)
PTA, pure tone average
QALY, quality-adjusted life-year
QOL, quality of life
SNHL, sensorineural hearing loss
SNR, signal-to-noise ratio
SRT, speech reception threshold

EVIDENCE SUMMARY

BACKGROUND

Epidemiology, Biology, and Consequences of Hearing Loss

Estimates based on national surveys suggest that 16% of adults have trouble hearing (ranging from a little trouble to deafness), that more than 30% of adults over the age of 64 have trouble hearing, and that prevalence of hearing impairment in adults is increasing. Prevalence of hearing loss in children has been estimated to be 5 per 1000 children.

Hearing loss can be due to conductive, sensorineural, or central causes. Conductive hearing loss is caused by disease affecting the external ear, or more commonly the middle ear, and is characterized by the inability of the ear to conduct sound waves to the cochlea (inner ear). Sensorineural hearing loss (SNHL) involves damage either to the cochlea or to the neural pathways from the retro cochlea to the brain. The most common form of SNHL occurs when the cilia lining the cochlea area are lost and there is no way for sound waves entering the cochlea to be transformed into nerve impulses. Hearing loss is often characterized as having occurred prelingually, with age 3 years serving as a common proxy for speech development, or postlingually.

Hearing loss may cause serious linguistic, cognitive, emotional, educational, and social problems for children. Problems are intensified when the deafness is bilateral. Hearing loss has also been shown to be linked to depression, impaired activities of daily living (ADL), and deteriorating quality of life in adults and may even contribute to dementia. A substantial proportion of adults with hearing loss who are older than 60 years experience tinnitus.

Treatment

For some adults with hearing loss, acoustic amplification with an external hearing aid is sufficient, but as SNHL increases, frequency selectivity is lost and other forms of distortion occur so that speech perception becomes very difficult. Children with residual hearing may also benefit from hearing aids. However, traditional hearing aids tend to be ineffective when SNHL is severe to profound.

If the neural elements that transmit information from the cochlea to the auditory cortex of the brain are intact and functional, as is generally the case with SNHL, it is possible to stimulate auditory nerve impulses with a prosthetic cochlear implant (CI) device designed to perform the function of cochlear hair cells. With CI, externally worn components—including a microphone, a speech processor, and a transmitter—capture sounds from the environment and transform these sounds into electronic impulses that are sent to an implanted receiver/stimulator, which conveys the impulses to the auditory nerve via electrodes implanted in the cochlea. By electrically stimulating the auditory nerve, CI performs the function normally performed by cochlear hair cells, thereby restoring some degree of hearing. CIs are not appropriate for conductive or central deafness.

Bilateral Versus Unilateral CI

Initially, CI was performed unilaterally but bilateral implantation is becoming more common. The use of cochlear implants in general is widespread in developed countries, but the use of two implants is a relatively new practice. The additional cost of a second implant and uncertainty about the added benefit versus added risks has prevented bilateral implantation from becoming routine. Dual-ear stimulation allows left-right discrimination of sound location and makes it possible for the hearer to benefit from phenomena known as the head shadow effect, binaural summation, binaural redundancy, and binaural squelch. Bilateral implantation has the theoretical potential to achieve these effects for the user. Additionally, a second implant provides more electrodes that can compensate for asymmetric spiral ganglion cell loss, as well as a backup in case of device malfunction. In describing the rationale for exploring the effects of a second CI, one group of researchers cited studies of children with untreated unilateral hearing loss and described the studies as having shown that compared with normal hearing children, these children have deficits in language learning and speech perception. The authors suggest that unilateral implantation in children with bilateral hearing loss leaves children in a condition comparable to unilateral hearing loss. Other researchers point out that localization of sound, which is dependent on binaural timing and intensity cues, might be particularly enhanced by bilateral localization. The expectation of researchers interested in bilateral CI is that the benefits would be especially critical in noisy classroom settings for school children and in outdoor settings that involve hazards such as those associated with crossing the street.

Bilateral CI can be accomplished through simultaneous implantation or sequential implantation. It was originally thought that there was an advantage in saving one ear for future more sophisticated devices through sequential implantation, although reimplantation is a possibility. On the other hand, some experts believe that simultaneous implantation, or sequential implantation with little delay between the procedures, is potentially more advantageous in that it may prevent a lack of coordination between the two devices that could diminish binaural cues and avoids timing differences in auditory brainstem activity that can develop during the time between implants.

CI Eligibility

CI is undertaken in patients with bilateral cochlear hair cell–related SNHL who obtain minimal benefit from amplification, as determined by scores on speech perception tests administered with patients using appropriately fitted hearing aids, often described as the best-aided listening condition. Initially, CI was approved by the Food and Drug Administration (FDA) only for adults (age ≥ 18 years) who developed profound hearing loss (deafness) after acquiring speech, i.e., adults with postlingual deafness. Later, approved indications were expanded to include adults with residual hearing who are either prelingually or postlingually deaf and who have moderate to profound SNHL in the low frequencies or profound SNHL in the mid to high frequencies. Expanded FDA-approved indications also have come to include children as young as 12 months of age.

Audiological assessment of sound and speech perception is the first step in determining eligibility for CI. To evaluate hearing levels, thresholds (required sound intensity) for detection of pure tones at various frequencies, usually 500 to 4000 Hz (Hertz), are measured and averaged to yield a pure tone average (PTA). The PTA is expressed in terms of decibels hearing level (dB HL). Since the decibel scale is logarithmic, a 1 dB decrease in PTA or in an individual's threshold for correct response to a speech test, actually represents a 10-fold decrease in actual sound intensity. It is also important to note that the sound intensity results of audiological assessments are on a relative scale, with 0 corresponding to the

very faintest sound that is humanly audible rather than to an absolute absence of sound. The ability to detect tones at an average level < 20 dB HL is considered to be normal hearing. Hearing loss is classified as profound if the PTA is ≥ 95 dB HL and as severe if PTA is 70 to 90 dB HL.

If pure tone audiometry suggests that a CI may be appropriate, a trial of a few months with acoustic hearing aids may follow to confirm that hearing level in the best-aided condition remains sufficiently impaired to warrant a CI. Communication abilities are assessed, which may require the involvement of speech and language specialists in prelingual children. Medical evaluation is necessary to assure fitness for surgery and to identify comorbidities that could interfere with success. Imaging studies may be undertaken to rule out any anatomical contraindications. Lastly, psychological assessment is important to assure that patients and/or parents have realistic expectations from CI.

Outcome Measures

A wide variety of speech perception tests (also called speech recognition or speech discrimination tests), speech comprehension tests, and speech production tests are available for administration in an audiology laboratory or other clinical setting. Sound detection and sound localization in an auditory laboratory setting are also often measured according to a variety of protocols. Most assessments of localization measure left-right discrimination by using a semicircle arrangement of loudspeakers on a horizontal plane and evaluating the patient's ability to identify the source of speech or everyday sound signals. Speech perception and sound localization tests might be considered strictly surrogate measures of hearing-related function. Tests of speech comprehension and speech production, while based on evaluation in a clinical setting by an audiologist or speech pathologist, are designed to more closely mirror real-life situations.

Questionnaires for measuring actual self-reported or parent-reported hearing-related function in real-life situations are available. Disease-specific and generic scales for assessing health status and quality of life (QOL) have been used in a small number of studies. For assessment of children according to a functional, health, or QOL questionnaire, investigators typically ask parents to complete the questionnaire.

See **Appendix I** for descriptions of the tests and questionnaires used in evidence selected for this report. The literature did not identify any test or questionnaire as a standard.

Policy Context

Although several systematic reviews and technology assessments have concluded that unilateral cochlear implantation is effective, the added benefit of a second implant, particularly in terms of functional measures, is less certain. The incremental benefits must also be balanced against the added safety risks and cost of bilateral CI. Only in recent years has sufficient evidence accumulated to allow an assessment of the benefits of bilateral implantation, particularly with respect to potential effect modifiers such as age of implantation in children. The Washington State Health Care Authority has, therefore, commissioned a health technology assessment comparing bilateral implantation with unilateral implantation in pediatric populations and in adults.

Washington State Agency Experience

Figure 1 – Cochlear Implant Procedures - Paid Amounts by Agency/Year, 2008-2011

Agency/Year PEB[1]	2008	2009	2010	2011	4 Yr Overall[2]	Average % Change	
Agency Pop.	204,804	210,501	213,487	212,596		1.3%	
All Cochlear Implant Procedures:							
Patient Count[2]	9	11	11	4	32	-15.3%	*
Procedure Count	10	11	11	4	36	-19.3%	*
Amount Paid	$320,669	$543,480	$437,530	$166,780	$1,468,459	-3.7%	*
Per Procedure Average[3]	$32,067	$49,407	$39,775	$41,695	$52,778		
Per Procedure Maximum	$71,913	$159,289	$78,637	$88,777	$159,289		
Unilateral Cochlear Implants (Non-Medicare)							
Procedure Count	6	5	6	2	16		
Per Procedure Average	$52,611	$75,282	$71,496	$81,898	$70,874		
Bilateral Cochlear Implant Average (1 only)							
Per Procedure Average		$159,289					
Procedures Including Device Malfunction							
Procedure Count			1		1		
Medicaid	**2008**	**2009**	**2010**	**2011**	**4 Yr Overall[2]**	**Average % Change**	
Agency Pop. (Fee for Service)	392,808	416,871	424,230	435,187		3.5%	
All Cochlear Implant Procedures:							
Patient Count[2]	20	17	25	18	79	-1.7%	*
Procedure Count	20	17	27	19	83	1.6%	*
Amount Paid	$397,337	$391,359	$540,395	$606,041	$1,935,132	12.6%	*
Per Procedure Average[3]	$19,867	$23,021	$20,015	$30,302	$23,037		
Per Procedure Maximum	$26,822	$48,071	$27,267	$74,306	$74,306		
Unilateral Cochlear Implants (Excluding 6 Medicare Procedures - $400 Total)							
Procedure Count	20	15	23	19	77		
Per Procedure Average	$19,867	$21,380	$21,572	$30,001	$23,172		
Bilateral Cochlear Implant Average (None Were Done Under Medicare)							
Procedure Count	0	2	4	1	7		
Per Procedure Average	0	$35,326	$11,059	$36,029	$21,559		
Procedures Including Device Malfunction							
Procedure Count	3	1	1**	1	5		
Percent Total Procedures	15.0%	5.9%	3.7%	5.3%	6.0%		

Figure 1 Notes:

*Average % Change adjusted for population.

**Bilateral procedure including device malfunction

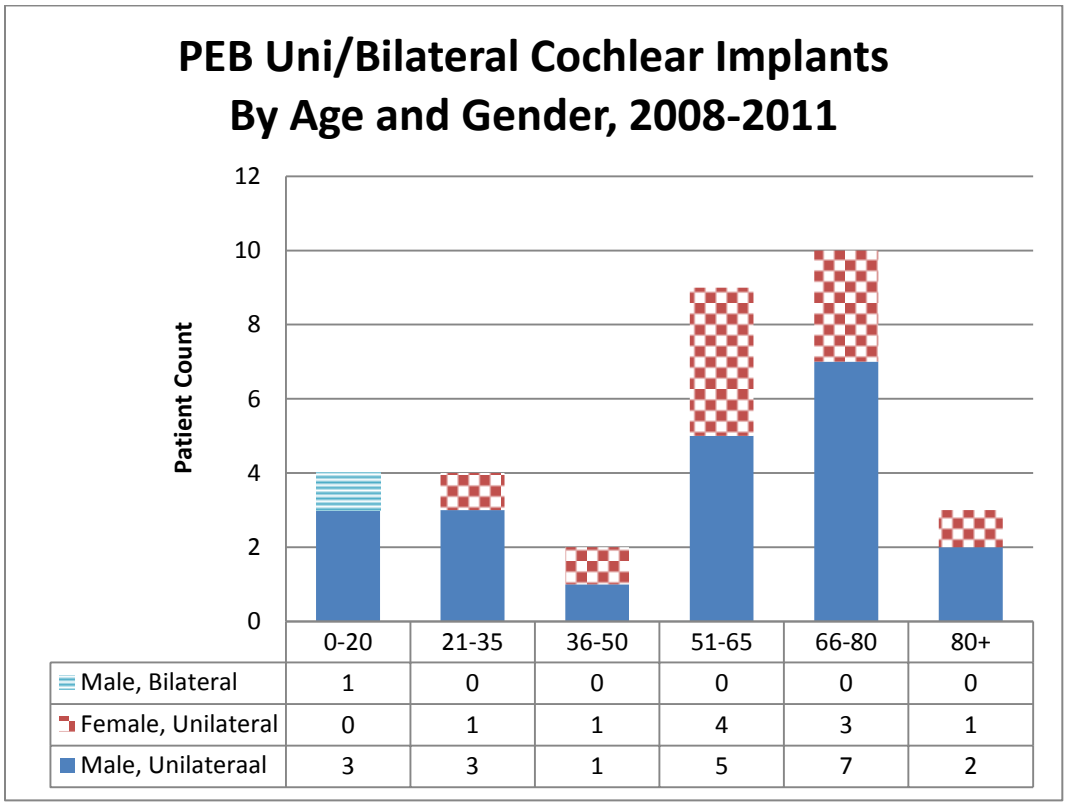
[1] Public Employee Benefits

[2] Patients who receive treatment in multiple years are counted only once in the "4 Yr Overall" total.

[3]Procedure charges include preoperative exams, day of procedure related charges, plus testing, speech and hearing services and implant analysis charges for 90 days post-procedure.

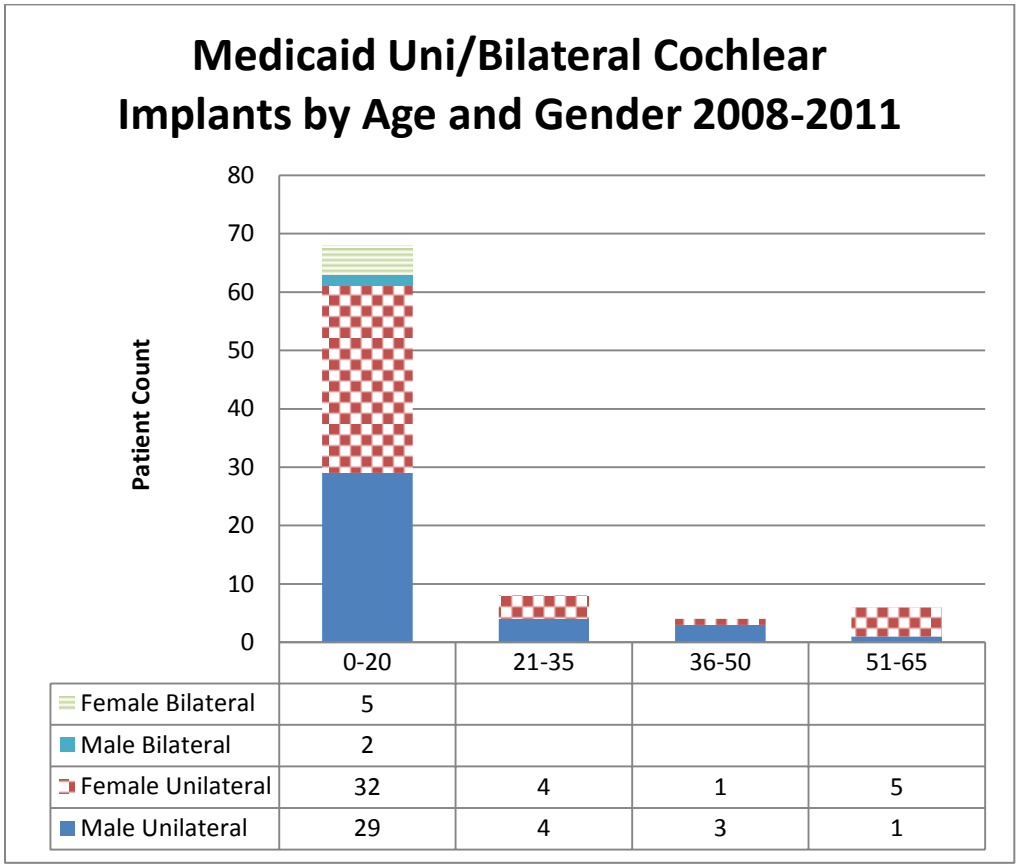
NOTE: L&I reports no claims for uni- or bi-lateral cochlear implants during the 2008-2011 period.

Figure 2a. PEB Cochlear Implant Patients by Age and Gender, 2008-2011



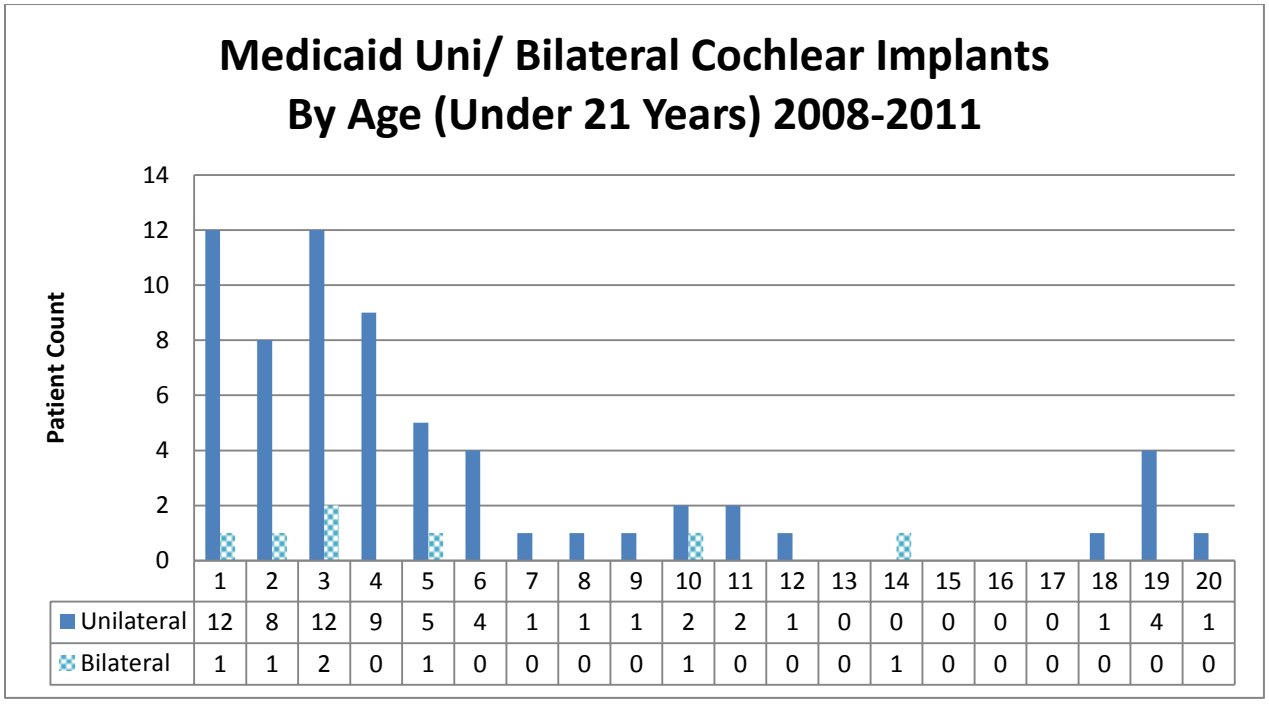
	0-20	21-35	36-50	51-65	66-80	80+
Male, Bilateral	1	0	0	0	0	0
Female, Unilateral	0	1	1	4	3	1
Male, Unilateraal	3	3	1	5	7	2

Figure 2b. Medicaid Cochlear Implant Patients by Age and Gender, 2008-2011



	0-20	21-35	36-50	51-65
Female Bilateral	5			
Male Bilateral	2			
Female Unilateral	32	4	1	5
Male Unilateral	29	4	3	1

Figure 2c. Medicaid Cochlear Implant Patients by Age (under 21 Years), 2008-2011



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Unilateral	12	8	12	9	5	4	1	1	1	2	2	1	0	0	0	0	0	1	4	1
Bilateral	1	1	2	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0

Figure 3 Cochlear Implant Cost Breakdown, Allowed Amount 2008-2011

Agency and Implant Type (Procedure Count)	Medicaid Unilateral (64)*	Medicaid Bilateral (7)	Medicaid Medicare, Unilateral (6)	PEB Primary, Unilateral (19)	PEB Primary, Bilateral (1)	PEB Medicare (16)
Cost Breakdown 1						
Facility	$27,418	$29,923	$33,331	$66,280	$154,089	$96,792
Professional	$1,402	$2,152	$1,229	$2,535	$5,300	$423
Cost Breakdown 2						
Implant (Facility and Professional)	$23,818	$22,021	$33,080	$41,389	$35,144	$24,607
Post Procedure Hearing & Implant Testing, Analysis & Reprogramming	$632	$515	$178	$992	$1,583	$650
Other Day of Treatment Costs**	$3,919	$9,539	$1,302	$25,243	$122,662	$71,958
Per Procedure Average	**$28,370**	**$32,075**	**$34,560**	**$67,624**	**$159,389**	**$97,215**

*Medicaid unilateral average excludes 16 outlier procedures with charges less than 3 standard deviations below the mean, all with missing facility charges.

**Anesthesia, eardrum/ear surgery, observation, and the Cochlear Device/System, which was irregularly reported (reported for 7 PEB Primary patients only; average reported $54,923, reported twice for PEB's bilateral patient at $53,488 each).

Related Medical Codes

Type	Code	Description	Category
HCPCS	L7500/ 10/20	Repair of prosthetic device, repair or replace minor parts for cochlear devices	Repair
HCPCS	L8614	Cochlear device, includes all internal and external components	Equipment
HCPCS	L8615	Headset/headpiece for use with cochlear implant device, replacement	Repair/Replace
HCPCS	L8616	Microphone for use with cochlear implant device, replacement	Repair/Replace
HCPCS	L8617	Transmitting coil for use with cochlear implant device, replacement	Repair/Replace

Type	Code	Description	Category
HCPCS	L8618	Transmitter cable for use with cochlear implant device, replacement	Repair/Replace
HCPCS	L8619	Cochlear implant,external speech processor/controller, integrated system, repl	Repair/Replace
HCPCS	L8621	Zinc air battery for use with cochlear implant device, replacement, each	Repair/Replace
HCPCS	L8622	Alkaline battery for use w/ cochlear implant device, any size, replacement, each	Repair/Replace
HCPCS	L8623	Lithium ion battery for use with speech processor	Repair/Replace
HCPCS	L8624	Lithium ion battery for use with speech processor; ear	Repair/Replace
HCPCS	L8627	Cochlear implant, external speech processor, component replacement	Repair/Replace
HCPCS	L8628	External Controller	Repair/Replace
HCPCS	L8629	Transmitting coil and cable, integrated for use with cochlear implant device	Repair/Replace
HCPCS	L9900	Accessory and/or replacemt parts for other HCPCS codes	Repair/Replace
CPT	69930	Cochlear device implantation, with or without mastoidectomy	Implant
CPT	69949	Unlisted procedure, inner ear	Removal
CPT	92601	Diagnostic analysis of cochlear implant, patient younger than 7 years of age; with programming	Implant Analysis
CPT	92602	Subsequent reprogramming	Implant Analysis
CPT	92603	Diagnostic analysis of cochlear implant, age 7 years or older; with programming	Implant Programming
CPT	92604	Subsequent reprogramming	Implant Programming

TECHNOLOGY DESCRIPTION

Although a variety of cochlear implantation (CI) systems are available, all such systems require and use four basic components: (1) external receiver (microphone) mounted on (2) an external speech processor (generally worn behind the ear); (3) an internal receiver/stimulator (under the skin and behind the ear); and (4) an array of electrodes proceeding from the receiver/stimulator and into the cochlea. The external processor typically transmits signals to the internal receiver/stimulator via radiofrequency waves. After the surgical sites have healed, approximately 1 month after surgery, the external components of the CI device are linked to the internal receiver/stimulator apparatus and the CI device is activated. The external speech processor and the internal receiver/stimulator unit must be programmed individually to maximize auditory benefit and minimize discomfort from sound that is too loud. Achieving this goal may require many sessions and take as long as 3 to 6 months.

Food and Drug Administration (FDA) Approval

The FDA has approved cochlear implant devices from three manufacturers under the Premarket Approval (PMA) process under product code MCM. The three manufacturers are Advanced Bionics LLC, Cochlear® Americas (previously Cochlear Corporation), and Med-El Limited. For adults ≥ 18 years of age, approved indications are generally for severe to profound bilateral SNHL (severe defined as ≥ 70 dB); one device, the Nucleus® (Cochlear Americas), is also approved for use in individuals who have *moderate* to profound hearing loss. For pediatric populations, approvals apply to children who are ≥ 12 or ≥ 18 months of ageand have severe to profound, bilateral SNHS. Approvals include various stipulations regarding maximum performance on speech recognition tests in best-aided listening conditions (adults and older children) or lack of progress in auditory skills (younger children).

Safety Issues

The types of potential adverse events are similar between adults and children. The inserted electrodes can damage spiral ganglion cells and thereby reduce the potential effectiveness of the implant. Other complications resulting from trauma include intracochlear fibrosis and ossification, ear drum perforation, cholesteatoma, and facial nerve damage, all of which can lead to the need for revision surgery. Over the last decade, electrode designs and surgical techniques have improved and diminished the risk of trauma. Postimplant inflammation, flap breakdown, and electrode degenerationare other potential adverse events. Lastly, penetration of the sterile environment of the inner ear presents the possibility of infection (otitis media or meningitis). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends age-appropriate immunization against *Streptococcus pneumoniae* in children and adults who have received or are candidates for CI.

A small percentage of implantees require an explantation and a reimplantation procedure because of major adverse events such as those described above. Serious complications that may not require further surgery but are life-threatening, such as meningitis or other severe infection, would also be considered major complications. Minor complications are also possible; these are generally defined as complications that do not require a repeat surgery, or do not require other than minor surgery, and are not life-threatening. Minor complications include wound infections, flap edema, hematoma, facial nerve stimulation, tinnitus, and temporary vertigo.

REVIEW OBJECTIVES

The scope of this report is defined by the following PICO statement:

> **Populations:** Children, adolescents (20 years of age and younger), and adults with hearing loss.
>
> **Intervention:** Bilateral implantation of multichannel cochlear devices that use whole-speech processing coding strategies.
>
> **Comparators:** Unilateral CI only, unilateral CI plus acoustic hearing aid.

Outcomes:
Primary: Detection of sound (measured directly or measured indirectly by hearing aid use), neurocognitive development, perception and production of speech, functional status, quality of life (QOL), procedure- and device-related complications.
Secondary: Tinnitus, telephone usage, patient acceptance, employment or job performance, educational outcomes.

Key Questions

This report addresses the following key questions:

1. Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?
2. Is bilateral cochlear implantation safe?
3. Does the effectiveness or safety of bilateral cochlear implantation vary according to age at implantation, prelingual versus postlingual onset of hearing loss, duration or degree of deafness, choice of implanted ear, time interval between implantations, specific device, or provider characteristics?
4. What are the cost implications, including cost-effectiveness, of bilateral cochlear implantation?

METHODS

Search Strategy and Selection Criteria

In addition to the systematic searches described here, manual bibliography searches within the selected reviews and studies were also conducted.

Core sources for systematic reviews and guidelines, the websites of relevant professional societies, and MEDLINE were searched for publications within the last 5 years. No systematic reviews that included both a substantial volume of the available evidence and that reported sufficient detail to provide good answers to the key questions were identified. Therefore, a de novo approach, i.e., assessment of primary studies only, was taken.

Primary studies that were published before July 2009 were identified by a manual search of the included study lists in published systematic reviews. Primary studies published in July 2009 or later were identified through a search of the MEDLINE and Embase databases. The initial search was conducted on November 28, 2012, and an update search was conducted on February 17, 2013.

Eligible Studies

- Studies of sequential or simultaneous bilateral CI designed to allow a comparison of outcomes or harms between bilateral CI and unilateral CI.

- Studies assessing the relationship between patient- or procedure-related factors, as listed in Key Question #3, and the outcomes of bilateral versus unilateral implantation.
  Studies assessing outcomes following a second implantation, but without comparison with unilateral implantation or with monaural activation, for potentially useful data on adverse events attributed to bilateral CI or predictors of benefit/harms attributable to bilateral CI.

Exclusion Criteria

- Non-English language publication. (A single study of 7 participants was excluded for this reason [Luntz et al., 2010]).
- < 20 evaluable patients who underwent CI. (This cutoff point corresponded to a median value for sample size among all studies with ≥ 5 patients, within both the pediatric and adult sets. It is also a commonly used cutoff for selecting the best evidence when the volume of studies is high.)
- Outcomes assessment without the use of either objective measurement or a formal instrument.

See the **METHODS** section of the full report and **Appendix II** for details.

Quality Assessment

Clinical Studies Selected to Answer Key Questions

Appendix III outlines the process used by Hayes for assessing the quality of primary studies and bodies of evidence, a process that is in alignment with the GRADE system. Internally developed Quality Checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*.

The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account not only methodological quality in individual studies but also these features of collective bodies of evidence:

- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

Bodies of evidence for particular outcomes are labeled as being of *high*, *moderate*, *low*, or *very low* quality. These labels can be interpreted in the following manner:

> **High:** Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.
>
> **Moderate:** Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.
>
> **Low:** We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

Very low: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Supplemental Studies

Large case series without a bilateral-unilateral comparison were selected to supplement the safety and differential effectiveness/safety data available from comparative trials. Such studies are by definition of very poor quality for demonstrating treatment-attributable benefits and harms. However, their larger sample sizes may yield more reliable adverse event rates, and results can be analyzed to identify predictors of treatment success in populations undergoing the treatment of interest. In the evidence tables, comments are made about the adequacy of analyses.

Guidelines

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2012), along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines.

Special Issues Regarding Study Designs

The ideal study design for a comparison of the effect of bilateral versus unilateral implantation on hearing skills would be a randomized trial. Patients might be randomized to unilateral versus bilateral CI. Another approach might be to randomize patients following unilateral CI to a waiting list for bilateral CI or to immediate receipt of second implant. No such trials have been published in pediatric populations. Among studies of adult populations, 1 randomized wait list trial was identified. The available analyses follow several different designs, some of which have serious limitations. **Table 1** in the full report describes these analyses. The assumed starting quality for each study design is also given in Table 1. These quality assumptions apply to the internal validity of each study for demonstrating a bilateral versus unilateral effect.

SEARCH RESULTS

Studies selected to answer the Key Questions are summarized as follows:

Key Question #1:
- Children and adolescents: 18 studies, published as 21 reports (see Box 2 in the full report for a list of studies)
- Adults: 17 studies, published as 19 reports (see Box 3 for a list of studies)

Key Question #2: 1 technology assessment, 4 case series
Key Question #3: Studies selected for Key Question #1, where applicable. In addition, 2 comparator trials and 2 case series with success predictor analyses involving children.
Key Question #4: A systematic review of economic evaluations

Key Question #1: ***Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?***

CHILDREN, KEY QUESTION #1

The 18 selected studies had sample sizes ranging from 20 to 73 children, with the exception of 1 small study (n=9) that was selected because it provided additional data on adolescents. No randomized controlled trials (RCTs) were available. Studies that compared groups or listening conditions at one point in time (Designs A and B according to Table 1 in the main body of the report) were considerably more common than those that evaluated change over time (Designs C and D). The findings from these studies generally apply to children or young adolescents who have prelingual, severe to profound deafness. Age at the time of a second implantation ranged from a mean of 21 months to a mean of 8 years in most studies and from 10 to 20 years in the study of adolescents. Follow-up intervals, i.e., the time between the last implant and final testing, ranged from 1 to 4 years, except in 2 studies that tested only at 3 months in some or all children.

*Please note that hyperlinks for each outcome have been provided to corresponding detailed discussion in the **LITERATURE REVIEW**, and clicking on hyperlinks in the LITERATURE REVIEW will bring the reader back to the EVIDENCE SUMMARY.* Evidence tables are found in **Appendix IV**.

Summary of Findings and Quality Assessment

In the following discussion, *analyses* refer to the multiple comparisons involving different measures, comparators, and/or listening conditions for the same outcome that were conducted by some studies. See **Appendix I** for descriptions of the tests, scales, and questionnaires used in evidence selected for this report.

Sound Detection: The evidence (1 poor-quality study) was insufficient to permit conclusions.

Neurocognitive Development: No studies evaluated this type of outcome.

Speech Perception in Quiet: Eight studies (total, n=340; 3 good, 2 fair, 2 poor, 1 very poor), reported positive statistically significant results for at least one analysis. In two studies (1 good; 1 poor), although all differences were positive, they were nonsignificant in a Design B comparison (intrasubject comparison of binaural with monaural listening) while significant in comparisons of bilateral CI with a preoperative bimodal condition (Design C); in this report, Design B is considered to have greater validity than Design C (see Table 1). Most of the analyses were based on open-set word recognition tests. Taking into account fair to good quality in 5 studies but the small sample sizes and some lack of statistical significance, this body of evidence is of moderate quality for speech perception as an outcome of interest.

Speech Perception in Noise: Eight of 10 studies (total, n=278; 3 good, 2 fair, 3 poor, 2 very poor) provided positive and statistically significant evidence showing bilateral CI to provide an advantage over unilateral CI in noise conditions. Most of the analyses were based on open-set word recognition tests. The only exceptions to these positive results were 2 poor-quality studies that found no effect. In studies that tested children both in quiet and in noise, benefits tended to be larger in the noise condition. Taking into account the fair to good quality of 5 of the studies but the small sample sizes, this body of evidence is of moderate quality for speech perception as an outcome of interest.

Sound Localization (Right-Left Discrimination): Five studies (total, n=170; 2 good, 2 fair, 1 poor) demonstrated a significant association favoring bilateral CI. Most tests were conducted in quiet. Performance in terms of percentage correct scores was generally at the chance level in unilateral CI groups and conditions. Taking into account the generally fair to good study quality but the small sample sizes, the body of evidence is considered to be of moderate quality.

Speech Comprehension and Speech Production Tests: Four studies (total, n=188; all very poor) conducted tests of speech comprehension or speech production or performed laboratory assessment of behavioral responses to speech. The findings were inconsistent. Because of the very poor study quality, the small quantity of data, and inconsistency, this body of evidence is considered to be of very low quality.

Functional and QOL Outcomes: The findings from 5 studies (total, n=175; all poor), including the one involving adolescents and young adults, suggested that a second CI improves disease-specific factors, especially functional hearing and conversation, but may not improve general health or QOL. All 5 studies used one or more of several disease-specific instruments for assessing hearing function in real-life situations and reported generally positive, statistically significant results; exceptions were 1 study with positive nonsignificant results and 1 study with significant positive findings on 1 scale and no difference on another. Two poor-quality studies each detected no difference according to one measure of functional hearing but positive, significant differences on one or more other measures of functional hearing. One study each documented improvements in mainstream school attendance and disease-specific health. No benefit according to 1 study's assessment of general health and 2 studies' assessment with two generic QOL instruments was observed. One study reported mixed findings with respect to disease-specific QOL. It may be that generic instruments are not sensitive enough to detect real improvements in QOL. No studies followed children long enough to assess ultimate educational or professional achievement. Because of poor study quality, small sample sizes, and short follow-up, this body of evidence is considered to be of low quality.

See *Quality Assessment Issues* for Key Question #1 in pediatric populations in the **LITERATURE REVIEW** for a more detailed discussion of quality assessment.

Relevance of Findings to Patients

There is no consensus regarding the magnitude of benefit as measured by auditory tests, or even on more complex measures of comprehension and language, that is considered clinically or functionally important.

*See the **Summary of Findings Table** on the following page.*

(CHILDREN) Summary of Findings for Key Question #1: ***Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?***

Quality Assessment						Comparator Results*†‡ (all forms of comparison)	Bilateral CI Results*†‡
Quantity of Data (# studies, # participants) Study Characteristics	**Study Quality**	**Inconsistent Findings**	**Applicability to PICO**	**Publication Bias**	**Overall Quality of Evidence**	(Range of *all* study results is presented separately for bilateral CI and for comparator, followed by detail pertaining to statistically significant differences; see footnotes for further interpretation guidance)	
Speech Perception‡							
In Quiet 8 (340) Age at last cochlear implant (CI): Mean 21 mos to mean 8 yrs 1st CI to 2nd CI: 6 mos to mean 9 yrs F/u: Mean ≥1 yr in 6 studies	3 good, 2 fair, 2 poor, 1 very poor	No serious inconsistency	No serious issues	No information available	Moderate for small sample sizes	% correct: 60%-89% Binaural-monaural reduction in SRT-79.4%: –3 dB *SRT-71%: 42-45 dB*	% correct: 79%-94% Binaural-monaural reduction in SRT-79.4%: 4 dB *SRT-71%: 42-48 dB*
						+ significant results in all 8 studies; also some + but NS analyses in 2 studies. Where reported, *statistically significant* absolute differences by study analysis were 4%-25% for % correct scores and 5-7 dB for SRTs. Clinical and functional significance are uncertain.	
In Noise 10 (278) Age at last CI: Mean 21 mos to -mean 8 yrs; age 10-20 yrs in 1 study 1st CI to 2nd CI: 6 mos to mean 9 yrs; 6-17 yrs in 1 study F/u: Mean ≥1 yr in 7 studies	3 good, 2 fair,3 poor, 2 very poor	No serious inconsistency	No serious issues	No information available	Moderate for small sample sizes	% correct: 36%-62% correct Binaural-monaural reduction in SRT: –2 to 0 dB *Signal-to-noise ratio (SNR): 2 dB*	% correct: 56%-79% Binaural-monaural reduction in SRT : 2-4 dB *SNR: –4 dB*
						+ significant results in 8 studies; no difference in 2 poor-quality studies. Where reported, *statistically significant* absolute differences by study analysis were 6%-37% for % correct scores and 4 dB for SRTs. Clinical and functional significance are uncertain.	
Localization (Left-Right Discrimination)							
5 (170) Age at last CI: <3 to mean 6 yrs 1st CI to 2nd CI: <2-4 yrs F/u: Mean 1-4 yrs	2 good, 2 fair, 1 poor	No serious inconsistency	No serious issues	No information available	Moderate for small quantity of data	% correct: 25%-58% (chance levels) *Minimum audible angle: ±78°*	% correct: 50% (where chance level was 25%) to 100% *Minimum audible angle: ±42°*
						+ significant results in all studies. Where reported, *statistically significant* absolute differences were 18%-36% for % correct scores and 36° for minimum audible angle. Clinical and functional significance are uncertain.	

Quality Assessment						Comparator Results*†‡ (all forms of comparison)	Bilateral CI Results*†‡
Quantity of Data (# studies, # participants) Study Characteristics	**Study Quality**	**Inconsistent Findings**	**Applicability to PICO**	**Publication Bias**	**Overall Quality of Evidence**	(Range of *all* study results is presented separately for bilateral CI and for comparator, followed by detail pertaining to statistically significant differences; see footnotes for further interpretation guidance)	
Speech Comprehension and Speech Production Tests							
4 (188) Age at last CI: 1-1.5 yrs 1st CI to 2nd CI: 0-3 yrs F/u: 3 mos to 2 yrs	4 very poor	Serious inconsistency	No serious issues	No information available	Very low for small samples sizes, poor study quality, and inconsistency	Mixed findings.	
Functional and Quality-of-Life Outcomes							
5 (175) Age at last CI: Mean 3.5 to 20 yrs 1st CI to 2nd CI: 2-17 yrs F/u: 1-4 yrs	5 poor	No unexplained consistency	Insufficient f/u for measurement of lifelong gains	No information available	Low for small sample sizes, poor study quality, and short f/u	Attendance at mainstream schools: 47%-59% Measures of oral communication: 3%-71% Disease-specific health/functional/QOL scales 0-51 scale : 33 0-1.0 scales: 0.48-0.74 0-10 scale: 4.85-5.88 –100 to 100 scale: Similar to bilateral 0-200 scale: 118 Generic health/QOL 0-1.0 scale: 0.78 0-100 scales: Similar to bilateral	Attendance at mainstream schools: 69%-79% Measures of oral communication: 35%-100% Disease-specific health/functional/QOL scales 0-51 scale : 34-40 0-1.0 scales: 0.62-0.78 0-10 scale: 7.47-7.55 –100 to 100 scale: Similar to unilateral 0-200 scale: 160 Generic health/QOL 0-1.0 scale: 0.83 0-100 scales: Similar to unilateral
						The only fairly consistently + findings had to do with functional hearing and conversation. *Statistically significant* absolute differences in disease-specific function: 6%-69%, 0.12-0.13 on a 0-1.0 scale, 1.67-2.62 on a 0-10 scale, and 42 on a 0-200 scale.	
Insufficient Evidence: Sound Detection, Neurocognitive Development							

*Some studies did not report actual scores or score differences; scores could be estimated from bar graphs in most instances.

†*For italicized data, a higher or positive value signifies poorer performance.* (Because a negative SRT denotes better performance, a *reduction* in SRT between a binaural and a monaural listening condition might be positive if there is a great difference favoring the binaural condition.)

‡Results expressed as *% correct* refer to the percentage of all responses across repetitions and/or lists that were correct. Results expressed as speech reception thresholds (*SRTs*) are in decibels (dB) and refer to the lowest sound intensity of speech or other signal at which a certain % correct, e.g.71%, responses was possible. Results expressed as signal-to-noise ratios (*SNRs*) are in dB and were adaptively identified for each patient so that the patient achieved a 50% correct score on the test. Since the dB scale is a logarithmic scale, a mean SNR of –4 implies that on average, respondents achieved 50% correct performance when the signal intensity was 4 dB lower than the noise intensity.

ADULTS, KEY QUESTION #1

The 19 selected studies (19 publications) had sample sizes of 20 to 182 adults. They included one randomized trial, in which patients who were eligible for a second CI were randomized to immediate second implantation or second implantation 1 year later; analysis was according to randomization for evaluation of QOL outcomes, but both arms were treated as a single group for evaluation of speech perception and sound localization. Analyses of intrasubject binaural versus monaural listening at a point in time after two implants (Design B) was the most common; several studies used a cross-sectional group comparison (Design A) or a longitudinal intrasubject assessment (Design D). Where reported, all study participants had postlingual deafness and the severity of deafness was severe to profound or profound. Generally, studies required that patients have received minimal or no benefit from a hearing aid (either alone or in combination with the first CI) before bilateral CI. A small number of studies provided specific definitions of minimal benefit from the stimulation configuration present before the second implant, and these varied considerably.

Mean duration of bilateral deafness prior to the first implant was 3 to 32 years. Mean age at the time of the second implantation procedure was usually not reported but fell in the range of 46 to 57 years in the studies that provided this information. Follow-up intervals, i.e. the time between the last implant and final testing, ranged from 1 to 17 months in most studies, with one study following patients for approximately 5 years. Patients were followed for at least 6 months in most studies. Evidence tables are found in Appendix V.

Summary of Findings and Quality Assessment

Sound Detection: No eligible studies evaluated sound detection.

Neurocognitive Development: No eligible studies evaluated this type of outcome.

Speech Perception in Quiet: Eleven studies (total, n=342; 5 good, 6 fair) reported somewhat conflicting results on open set word and sentence tests; one study reported results separately for sequential and simultaneous bilateral CI. Eight studies reported consistently positive and significant results favoring bilateral CI, with 4 studies providing data on sequential bilateral CI and 4 studies providing data on simultaneous bilateral CI or a mix of simultaneous/sequential implantation. However, 3 studies had negative or very inconclusive results for sequential or a mix of sequential and simultaneous bilateral CI. Taking into account the small sample sizes and the inconsistent findings, there is low-quality evidence that bilateral CI improves speech perception in quiet.

Speech Perception in Noise: Eight of 11 studies (total, n=350; 4 good, 5 fair, 2 very poor) reported data that showed bilateral CI to be associated with better performance on speech tests. Seven studies, including 2 good-quality studies, reported statistically significant effects; one fair-quality study reported positive findings but did not report statistical significance; one fair-quality study reported positive findings with variances that suggested nonsignificance; and two studies of fair or very poor quality reported negative findings. Taking into account the consistency in direction of findings except for two of the lesser quality studies but also the small sample sizes, there is moderate quality evidence that bilateral CI improves performance on speech tests conducted in noise conditions.

Sound Localization (Left-Right Discrimination): Five studies (total, n=172; 3 good, 2 fair) consistently reported findings favoring bilateral CI and results were statistically significant. Taking into account the fair to good study quality but the small sample sizes, evidence of a benefit in sound localization is of moderate quality.

Speech Production and Comprehension: The evidence was insufficient to allow conclusions regarding speech production and comprehension. A single very poor quality study evaluated one aspect of speech comprehension and no studies evaluated speech production.

Functional and Quality of Life Outcomes: Seven studies (total, n=432; 1 good, 2 fair, 2 poor, 2 very poor) evaluated functional and/or quality of life (QOL) outcomes. Five studies reported results from disease-specific functional scales that consistently favored bilateral CI and were statistically significant except in one study. Five studies reported inconsistent results with respect to QOL scales, but the inconsistencies followed a pattern: findings were favorable and statistically significant on disease-specific QOL scales, but measurement according to generic scales QOL showed no differences. Two studies (both fair quality) showed conflicting results with respect to improvement in tinnitus annoyance. Two studies (poor or very poor) using two different scales found music perception to be slightly better with bilateral CI, but differences were generally nonsignificant. No studies evaluated impact on employment status or job performance. In summary,

- Moderate quality evidence from 5 small studies shows bilateral CI to be associated with improvement on disease-specific measures of hearing function or OOL but not on generic measures of QOL.
- Evidence pertaining to improvement in tinnitus and music perception is insufficient to allow conclusions.

See *Quality Assessment Issues* for Key Question #1 in adult populations in the **LITERATURE REVIEW** for a more detailed discussion of quality assessment.

Relevance of Findings to Patients

As was the case with studies in pediatric populations, authors of studies in adult populations generally offered little guidance on how auditory test scores might translate to hearing-related function in real-life situations. Improvement in speech perception in noise across studies was of a similar order of magnitude to measurements of bilateral squelch and the head shadow effect in normal-hearing individuals, as described by one set of study authors. However, this is at best an indirect indication of the relevance of the study findings.

*See the **Summary of Findings Table** on the following page.*

(ADULTS) Summary of Findings for Key Question #1: ***Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?***

Quality Assessment						Comparator Results*†‡ (all forms of comparison)	Bilateral CI Results*†‡
Quantity of Data (# studies, # participants) Study Characteristics	**Study Quality**	**Inconsistent Findings**	**Applicability to PICO**	**Publica-tion Bias**	**Overall Quality of Evidence**	(range of *all* study results is presented separately for bilateral CI and for comparator, followed by detail pertaining only to statistically significant differences; see footnotes for further interpretation guidance)	
Speech Perception‡							
In Quiet 11 (342) Duration deafness: Mean 3-32 yrs F/u: 6 mos-1 yr	5 good, 6 fair	Substantial inconsistenc y	No serious issues	No informatio n available	Low for small sample sizes and unexplained inconsistency	% correct: 2%-95% + significant findings in 8 studies; negative or inconclusive results in 3 studies. Where reported, *statistically significant* absolute differences by study analysis ranged from 5% to 77%. 3 studies detected no difference. Clinical and functional significance are uncertain.	% correct: 59%-100%
In Noise 11 (350) Duration deafness: Mean 3-32 yrs F/u: 6 mos-1 yr	4 good, 5 fair, 2 very poor	No serious inconsistenc y	No serious issues	No informatio n available	Moderate for small sample sizes	% correct: 12%-55% (generally, better ear) *Signal-to-noise ratio (SNR): 5.42 to –7 dB (generally, better ear)* + significant findings in 7 studies; + findings without significance in 2 (fair); no difference in 2 (fair, very poor). Where reported, *statistically significant* absolute differences by study analysis ranged from for 8% to 37% for correct scores and 0.53 to 11 dB for SNRs. Clinical and functional significance are uncertain.	% correct: 42%-82% *SNR: –0.26 to –18*
Localization (Left-Right Discrimination)							
5 (172) Duration deafness: Mean 6-14 yrs F/u: Mean 3 mos-5 yrs	3 good, 2 fair	No serious inconsistenc y	No serious issues	No informatio n available	Moderate for small sample sizes	*Angle errors: 44°-87°* + significant findings in all 5 studies. Where reported, *statistically significant* absolute differences ranged from 8° to 43°. Clinical and functional significance are uncertain.	*Angle errors: 5°-50°*
Functional and Quality of Life Outcomes							
7 (432) Duration deafness: Mean 3.5-9 yrs F/u: Mean 6 mos to mean	1 good, 2 fair, 2 poor, 2 very poor	No unexplained consistency	Insufficient f/u for measurement of lifelong gains	No informatio n available	Moderate for small sample sizes and short f/u	Disease-specific functional/QOL scales: 1-7 scale: 3-4.4 0-10 scale 4.0-5.8 0-100 scale: 64	Disease-specific functional/QOL scales: 1-7 scale: 4.4-5.7 0-10 scale: 5.7-6.9 0-100 scale: 71

2.6 yrs •						<u>Generic QOL scales</u>: Similar to bilateral CI	<u>Generic QOL scales</u>: Similar to comparator
						+ results on disease-specific functional scales in 5 studies (significant in all but 1 study). + significant findings on disease-specific QOL scales in 2 studies. Where reported, *statistically significant* absolute differences were 1.3 to 1.4 on a 1-7 scale, 1.0-1.8 on a 0-10 scale; 6 on a 0-90 scale, and 7 on a 0-100 scale.	
Insufficient Evidence: Sound Detection, Neurocognitive Development, Speech Production and Comprehension, Tinnitus, Music Perception							

*Some studies did not report actual scores or score differences; scores could be estimated from bar graphs in most instances.

†*For italicized data, a higher or positive value signifies poorer performance.* (Because a negative SRT denotes better performance, a *reduction* in SRT between a binaural and a monaural listening condition might be positive if there is a great difference favoring the binaural condition.)

‡Results expressed as *% correct* refer to the percentage of all responses across repetitions and/or lists that were correct. Results expressed as signal-to-noise ratios (*SNRs*) are in dB and were adaptively identified for each patient so that the patient achieved a 50% correct score on the test. Since the dB scale is a logarithmic scale, a mean SNR of –4 implies that on average, respondents achieved 50% correct performance when the signal intensity was 4 dB lower than the noise intensity.

Key Question #2: ***Is bilateral cochlear implantation safe?***

CHILDREN AND ADULTS

The types of adverse events that are common in pediatric and adult populations are the same, and much of the available safety evidence presents combined data for both populations. Therefore, review findings for children and adults are discussed together. None of the studies in pediatric populations that were selected as evidence for Key Question #1 reported any assessment of adverse events. This was also true of most of the adult studies, except for 2 studies that reported conflicting evidence regarding new onset or worsening tinnitus.

Precise estimates of adverse events related to CI were not possible from the literature reviewed for this report; 1 technology assessment and 4 case series with data for both children and adults were used for sources of estimated rates of adverse events. Major complications, including surgical complications and device failure, generally required surgical intervention and ranged from a rate of 1.6 per 100 patient-years (incidence density) to an incidence of 8.9% over a mean follow-up of 4 years. (An incidence density rate adjusts for differences in follow-up times for different patients; an incidence density of 1.6 per 100 patient years is equivalent to an incidence of 1.6% among patients who are all followed for 1 year.) Data specific to device explantation, most often due to device failure, include estimates of 0.9% over 2 years of follow-up to between 5.1% and 10% after 11 years or more. Examples of minor complications include wound infection or tinnitus. Estimates of minor complications have ranged from 1% after a minimum follow-up of 6 months to 7.8% after a mean follow-up of 4 years in 2 studies published since 2009. The 2009 UK health technology assessment reported an incidence density of 35 per 100 patient-years (equivalent to 35% over a 1-year follow-up) for minor complications, based on unpublished data supplied by Med-El to the FDA.

Please click on the following hyperlink to see more individual study detail, examples of major and minor complications, and data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database: ***LITERATURE REVIEW, Key Question #2****.*

Key Question #3: ***Does the effectiveness or safety of bilateral cochlear implantation vary according to age at implantation, prelingual versus postlingual onset of hearing loss, duration or degree of deafness, choice of implanted ear, time interval between implantations, specific device, or provider characteristics?***

CHILDREN, KEY QUESTION #3

Seven of the bilateral-unilateral comparative studies included analyses of effect modifiers and/or success predictors. *Effect modifiers* are factors that change the comparative effect of bilateral CI versus unilateral CI, that is, that alter the bilateral advantage. *Success predictors* are factors that are simply associated with the absolute value of outcome measures following bilateral CI, without taking into account any comparison with unilateral CI. Two studies that did not provide any bilateral-unilateral comparative data but that analyzed success predictors in children were also identified. *Please click on the following hyperlink to see a more detailed discussion:* ***LITERATURE REVIEW, Key Question #3 (CHILDREN)****.* See also the **Appendix IV-F** evidence table.

Summary of Findings and Quality Assessment

Age: Very-low-quality evidence from 2 studies (1 good, 1 very poor; total, n=70) suggested no relationship between age *at deafness* and bilateral advantage. Low-quality evidence from 6 studies (2 good, 1 good/poor, 1 fair, 2 very poor) suggested no relationship of outcomes with age at the time of *first implant*. Very-low-quality evidence from 5 studies (2 good, 1 poor, 2 very poor; total, n=197) included some findings suggesting that younger age at the time of *second implant* may be associated with better auditory outcomes, but the results were inconsistent across studies. The overall findings regarding age did not confirm authors' expectations about the influence of age at the time of a second implant. However, given the very poor quality of the available evidence, future findings could alter current conclusions.

Time Between Implants: Moderate-quality evidence from 6 studies (3 good, 1 poor, 2 very poor; total, n=249) generally suggests no relationship between this factor and the *effectiveness* of bilateral versus unilateral CI with respect to speech perception or lateralization. Two very-poor-quality studies (total, n=155) provided conflicting *safety* evidence concerning the difference in cumulative analgesic and antiemetic medication use and differences in cumulative complications between children undergoing simultaneous and sequential bilateral CI.

Other Factors of Interest: Evidence was absent or insufficient for differential effectiveness according any other factor, including sex, ethnicity, race, or disability other than hearing loss. Evidence was also absent regarding differential safety according to any factor other than time between implants. The literature suggests that physical and developmental disabilities could potentially interfere with the successful adaptation to a CI. No studies investigating these effects were identified, and many of the selected studies specifically excluded patients who would be unable to comply with testing because of cognitive, behavioral, or developmental problems.

*See **Summary of Findings Table** on the following page.*

(CHILDREN) Summary of Findings for Key Question #3: ***Does the effectiveness or safety of bilateral cochlear implantation vary according to age at implantation, prelingual versus postlingual onset of hearing loss, duration or degree of deafness, choice of implanted ear, time interval between implantations, specific device, or provider characteristics?***

Quality Assessment						Main Findings
Quantity of Data (# studies, # participants) Study Characteristics	**Study Quality**	**Inconsistent Findings**	**Applicability to PICO**	**Publication Bias**	**Overall Quality of Evidence**	
Age at Deafness Onset						
2 (70)	1 good, 1 very poor	No inconsistency	No serious issues	No information available	Very low due to very small quantity of data	No relationship w/ speech perception or lateralization.
Age at 1st Cochlear Implant						
6 (247)	2 good, 1 good/poor, 1 fair, 2 very poor	Some inconsistency	No serious issues	No information available	Low due to small quantity of data	No relationship w/ speech perception, lateralization, or functional status in comparative studies. Mixed findings in noncomparative studies
Age at 2nd Cochlear Implant						
5 (197)	2 good, 1 poor, 2 very poor	Serious unexplained inconsistency	No serious issues	No information available	Very poor due to small sample sizes and inconsistency	The evidence is insufficient to allow conclusions.
Time Between 1st and 2nd Implants						
Effectiveness 6 (269)	3 good, 1 poor, 2 very poor	No unexplained inconsistency	No serious issues	No information available	Moderate due to small sample sizes	Evidence generally suggests no relationship with speech perception, or lateralization. Studies that reported findings suggesting an advantage from shorter interimplant intervals with respect to speech perception and language skills involved fewer patients and weaker analyses, compared w/ studies finding no difference.
Safety 2 (155)	2 very poor	Serious unexplained consistency	No serious issues	No information available	Very low due to very small quantity of data and unexplained consistency	Conflicting evidence regarding differences in analgesic and antiemetic medication use and minor complications, simultaneous vs sequential.
Insufficient Evidence: Differential effectiveness according to prelingual versus postlingual deafness, duration or degree of deafness, choice of first-implanted ear, specific device, or provider characteristics; differential safety according to any issue.						

ADULTS, KEY QUESTION #3

The evidence is insufficient to allow conclusions about differential effectiveness or safety. Comparable data from more than 1 study are not available for any particular factor, and no data are available for many of the factors of interest. One important gap in the evidence is the lack of data on the differential effectiveness of bilateral CI in patients with and without a concomitant disability such as blindness. *See **LITERATURE REVIEW, Key Question #3 (ADULTS)** for additional detail.*

Key Question #4: *What are the cost implications, including cost-effectiveness, of bilateral cochlear implantation?*

CHILDREN AND ADULTS

Since the data on cost-effectiveness for both pediatric and adult populations came from a single source, Key Question #4 findings for the two populations are discussed together. A good-quality systematic review, which includes all economic evaluations (N=5) that have been published as of the date of the current report, was used for cost-utility data. Additionally, 2 very-poor-quality pediatric studies (total, n=155) reported shorter hospital stay in the simultaneous group compared with cumulative stay in the sequential group. In one study the results were a mean of 1.1 day in the simultaneous group and a mean of 2.13 days (P<0.0001) in the sequential group; in the other study, the results were 1.24 versus 3.00 days (P<0.001). ***LITERATURE REVIEW, Key Question #4***. See also the **Appendix VI** evidence table.

Summary of Findings and Quality Assessment

Five cost-utility studies conducted in the U.S. (1 study) and the UK (4 studies) have suggested that from a payer perspective, either sequential or simultaneous bilateral CI may be a cost-effective alternative to unilateral CI. However, findings have varied widely (2009 dollars):

- $39,115/QALY to $94,340/QALY for sequential bilateral CI in children
- $30,100/QALY to $70,470/QALY for simultaneous bilateral CI in children
- $38,189/QALY to $127,767/QALY for sequential bilateral CI in adults
- $86,425/QALY to $118,387/QALY for simultaneous bilateral CI in adults

Conversion of the 2009 dollar figures presented in the systematic review to 2013 U.S. dollars results in ICERs ranging from $32,074/QALY to $136,179/QALY.

The body of evidence is of very low quality because of inconsistency, largely due to variation in assumptions about effectiveness in improving QOL. Each of these cost-utility studies used a single, poor-quality source for utility gains (score increases on generic QOL instruments), which were then converted to QALY gains. The sources of utility gains included very small clinical studies involving bilateral CI patients and surveys of normal-hearing volunteers. These sources yielded great variability in assumed utility gains (0.03 to 0.09 for sequential implantations and 0.03 to 0.076 for simultaneous implantations). The most frequently used estimate (0.03), which was applied by a UK technology assessment to both children and adults, was derived from a very small randomized controlled trial (RCT) (Summerfield et al., 2006) involving only adults. This estimate was not statistically significant in the

source trial and applies only to individuals who do not experience an increase in tinnitus following bilateral CI.
Furthermore, analysis by the systematic review authors provides indirect evidence suggesting that the cost-utility findings are very sensitive to assumptions about the degree of improvement in QOL. In a more recently published poor-quality clinical study of children, a significant utility gain of 0.05 on the disease-specific QOL instrument, the Nijmegen Cochlear Implant Questionnaire (NCIQ), was detected (Sparreboom et al., 2012). The current body of evidence in adult populations includes a very recent fair-quality study (Olze et al., 2012) showing nearly an 8-point gain on a 0 to 100 version of the NCIQ. (See **Appendix IV-E** evidence tables.) On the other hand, recent studies in both pediatric and adult populations suggest that bilateral CI does not provide incremental gains in generic QOL. These findings might provide some context for the 0.03 estimate on a 0 to 1.0 generic scale (Summerfield et al., 2006) that has dominated in cost-utility research. The effectiveness of bilateral CI in terms of improving either disease-specific or generic QOL is still very uncertain, although improvement in disease-specific function has been shown, at least in adults.

Other deficiencies in this body of cost-effectiveness evidence include the use of cost and utility data from different sources and the general lack of studies using current and U.S.-specific cost data. The authors of the systematic review concluded that current evidence on the cost-utility of bilateral CI is sparse and ambiguous and that more empirical data are required.

PRACTICE GUIDELINES

Two practice guidelines with relevant recommendations were identified:

- The Cincinnati Children's Hospital and Medical Center has concluded that the evidence is sufficient to allow a recommendation regarding *sequential* bilateral CI, compared with unilateral CI, for the purpose of improving QOL in children with hearing loss. (poor quality)
- Guidance from the National Institute for Health and Clinical Excellence (NICE) recommends *simultaneous* bilateral CI as an option for (a) children with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids and (b) adults with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids *and* who are also blind or have other disabilities that increase their reliance on auditory stimuli as a primary sensory mechanism for spatial awareness. For children, adequate hearing aid benefit is defined as speech, language, and listening skills appropriate to age, developmental stage, and cognitive ability. For adults, adequate hearing aid benefit is defined as ≥ 50% score on Bamford-Kowal-Bench (BKC) sentence testing at a sound intensity of 70 dB SPL (sound pressure level, i.e., sound intensity).
- NICE does not recommend *sequential* bilateral CI but does make exceptions for individuals who had received a unilateral implant prior to publication of the 2009 guidance. (good quality but not reflective of substantial recent evidence)

SELECTED PAYER POLICIES

The Centers for Medicare & Medicaid Services (CMS), Aetna, Regence Group, and GroupHealth cover CI for individuals with bilateral hearing loss. All policies except the CMS policy explicitly cover both prelingual and postlingual hearing loss as well as both bilateral and unilateral CI; CMS does not make any exclusions based on age at time of deafness (pre- versus postlingual) or bilateral versus unilateral

implantation. Adult candidates are required to have hearing loss at the level of ≥ 70 dB and to have scores of ≤ 40% (CMS, Aetna, and GroupHealth) or ≤ 50% (Regence Group) on open-set *sentence* recognition tests. These particular thresholds have been used as inclusion criteria in 2 different studies of simultaneous bilateral CI; they are not supported by more than 1 study each. CMS also allows coverage for adults scoring ≤ 60% on such tests if they are participants in an approved clinical trial. Children (minimum age 12 months according to Aetna, Regence Group, and GroupHealth policy) are required to have a PTA of ≥ 90 dB HL, documentation of a plateau in auditory development or, if they are old enough, to score below a certain level (various specifications) on open-set *word* recognition tests. The test score requirements for both adults and children apply to testing under best-aided conditions, i.e., when using appropriately fitted bilateral hearing aids. All policies stress the importance of speech and auditory rehabilitation following CI.

OVERALL SUMMARY AND DISCUSSION

Evidence-Based Summary Statement

Children and Adolescents

A large quantity of very small studies, generally using patients as their own controls, has shown that bilateral CI improves scores on auditory tests measuring speech perception, especially speech perception in noise, and sound localization in children with severe to profound bilateral sensorineural hearing loss (SNHL). Available studies include very few children with postlingual deafness. It should be noted that benefits to spatial hearing (localization) were especially dramatic. A small quantity of research suggests that measures of more complex language skills, hearing function in real-life situations, and disease-specific quality of life (QOL) are also improved by bilateral as opposed to unilateral CI, but this body of evidence is of low quality. The long-term impact of bilateral CI on educational achievement or employment has not been studied. The magnitude of gains in auditory testing measures that can be expected to lead to more patient-important outcomes is unknown. Thus, an inference of health, functional, and QOL benefits based on the evidence showing improved test scores is not well supported.

Serious adverse effects are possible with bilateral CI, including the need for explantation. Precise estimates of risk were not possible from the evidence available for this report, but major complications may be as high as 10% or more over the long term. The evidence does not allow conclusions about differential effectiveness or differential safety according to patient, device, or provider factors except for moderate-quality evidence suggesting no difference in effectiveness between simultaneous or short-delay sequential bilateral CI and long-delay bilateral CI. The cost-effectiveness of bilateral CI in children and adolescents is unknown because no cost-effectiveness studies using a reliable estimate of utility or another effectiveness measure have been published. Published studies to date have included at most small minorities of individuals who received a second implant as an adolescent.

Applicability (Generalizability to Real-World Practice): This issue was not considered in evaluating the quality of the evidence since setting and specific population characteristics were not prespecified. However, generalizability has implications for how relevant the evidence is to the population served by the Washington State Health Care Authority. No studies enrolled children for whom a first CI had been unsuccessful, i.e., all children participating in the selected studies had acquired speech capabilities prior to the second implant (except in cases of simultaneous bilateral CI, which were a small minority of the study participants). Few studies conducted analyses that controlled for the socioeconomic status of the

families involved, or even reported the status of the enrollees' parents. According to one group of investigators, children receiving bilateral implants typically come from families with more education and greater motivation to try new technologies (Peters et al., 2007). Several studies required or reported enrollment in auditory-verbal training programs. There was no evidence pertaining to bilateral implantation in children who have significant disabilities in addition to hearing loss, such as visual impairment, and many of the selected studies specifically excluded patients with structural abnormalities.

In summary, the available evidence pertains most directly to children who have prelingual deafness, who had good success with their initial implant, who will be able to follow through with auditory and language training, who have no significant disabilities other than hearing loss, who receive their second implant before adolescence, and who have no structural abnormalities that might interfere with the success of the implantation.

Adults

A large quantity of very small studies, generally using patients as their own controls, have shown that bilateral CI improves scores on auditory tests measuring speech perception, at least speech perception in noise, and sound localization in adults with severe to profound bilateral SNHL. Almost all study participants have had postlingual deafness. The evidence also supports a moderate level of confidence that bilateral CI improves disease-specific function and disease-specific QOL. Serious adverse effects are possible with bilateral CI, including the need for explantation. Precise estimates of risk were not possible from the evidence available for this report, but major complications, including the need for explanation and reimplantation, may be as high as 10% or more over the long term. The evidence does not allow conclusions about differential effectiveness or differential safety according to patient, device, or provider factors. The cost-effectiveness of bilateral CI in adults is unknown because no cost-effectiveness studies using a reliable estimate of utility or another effectiveness measure have been published.

Applicability (Generalizability to Real-World Practice): Two studies specifically excluded patients lacking the cognitive ability to participate in testing or to complete questionnaires, and presumably, such patients were not enrolled in the other studies. Studies did not report whether any of the participants had physical comorbidities or disabilities, such as blindness.

Gaps in the Evidence

- Optimal age at which to offer a second implant, and whether age at the time of the previous implant makes a difference.
- Evidence relevant to these subpopulations
    - Adolescents
    - Children with postlingual hearing loss
    - Adults with prelingual hearing loss
    - Individuals with only moderate hearing loss, either bilaterally or in the unimplanted ear
    - Individuals with significant disabilities other than hearing loss
- Further investigation of disease-specific and generic function and QOL, educational achievement, and employment gains, especially over the long term.

- Studies designed to translate gains on auditory tests to categories of functional hearing and/or to map test score improvements to improvement on generic functional and QOL scales.
- Comparative effectiveness of different devices and speech processors.

Other Considerations

- Bilateral CI provides a "spare" device for use in case of device failure, and this may be especially important since children who undergo CI are much less likely to have mastered sign language. One of the studies selected for this review included data on the benefit of a first CI as well as the incremental benefit from a second CI (Olze et al., 2012). In a group of 40 adults, gains in disease-specific QOL and reduction of tinnitus were substantially greater with the first CI than with the second. On the other hand, the comparative studies conducted in children generally found that localization performance was no better than chance with monaural hearing children but substantially greater than chance with binaural hearing.
- A small number of studies of children included normal-hearing control groups and demonstrated that bilateral CI does not achieve normal auditory performance.
- A planned RCT has been described in the literature in which one group of children will undergo simultaneous bilateral CI and the control group will be placed on a wait list (for the second CI) for 2 years (Smulders et al., 2011). The authors suggest that a dose finding study (presumably a study in which different treatment arms were defined by different interimplant intervals, starting with 0) would provide even better data concerning the differential effectiveness of simultaneous and sequential bilateral CI. However, the trial does not appear on ClinicalTrials.gov.

FULL REPORT

BACKGROUND

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimates that in 2011, 37 million adults (16%) had trouble hearing (ranging from a little trouble to deafness), which represents a considerable increase over the 2000 estimate of 31.5 million. Hearing difficulty affected 30% of adults aged 65 to 74 years, and 47% of adults > 74 years of age (NCHS, 2012). In various surveys conducted in the last several years by the CDC, the prevalence of hearing loss in children has been estimated to be 5 per 1000 children according to parent report in the 1997-2005 National Health Interview Survey (NHIS), 1.3 per 1000 children 8 years of age according to a surveillance program in the city of Atlanta, and 1.4 per 1000 babies according to state screening records (NCBDDD, 2012). A CDC study that followed school-aged children with hearing loss into young adulthood (age 21 to 25 years) found that 40% of those young adults were experiencing at least one limitation in daily functioning and only 70% were employed (NCBDDD, 2012).

Biology of Hearing

Hearing depends on a series of mechanical and neural processes. The outer ear consists of the external part of the ear, known as the pinna or auricle, and the ear canal, or external auditory meatus. The middle ear consists of the eardrum, or tympanic membrane, and an air-filled chamber containing a chain of three tiny bones, or ossicles, including the hammer (malleus), anvil (incus), and stirrup (stapes), which are successively connected from the eardrum to the oval window at the entrance to the inner ear. The inner ear, or labyrinth, contains the cochlea, which provides the essential organs of hearing, and the vestibule, which provides the organs of balance. The cochlea is a hollow tube that spirals like a snail's shell and contains thick fluid and the organ of Corti, which consists of more than 20,000 tiny specialized cells (hair cells) with hair-like projections (cilia) that extend into the fluid. Sound waves captured by the pinna of the outer ear travel through the ear canal and produce vibrations on the eardrum. These vibrations are mechanically amplified and transmitted by the ossicles in the middle ear to the oval window of the inner ear, causing the fluid and cilia of the cochlea to vibrate. Different hair cells respond to different sound frequencies and convert them to nerve impulses, which are transmitted along fibers of the auditory nerve to the auditory cortex of the brain, where they are interpreted as auditory sensations, or sound (Ruben, 2006).

Hearing loss can be due to conductive, sensorineural, or central causes. Conductive hearing loss is caused by disease affecting the external or, more commonly, middle ear and is characterized by the inability of the ear to conduct sound waves to the cochlea (inner ear). Sensorineural hearing loss (SNHL) involves damage either to the cochlea or to the neural pathways from the retro cochlea to the brain. The most common form of SNHL occurs when the cilia lining the cochlea area are lost and there is no way for sound waves entering the cochlea to be transformed into nerve impulses. A much less common form of SNHL is auditory neuropathy spectrum disorder (ANSD), which is characterized by intact *outer* cochlear hair cell function but absent or severely abnormal auditory brainstem response (ABR). The abnormal ABR is thought to result from damage at one or more sites: *inner* cochlear hair cells, the

synapse between the inner hair cell and auditory nerve, or the auditory nerve itself (Copeland and Pillsbury, 2004; Bond et al., 2009; Raman et al., 2011; Roush et al., 2011; Hang et al., 2012).

SNHL can result from congenital abnormalities, childhood infection (mumps, meningitis), congenital infection (toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis), viral infection of the inner ear (labyrinthitis), ototoxicity (including that caused by medications), otosclerosis, trauma, autoimmune diseases, and genetic disorders. SNHL can also occur as the result of degenerative changes that accompany aging and that may be exacerbated by systemic comorbidities. Presbycusis, which is SNHL that occurs with aging, is the most common form among the elderly in the U.S. SNHL is irreversible since the cochlear hair cells do not regenerate (NIDCD, 2002; Pillsbury and Rose, 2007; Bond et al., 2009; Raman et al., 2011).

Hearing loss is often characterized as having occurred prelingually, with age 3 years serving as a common proxy for speech development, or postlingually (Bond et al., 2009).

Consequences of Hearing Loss

Hearing loss may cause serious linguistic, cognitive, emotional, educational, social, and employment problems. Problems are intensified when the deafness is bilateral. Hearing loss has also been shown to be linked to depression, impaired activities of daily living (ADL), and deteriorating quality of life (QOL) in adults and may even contribute to dementia. Comorbidities commonly occur along with hearing loss, further contributing to loss of QOL. A substantial proportion of adults with hearing loss who are > 60 years of age experiences tinnitus. A high proportion of deaf individuals, especially those > 60 years of age, have additional types of physical disability (Bond et al., 2009; Raman et al., 2011).

Acoustic Amplification

For some adults with hearing loss, acoustic amplification with an external hearing aid is sufficient, but as SNHL increases, frequency selectivity is lost and other forms of distortion occur so that speech perception becomes very difficult. Children with residual hearing may also benefit from hearing aids. Traditional hearing aids tend to be ineffective when SNHL is severe to profound (Litovsky et al., 2006b; Raman et al., 2011).

Cochlear Implantation

If the neural elements that transmit information from the cochlea to the auditory cortex of the brain are intact and functional, as is generally the case with SNHL, it is possible to stimulate auditory nerve impulses with a prosthetic cochlear implant (CI) device designed to perform the function of cochlear hair cells. With CI, externally worn components— including a microphone, a speech processor, and a transmitter—capture sounds from the environment and transform these sounds into electronic impulses that are sent to an implanted receiver/stimulator, which conveys the impulses to the auditory nerve via electrodes implanted in the cochlea. By electrically stimulating the auditory nerve, CI performs the function normally performed by cochlear hair cells, thereby restoring some degree of hearing (Copeland and Pillsbury, 2004). One group of experts has referred to CI as standard care for individuals with severe to profound SNHL (Carlson et al., 2012). CIs are not appropriate for conductive or central deafness (Raman et al., 2011).

Although CIs are designed to compensate for loss of hair cells in the cochlea, they have been used in children with ANSD. There is controversy as to the appropriateness of CI for this form of SNHL (Roush et al., 2011).

Bilateral Versus Unilateral CI

Initially, CI was performed unilaterally but bilateral implantation is becoming more common. The use of cochlear implants in general is widespread in developed countries, but the use of two implants is a relatively new practice. The additional cost of a second implant, and uncertainty about the added benefit versus added risks, have prevented bilateral implantation from becoming routine. Dual-ear stimulation allows left-right discrimination of sound location and makes it possible for the hearer to benefit from phenomena known as the head shadow effect, binaural summation, and binaural squelch (see Box 1 for a definition of these binaural effects). Bilateral implantation has the theoretical potential to achieve these effects for the user. Additionally, a second implant provides more electrodes that can compensate for asymmetric spiral ganglion cell loss, as well as a back-up in case of device malfunction. In describing the rationale for exploring the effect of a second CI, one group of researchers (Nittrouer et al., 2009) cited studies assessing children with untreated unilateral hearing loss and described these studies as having shown that compared with normal hearing children, these children have deficits in language learning and speech perception. Nittrouer and colleagues suggest that unilateral implantation in children with bilateral hearing loss leaves children in a condition comparable to unilateral hearing loss. Other researchers point out that localization of sound, which is dependent on binaural timing and intensity cues, might be particularly enhanced by bilateral CI. Although individuals with a unilateral CI only might learn to deduce a change in location based on change in sound intensity, it is not possible to directly perceive sound location without binaural stimulation (Laszig et al., 2004)., The expectation of researchers interested in bilateral CI is that the benefits would be especially critical in noisy classroom settings for school children and in outdoor settings that involve hazards such as those associated with crossing the street (Laszig et al., 2004; Nopp et al., 2004; Ramsden et al., 2005; Schafer et al., 2006; Nittrouer and Chapman, 2009; Lovett et al., 2010; Tait et al., 2010; Carlson et al., 2012; Strøm-Roum et al., 2012).

Box 1. Elements of the Bilateral (Binaural) Advantage in Normal Hearing Individuals

Head Shadow Effect: Refers to the noise barrier created by the head and shoulder so that each ear is shielded from competing background noise on the contralateral side of the head. If the hearer has the choice of using either ear, the one that will benefit from the shadow effect can be used preferentially in listening. Aids *dichotic* listening, i.e., listening to a speech signal and noise coming from spatially separated sources. Measured separately for each ear by auditory and speech perception tests that involve a signal from straight ahead and noise delivered to one ear. For each ear, the head shadow effect is the difference in test score for the two CIs when each is used alone. Quantitatively, it is the difference in test scores between the ear that is ipsilateral to the noise and the ear that is contralateral to the noise, or the reverse.

Bilateral (Binaural) Summation: Refers to the additive effects of identical sounds processed by two ears and aids in *diotic* listening, i.e., listening to a signal and noise coming from the same direction. Measured by subtracting test scores obtained with one CI activated from test scores obtained with both CIs activated.

Bilateral (Binaural) Redundancy: Measured by subtracting test scores obtained with only the *best performing* CI activated from test scores obtained with *both* CIs activated, or the reverse; noise and signal are coming from the same location. This calculation controls for binaural summation but cannot control for the possibility that performance is better under the bilateral testing condition simply because that condition matches the everyday experience the patient has become accustomed to since the second implant.

Bilateral (Binaural) Squelch: Refers to effect of interaural differences in the timing, level, and frequency of received sounds, which allows better discrimination between the speech or other signal of interest and background noise. Like the head shadow effect, it aids *dichotic* listening, and is reflected in comparisons of bilateral versus unilateral hearing with tests that involve a signal from straight ahead and noise delivered to the one ear. It is quantified by the difference between test scores associated with both cochlear implant devices activated and scores associated with activation of the device contralateral to the noise alone.

Sources: Nopp et al. (2004); Ramsden et al. (2005)

Bilateral CI can be accomplished through simultaneous implantation or sequential implantation. It was originally thought that there was an advantage in saving one ear for future more sophisticated devices through sequential implantation although reimplantation is a possibility (Bond et al., 2009; Masterson et al., 2012; Grieco-Calub and Litovsky, 2012). On the other hand, some experts believe that simultaneous implantation, or sequential implantation with little delay between the procedures, is potentially more advantageous in that it may prevent a lack of coordination between the two devices that could diminish binaural cues and avoids timing differences in auditory brainstem activity that can develop during the time between implants (Smulders et al., 2011).

Factors That Might Contribute to the Effectiveness of CI

The most recently published, good-quality systematic review of cochlear implantation in children concluded that earlier age at implantation and a shorter duration of deafness before implantation may be associated with better outcomes (Bond et al., 2009). The review did not analyze whether these factors were also associated with the benefit of bilateral versus unilateral implantation. Evoked potential studies have suggested that the plasticity of the human auditory system generally starts to diminish a few years after birth, which has implications for the optimal age of both initial implantation and a second implant (Asp et al., 2011).

Concomitant disabilities can interfere with the effectiveness of CI. A retrospective review of CI procedures in 88 children and adolescents at a tertiary care center in Australia found that 33% of these children had disabilities other than hearing loss. First, simultaneous, and second implants were analyzed together. The additional disabilities included developmental delay, cerebral palsy, visual impairment, autism, and attention deficit disorder. At 1 year following the CI procedure, 96% of children with no additional disability had a score ≥ 5 (on a 1 to 7 scale) on a common speech perception test, while only 52% of the children with additional disability had a score this good (Birman et al., 2012).

CI Eligibility

CI is undertaken in patients with bilateral cochlear hair cell–related SNHL who obtain minimal benefit from amplification, as determined by scores on speech perception tests administered with patients

using appropriately fitted hearing aids, often described as the best-aided listening condition. Initially, CI was approved by the Food and Drug Administration (FDA) only for adults (age ≥ 18 years) who developed profound hearing loss (deafness) after acquiring speech, i.e., adults with postlingual deafness (CMS, 2005; Raman et al., 2011). Later, approved indications were expanded to include adults with residual hearing who are either prelingually or postlingually deaf and who have moderate to profound SNHL in the low frequencies or profound SNHL in the mid to high frequencies (Raman et al., 2011). Expanded FDA-approved indications also include children as young as 12 months of age (CDRH, 2000; Regence Group, 2012).

Audiological assessment of sound and speech perception is the first step in determining eligibility for CI. To evaluate hearing levels, thresholds (required sound intensity) for detection of pure tones at various frequencies, usually 500 to 4000 Hz (hertz), are measured and averaged to yield a pure tone average (PTA). The PTA is expressed in terms of decibels hearing level (dB HL) (Bond et al., 2009). Since the decibel scale is logarithmic, a 10 dB decrease in PTA or in an individual's threshold for correct response to a speech test actually represents a 10-fold decrease in actual sound intensity. It is also important to note that the sound intensity results of audiological assessments are on a relative scale, with 0 corresponding to the very faintest sound that is humanly audible rather than to an absolute absence of sound (Bauman, 2003). The ability to detect tones at an average level < 20 dB HL is considered to be normal hearing. Hearing loss is classified as profound if the PTA is ≥ 95 dB HL and as severe if PTA is 70 to 90 dB HL (Raman et al., 2011; Bond et al., 2009).

If pure tone audiometry suggests that a CI may be appropriate, a trial of a few months with acoustic hearing aids may follow to confirm that hearing level in the best-aided condition remains sufficiently impaired to warrant a CI. Communication abilities are assessed, which may require the involvement of speech and language specialists in prelingual children. Medical evaluation is necessary to assure fitness for surgery and to identify comorbidities that could interfere with success. Imaging studies may be undertaken to rule out any anatomical contraindications. Lastly, psychological assessment is important to assure that patients and/or parents have realistic expectations from CI (Bond et al., 2009).

Outcome Measures

A wide variety of speech perception tests (also called speech recognition or speech discrimination tests), speech comprehension tests, and speech production tests are available for administration in an audiology laboratory or other clinical setting. Sound detection and sound localization in an auditory laboratory setting are also often measured according to a variety of protocols. Most assessments of localization measure left-right discrimination by using a semicircle arrangement of loudspeakers on a horizontal plane and evaluating the patient's ability to identify the source of speech or everyday sound signals. Speech perception and sound localization tests might be considered strictly surrogate measures of hearing-related function. Tests of speech comprehension and speech production, while based on evaluation in a clinical setting by an audiologist or speech pathologist, are designed to more closely mirror real-life situations.

Questionnaires for measuring actual self-reported or parent-reported hearing-related function in real-life situations are available. Additionally, disease-specific and generic scales for assessing health status and QOL have been used in a small number of studies. For assessment of children according to a functional, health, or QOL questionnaire, investigators typically ask parents to complete the questionnaire.

See **Appendix I** for descriptions of the tests and questionnaires used in evidence selected for this report. The literature did not identify any test or questionnaire as a standard.

TECHNOLOGY DESCRIPTION

Although a variety of cochlear implantation (CI) systems are available, all such systems require and use four basic components: (1) external receiver (microphone) mounted on (2) an external speech processor (generally worn behind the ear); (3) an internal receiver/stimulator (under the skin and behind the ear); and (4) an array of electrodes proceeding from the receiver/stimulator and into the cochlea. The external receiver (part 1) captures sounds in the environment as analog signals and transmits these signals by a direct wire connection to the battery-powered external speech processor (part 2), which converts the analog signals to digital signals and transmits them to the implanted receiver/stimulator (part 3) usually by radiofrequency waves. The implanted receiver/stimulator consists of a magnet, a telemetry coil, and a hermetically sealed electronics package; this particulardevice modifies the receiving electrical signals according to complex coding strategies before sending them to individual cochlear electrode channels (part 4), which, in turn, stimulate the auditory nerve. The purpose of the coding strategy software is to provide neural stimulation in patterns that are meaningful to the central auditory system. The key development of the last two decades has been the improvement of sound-coding strategies. The original implants used single-channel electrodes, but currently marketed devices use multichannel electrodes. Although current implants might include up to 22 electrodes, users typically can perceive no more than 10 unique channels because of various factors that limit the spatial specificity of the electrical stimulation. In other words, the number of discrete spiral ganglion cell populations that can be selectively stimulated is limited (Carlson et al., 2012).

Surgery for CI devices typically requires approximately 2 to 3 hours and is performed as an outpatient procedure with the patient under general anesthesia. It involves creation of an incision behind the superior portion of the ear and a postauricular skin flap, removal of the bone and other tissue associated with the mastoid, creation of a well in the postauricular skull in which to place the receiver/stimulator portion of the implant, and a cochleostomy for placement of the electrodes (Copeland and Pillsbury, 2004).

After the surgical sites have healed, approximately 1 month after surgery, the external components of the CI device are linked to the internal receiver/stimulator apparatus and the CI device is activated. The external speech processor and the internal receiver/stimulator unit must be programmed for each individual patient to maximize auditory benefit and minimize discomfort from sound that is too loud. Achieving this goal may require many sessions and take as long as 3 to 6 months. Implants can store multiple individualized programs, or maps, for different listening situations. Some adaptability is built into the devices since very young patients or those with limited language ability cannot contribute to the mapping process. For many patients, sound provided by the full array of electrodes is too much to handle at first. This is particularly true for prelingually deafened children, who may be able to tolerate sound from only 2 additional electrodes per session (Manrique et al., 2005). Current external sound processors of the devices available in the U.S. weigh 10.1 to 13.5 grams, with the lightest battery options. They are water-resistant but not water-proof (Carlson et al., 2012).

Food and Drug Administration (FDA) Approval

The FDA has approved cochlear implant devices from three manufacturers under the Premarket Approval (PMA) process under product code MCM. The three manufacturers are Advanced Bionics LLC, Cochlear® Americas (previously Cochlear Corporation), and Med-El Limited. For adults ≥ 18 years of age, approved indications are generally for severe to profound bilateral sensorineural hearing loss (SNHL)

(severe defined as ≥ 70 decibels [dB]); one device, the Nucleus® (Cochlear Americas), is also approved for use in individuals who have *moderate* to profound hearing loss. For pediatric populations, approvals apply to children who are ≥ 12 or ≥ 18 months of age and have severe to profound, bilateral SNHL. Approvals include various stipulations regarding maximum performance on speech recognition tests in best-aided listening conditions (adults and older children) or lack of progress in auditory skills (younger children) (Raman et al., 2011; Carlson et al., 2012; CDRH, 2013).

Safety Issues

The types of potential adverse events are similar between adults and children. The inserted electrodes can damage spiral ganglion cells and thereby reduce the potential effectiveness of the implant. Other complications resulting from trauma include intracochlear fibrosis and ossification, ear drum perforation, cholesteatoma, and facial nerve damage, all of which can lead to the need for revision surgery. Over the last decade, electrode designs and surgical techniques have improved and diminished the risk of trauma. Such improvements include precurved designs and accompanying insertion guides. Postimplant inflammation, flap breakdown, electrode degeneration, and infection are other potential adverse events. Lastly, penetration of the sterile environment of the inner ear presents the possibility of infection (otitis media or meningitis) (Bond et al., 2009; Rubin and Papsin, 2010; Carlson et al., 2012). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends age-appropriate immunization against *Streptococcus pneumoniae* in children and adults who have received or are candidates for CI (CDC, 2013).

Another risk is that electrode insertion can cause intracochlear trauma. The longer the electrode, the more often it must bend to follow the shape of the cochlea, and the greater the risk of damage. This is particularly of concern in individuals who have preserved low frequency hearing, i.e., preserved hair cells in the innermost region of the cochlea. These individuals are not considered candidates for conventional CI. However, if their preserved hearing is insufficient to allow them to benefit from conventional hearing aids, they are sometimes treated with electric-acoustic stimulation (EAS) strategies. EAS involves insertion of a shorter electrode that serves to stimulate only the basal cochlea, thereby achieving mid- to high-frequency hearing without jeopardizing the remaining low-frequency hearing (Bond et al., 2009; Carlson et al., 2012).

A small percentage of all implantees require an explantation and a reimplantation procedure because of major adverse events such as those just described. Serious complications that may not require further surgery, but are life-threatening, such as meningitis or other severe infection, would also be considered major complications. Minor complications are also possible; these are generally defined as complications that do not require a repeat surgery, or other than minor surgery, and are not life-threatening. Minor complications include wound infections, flap edema, hematoma, facial nerve stimulation, tinnitus, and temporary vertigo (Bond et al., 2009; Ciorba A. et al., 2012). Patients have reported phenomena such as electric shock with loud sounds or nonauditory stimulation and these are sometimes severe enough to require explantation and reimpantation (Masterson et al., 2012; MAUDE, 2013).

REVIEW OBJECTIVES

The scope of this report is defined by the following PICO statement:

Populations: Children, adolescents (20 years of age and younger), and adults with hearing loss.

Intervention: Bilateral implantation of multichannel cochlear devices that use whole-speech processing coding strategies.

Comparators: Unilateral CI only, unilateral CI plus acoustic hearing aid.

Outcomes:
Primary: Detection of sound (measured directly or measured indirectly by hearing aid use), neurocognitive development, perception and production of speech, functional status, quality of life (QOL), procedure- and device-related complications.
Secondary: Tinnitus, telephone usage, patient acceptance, employment or job performance, educational outcomes.

Key Questions

The following key questions will be addressed:

1. Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?
2. Is bilateral cochlear implantation safe?
3. Does the effectiveness or safety of bilateral cochlear implantation vary according to age at implantation, prelingual versus postlingual onset of hearing loss, duration or degree of deafness, choice of implanted ear, time interval between implantations, specific device, or provider characteristics?
4. What are the cost implications, including cost-effectiveness, of bilateral cochlear implantation?

METHODS

Search Strategy and Selection Criteria

In addition to the systematic searches described here, manual bibliography searches within the selected reviews and studies were also conducted.

Systematic Reviews and Practice Guidelines

Core sources for systematic reviews and guidelines, the websites of relevant professional societies, and MEDLINE were searched for publications within the last 5 years. See **Appendix II** for details.

Pediatric Populations: Most of the larger primary studies of bilateral cochlear implantation (CI) in pediatric populations, i.e., studies with ≥ 20 participants, and most of the pediatric studies with functional and quality of life (QOL) outcomes have been published in very recent years and thus were not included in the available systematic reviews. In fact, more studies have been published since the search dates reported by systematic reviews than are included in any of those reviews. Therefore, a de novo approach was taken for evaluation of bilateral implantation in pediatric populations.

Adult Populations: A technology assessment prepared for the Centers for Medicare & Medicaid Services (CMS) (Raman et al., 2011) and 6 other systematic reviews were considered as evidence sources. The Agency for Healthcare Research and Quality (AHRQ) report was found to be lacking in detail regarding quantitative study results, and thus to be inadequate for assessing magnitude of benefits, and to have an unclear approach to assessing study design. Reviews published before the AHRQ report included fewer and smaller studies than those represented by the AHRQ report (Murphy and O'Donoghue, 2007; Bond et al., 2009; Hayes, 2009; Berrettini et al., 2011). A systematic review (Crathorne et al., 2012) published after the AHRQ report was also lacking quantitative study results; this review was intended as an update of an earlier report (Bond et al., 2009) prepared for the National Institute for Health Research (NIHR) in the UK. Therefore, a de novo approach was also taken for evaluation of bilateral implantation in adult populations.

Primary Studies

Identification of Pediatric Studies: Primary studies of pediatric populations that were published before July 2009 were identified by a manual search of the included study lists in the following systematic reviews: Hayes, 2009; Berrettini et al., 2011; a technology assessment produced by the NIHR in the UK (Bond et al., 2009); and other systematic reviews that were identified in MEDLINE (Murphy and O'Donoghue, 2007; Sparreboom et al., 2010; Black et al., 2011; Roush et al., 2011; Schafer et al., 2011; Smulders et al., 2011). Primary studies published in July 2009 or later were identified through a search of the MEDLINE and Embase databases. The initial search was conducted on November 28, 2012, and an update search was conducted on February 17, 2013. See **Appendix II** for details.

Identification of Adult Studies: Primary studies of adult populations were identified through the same search starting in July 2009 that was conducted to identify studies of pediatric populations. In addition, the included study lists of the following systematic reviews were manually searched: Hayes, 2009; the UK technology assessment (Bond et al., 2009); the AHRQ technology assessment (Raman et al., 2011);

and 2 other systematic reviews identified in MEDLINE (Murphy and O'Donoghue, 2007; Berrettini et al., 2011).

Eligible Studies:

- Studies of sequential or simultaneous bilateral CI designed to allow a comparison of outcomes or harms between bilateral CI and unilateral CI.
- Studies assessing the relationship between patient- or procedure-related factors, as listed in Key Question #3, and the outcomes of bilateral versus unilateral implantation.
- Studies assessing outcomes following a second implantation, but without comparison with unilateral implantation or with monaural activation, for potentially useful data on adverse events attributed to bilateral CI or predictors of benefit/harms attributable to bilateral CI.

Exclusion Criteria:

- Non-English language publication. (A single study of 7 participants was excluded for this reason [Luntz et al., 2010]).
- < 20 evaluable patients who underwent CI. (This cutoff point corresponded to a median value for sample size among all studies with ≥ 5 patients, within both the pediatric and adult sets. It is also a commonly used cutoff for selecting the best evidence when the volume of studies is high.)
- Outcomes assessment without the use of either objective measurement or a formal instrument.

Quality Assessment

Clinical Trials Selected to Answer Key Questions

Appendix III outlines the process used by Hayes for assessing the quality of primary studies and bodies of evidence, a process that is in alignment with the GRADE system. Internally developed Quality Checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*.

The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account not only methodological quality in individual studies but also these features of collective bodies of evidence:

- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

NOTE: Two terms related to applicability are *directness* and *generalizability. Directness* refers to how applicable the evidence is to the outcomes of interest (i.e., surrogate or intermediate outcomes versus health outcomes) or to the comparator of interest (indirect comparison of two treatments versus head-to-head trials). *Generalizability* usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICOS (population-

interventions-comparator-outcomes-*setting*) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision*, which refers to findings based on such a small quantity of data that either the confidence interval surrounding a pooled estimate includes both clinically important benefits and clinically important harms or results other than large effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of *high*, *moderate*, *low*, or *very low* quality. These labels can be interpreted in the following manner:

High: Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

Moderate: Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

Low: We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

Very low: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Supplemental Studies Selected to Answer Key Questions #2 and #3

Large case series without a bilateral-unilateral comparison were selected to supplement the safety and differential effectiveness/safety data available from comparative trials. Such studies are by definition of very poor quality for demonstrating treatment-attributable benefits and harms. However, their results can be analyzed to identify predictors of treatment success in populations undergoing the treatment of interest. In the evidence tables, comments are made about the adequacy of analyses.

Guidelines

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2012), along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines.

Special Issues Regarding Study Designs

The ideal study design for a comparison of the effect of bilateral versus unilateral implantation on hearing skills would be a randomized trial. Patients might be randomized to unilateral versus bilateral CI. Another approach might be to randomize patients following unilateral CI to a waiting list for bilateral CI or to immediate receipt of second implant. No such trials have been published in pediatric populations. Studies of adult populations that met selection criteria included 1 randomized wait list trial (the wait list group waited for a second CI). The available analyses follow several different designs. Table 1 describes these analyses. The assumed starting quality for each study design is also given in Table 1. These quality assumptions apply to the internal validity of each study for demonstrating a bilateral versus unilateral

effect. Additional issues such as dropout rates and control for known confounders were also considered in assigning final quality ratings to individual studies.

Table 1. Designs Other Than Randomized Controlled Trials Represented by Selected Studies of Bilateral CI Versus Unilateral CI

Timing of Outcome Assessment	Bilateral Group Versus Unilateral Group or Versus Bimodal Stimulation (CI Plus Hearing Aid) Group	Patients Serve as Their Own Controls
Simultaneous Data Collection Treatment and outcomes data are collected at a single point in time.	**Design A:** A cross-sectional or case-control study comparing individuals who have already had bilateral implants and a different group of individuals who have received only a unilateral implant. *Potential Sources of Bias:* • Known and unknown confounders due to group differences and lack of randomized treatment assignment. For example, children with bilateral implants may have better speech perception scores than children with unilateral implants because of the second implant, or it may be that children who have better speech perception scores following an initial implant, or better support at home, are more likely to get a second implant. • No opportunity to establish a temporalrelationship, which can lend credibility to an observed association. *Starting Quality:* Considered *very poor* quality by virtue of study design alone. Very complete adjustment for confounders might warrant an upgrade to *poor*.	**Design B:** Intrasubject comparison of outcomes between a binaural condition (both devices activated) and a monaural condition (one device activated) following the second of sequential bilateral implants or after simultaneous implants. *Potential Sources of Bias:* • No internal bias since patient characteristics are perfectly controlled. *Starting Quality:* Considered *good* quality by virtue of study design alone. NOTE: Although the risk of internal bias is not an issue with this study design, there is a potential issue of indirectness with respect to the comparator of interest. The monaural listening condition after a second implant is not fully equivalent to unilateral cochlear implantation (CI). This issue is discussed in summaries of the quality of bodies of evidence.
Longitudinal Assessment Change in outcome measures is assessed.	**Design C:** A cohort study, nested case-control study, or study with historical controls involving a unilateral group and a bilateral group where hearing skills or other outcomes are measured at different matched time points, including measurement in the bilateral CI group prior to the second CI surgery. This design may allow an assessment of how soon the bilateral advantage appears and when it peaks but does not eliminate potential bias. In contrast to Design A, this also allows an assessment of between-group baseline differences before the second CI procedure. *Potential Sources of Bias:* • Known and unknown confounders due to group differences and lack of randomized treatment assignment. *Starting Quality:* Considered *poor* quality by virtue of study design alone. Very complete adjustment for confounders might warrant an upgrade to *fair*.	**Design D:** Intrasubject before-and-after comparison where hearing skills measured just before the second CI are compared with hearing skills measured after participants have had time to become accustomed to the second CI. *Potential Sources of Bias:* • Maturation bias, especially in children (if follow-up exceeds 5 months after the 2nd CI, according to some authors [Zeitler et al., 2008]). Children would naturally continue to develop cognitive and language abilities between measurement times independent of the effects of the 2nd CI. Even purely perceptual abilities, such as spatial acuity, continue developing throughout childhood in normal-hearing children (Grieco-Calub and Litovsky, 2012). • Performance bias since both children and adult patients would be more familiar with the testing procedures when they were measured after the second implant. • The therapy required for fitting the second CI may account for some of the before-and-after improvements in situations where bilateral CI is compared with preoperative performance rather than performance just following the 1st CI. • Other unknown confounders related to the different testing times.

Timing of Outcome Assessment	Bilateral Group Versus Unilateral Group or Versus Bimodal Stimulation (CI Plus Hearing Aid) Group	Patients Serve as Their Own Controls
		Starting Quality: Considered *poor quality for children* and *fair quality for adults* by virtue of study design alone. Very complete adjustment for potential temporal effects might warrant an upgrade to *fair*.

LITERATURE REVIEW

Search Results

Pediatric Populations

Because of the paucity of data on adolescents, 1 small study with fewer than 20 participants (n=9) was selected (Galvin et al., 2010) since it focused on adolescents and young adults. Galvin and colleagues asserted that prior to their study, no studies reporting results specific to adolescent recipients of a second implant had been published, nor had any studies of bilateral implantation been published that enrolled young adults who had suffered early childhood onset of deafness.

Since the eligible studies of pediatric populations involved predominately prelingually deaf children, studies excluded because of sample size were reviewed to assure that no meaningful data on postlingually deaf children had been missed. These smaller studies also included only or predominately prelingually deaf children.

A recent systematic review (Roush et al., 2011) identified 15 very small case series and case reports (n=1 to n=26) of cochlear implantation (CI) in children with auditory neuropathy spectrum disorder (ANSD), but study details provided by the review suggested that either these studies all involved unilateral implantation or no distinction was made between unilateral and bilateral implantation. Studies involving > 5 participants were retrieved to verify that none included bilateral-unilateral comparisons. The search for primary studies published since July 2009 identified only 1 study of CI and ANSD with a sample size ≥ 5 and not included in the review by Roush and colleagues; this study did not differentiate between unilateral and bilateral implantation (Schramm and Harrison, 2010).

For one of the included studies, only the results pertaining to one outcome measure (functional hearing) were considered (Kim et al., 2013). The authors' conclusions concerning speech perception in quiet were unclear, and their conclusions regarding speech perception in noise seemed to be inconsistent with the reported findings; these findings were discarded to avoid possible misinterpretation of the study.

Studies selected to answer the Key Questions are summarized as follows:

Key Question #1: 18 studies, published as 21 reports (see Box 2 for a list of studies)
Key Question #2: 1 technology assessment, 3 case series
Key Question #3: Studies selected for Key Question #1, where applicable; 2 comparator trials; 2 case series with success predictor analyses
Key Question #4: A systematic review of economic evaluations

Adults

Since the eligible studies of adult populations involved predominately postlingually deaf individuals, the studies excluded because of sample size were reviewed to assure that no meaningful data on prelingually deaf adults had been missed. These smaller studies also included only or predominately postlingually deaf adults.

Studies selected to answer the Key Questions are summarized as follows:

Key Question #1: 17 studies, published as 19 reports (see Box 3 for a list of studies)
Key Question #2: 1 technology assessment, 4 case series
Key Question #3: Studies selected for Key Question #1, where applicable
Key Question #4: A systematic review of economic evaluations

Cost Studies and Economic Evaluations (Key Question #4)

A good-quality systematic review (Lammers et al., 2011) provided a summary of all available economic evaluations. No economic evaluations published after the review by Lammers and colleagues were identified. Two small studies with additional utilization data were identified.

Key Question #1: ***Compared with unilateral cochlear implantation or with unilateral cochlear implantation plus acoustic hearing aid, does bilateral cochlear implantation for hearing loss improve detection of sound, neurocognitive development, perception or production of speech, functional status, quality of life (QOL), or other patient-important outcomes?***

Children, Key Question #1

Study Characteristics

The 18 selected studies (21 publications) are listed in Box 2. Sample sizes ranged from 20 to 73 children, with the exception of 1 small study (n=9) that was selected for additional data on adolescents. No randomized controlled trials (RCTs) were available (even among excluded studies that did not meet the sample size threshold of 20). All 4 study designs described in Table 1 were represented by the 21 studies. Studies that compared groups or listening conditions at one point in time (Designs A and B) were considerably more common than those that evaluated change over time (Designs C and D). Age at the time of a second implantation ranged from a mean of 21 months to a mean of 8 years in most studies and from 10 to 20 years in the study of adolescents (n=9). Some of the studies with ≥ 20 participants included a minority of individuals who received their second implant as young adolescents, but adolescent data were neither analyzed separately nor presented on an individual basis. Where reported, all or nearly all study participants had prelingual deafness and the severity of deafness was severe to profound (the few studies that defined inclusion criteria in terms of pure tone average [PTA] had specified cutoffs of 70, 80, or 90 dB hearing level [HL]). Several studies required or reported enrollment in auditory-verbal training programs. The small number of studies that provided school information indicated that more participants were in mainstream classrooms than were in specialized units. There was some variability regarding the use of hearing aids between implant procedures, and not all studies provided this information. Follow-up intervals, i.e., the time between the last implant and final testing, ranged from 1 to 4 years, except in 2 studies that tested only at 3 months in some or all children. Among the small number of studies that reported the time frame of the research, bilateral CI was performed in 2002 or later in most studies; in one study (Zeitler et al., 2008), procedures were performed between 1990 and 2006. The earliest study date was 2006; thus, it is assumed that this body of evidence pertains to implants that use multichhannel processors, as specified in the PICO statement.

Box 2. Selected Primary Studies of Bilateral Versus Unilateral CI in Pediatric Populations

Litovsky et al. (2006b) (*Bilateral cochlear implants in children: localization acuity*)
Schafer et al. (2006)
Peters et al. (2007)
Scherf et al. (2007); Scherf et al. (2009a); Scherf et al. (2009b)
Steffens et al. (2008)
Zeitler et al. (2008)
Gordon and Papsin (2009)
Nittrouer et al. (2009)
Galvin et al. (2010)
Lovett et al. (2010)
Tait et al. (2010)
Baudonck et al. (2011)
Sparreboom et al. (2011); Sparreboom et al. (2012)
Boons et al. (2012)
Grieco-Calub and Litovsky (2012)
Strøm-Roum et al. (2012)
Vincent et al. (2012)
Kim et al. (2013)

NOTE: In the following discussion, *analyses* refers to the multiple comparisons involving different measures, comparators, and/or listening conditions for the same outcome that were conducted by some studies. See **Appendix I-A** for a descriptions of the tests, scales, and measurement protocols used in evidence selected for this report.

Sound Detection

Only one poor-quality study reported a relevant comparison of minimum detectable sound levels (Scherf et al., 2007; Scherf et al., 2009a). The findings favored binaural as opposed to monaural hearing, and differences were significant at 3 years in children < 6 years of age at the time of the second implant but significant only up until 2 years in children > 6 years of age at the time of second implant. Binaural-monaural differences at 3 years in the two subgroups were < 5 decibels (dB), according to visual inspection of box plots. See **Appendix IV-A** evidence table.

Speech Perception

Eleven studies (total, n=371), reported in 12 publications, used various tests that primarily involved open-set word recognition to evaluate the effect of a second CI or simultaneous bilateral CI on speech perception (Litovsky et al., 2006b; Peters et al., 2007; Scherf et al., 2007; Steffens et al., 2008; Zeitler et al., 2008; Scherf et al., 2009a; Galvin et al., 2010; Gordon et al., 2011; Schafer et al., 2011; Sparreboom et al., 2011; Strøm-Roum et al., 2012; Vincent et al., 2012). Children in these studies received their second CI at a mean of 21 months to 9 years of age in most studies, and at 10 to 20 years of age in one very small (n=9) study (Galvin et al.). Follow-up (last measurement), where reported, occurred at 3 months to 3 years after the last implant. See **Appendix IV-B** evidence table for study-specific data regarding speech perception.

Speech Perception in Quiet: Of the 8 studies (9 publications) (total, n=340) that tested children in *quiet* conditions, all 8 reported positive statistically significant results in at least one analysis (Litovsky et al., 2006b; Peters et al., 2007; Scherf et al., 2007; Zeitler et al., 2008; Gordon and Papsin, 2009; Scherf et al., 2009a; Sparreboom et al., 2011; Strøm-Roum et al., 2012; Vincent et al., 2012). One of the studies reported results that favored bilateral CI but statistical testing combined both the quiet and noise conditions and was significant (Litovsky et al.). However, in two studies (Peters et al., 2007, good; Zeitler

et al., 2008, poor), although all differences were positive, they were nonsignificant in a Design B comparison (intrasubject comparison of binaural with monaural listening) while significant in comparisons of bilateral Ci with a preoperative bimodal condition (Design C); in this report, Design B is considered to have greater validity than Design C (see Table 1). Statistically significant differences ranged from 4% to 25% for percentage of correct scores and 5 to 7 dB for speech reception thresholds (the lowest sound intensity at which a certain percentage correct score was possible). Study quality was judged to be good (N=3), fair (N=2), poor (N=2), and very poor (N=1).

Speech Perception in Noise: Of the 10 studies (11 publications) (total, n=278) that tested children in *noise* conditions, 8 reported a statistically significant effect (Litovsky et al., 2006b; Schafer et al., 2006; Peters et al., 2007; Scherf et al., 2007; Stebbens et al., 2008; Zeitler et al., 2008; Gordon and Papsin, 2009; Scherf et al., 2009a; Galvin et al., 2010; Sparreboom et al., 2011; Vincent et al., 2012). In 1 of the 8 studies, significance was demonstrated in the intergroup comparison of children with bilateral and unilateral CI (Design C), while results were positive but nonsignificant in the intrasubject comparison of binaural with monaural listening (Design B) (Sparreboom et al., 2011); this is a reversal of the design-specific significance of results for speech perception in quiet for this study. As noted previously, globally significant and positive findings across both quiet and noise conditions were reported for the study by Litovsky et al. (2006b). Two of the 10 studies with noise data found no difference (Schafer et al., 2006; (Galvin et al., 2010), but these studies were considered to be of poor quality. It is noteworthy that the study by Schafer and colleagues was the only one of all 11 studies to use a sentence-recognition test (considered easier than word-recognition tests) and that the study by Galvin and colleagues was the only one that included more than a small percentage of adolescents. Where score values were reported, statistically significant absolute differences ranged from 6% to 37% for percentage of correct scores and 6 dB for speech reception thresholds. In the studies that tested children both in quiet and in noise, the benefits tended to be larger in the noise condition. Study quality was judged to be good (N=3), fair (N=2), poor (N=3), and very poor (N=1).

Sound Localization (right-left discrimination)

Five studies (total, n=170) evaluated the association between bilateral CI and improved ability to discriminate between right and left sources of sound (Steffens et al., 2008; Lovett et al., 2010; Sparreboom et al., 2011; Grieco-Calub and Litovsky, 2012; Vincent et al., 2012). The children in these studies were relatively young (mean ages at second implant < 3 to 5.6 years of age). Follow-up was approximately 1 to 4 years. See **Appendix IV-C** evidence table.

Fixed Sound Intensity: Four studies (total, n=147) demonstrated a significant association favoring bilateral CI under conditions of fixed sound intensity (Steffens et al., 2008; Lovett at al., 2010; Sparreboom et al., 2011; Grieco-Calub and Litovsky, 2012). The magnitude of differences, where available, was 15% to 36% mean difference or absolute difference in means for percentage correct scores , and a 36° absolute difference in the minimum audible angle at which discrimination was possible. Most tests were conducted in quiet. Study quality was judged to be good (N=2), fair (N=1), and poor (N=1).

Roving Sound Intensity: Grieco-Calub and Litovsky (2012), as well as a study by Vincent et al. (2012), designed testing protocols that involved roving (variable) sound intensity, which eliminates some of the natural spatial cues available with fixed sound intensity. Missing data in the study by Grieco-Calub and Litovsky preclude any conclusions; Vincent and colleagues (n=23) reported that the mean percentage

correct score was significantly and substantially (86% versus 50% correct) superior in binaural over monaural listening. The study by Vincent et al. was of fair quality.

Fixed or Roving Sound Intensity: Performance in terms of percentage correct scores were generally at the chance level in unilateral CI groups and conditions.

Speech Comprehension and Speech Production Tests

Four studies (total, n=188) evaluated the advantage of bilateral implantation with tests of speech comprehension or speech production or with laboratory assessment of behavioral responses to speech (Nittrouer and Chapman, 2009; Tait et al., 2010; Baudonck et al., 2011; Boons et al., 2012). Age at last implant ranged from 1 to 5 years. Where reported, follow-up was at 3 months to 3 years after the last implant. Two additional studies (Scherf et al., 2009b; Vincent et al., 2012) reported scores for tests of comprehension and speech production, but since no comparison with a unilateral CI group or monaural listening condition was made for these measures, these studies were not included in the evidence table (**Appendix IV-D**) or in the synthesis of study findings.

Two studies (n=77) reported results that favored bilateral CI. In the positive study using more objective measures, mean intrasubject differences were in the range of 9.4 to 15.7 on a 100-point scale (Boons et al., 2012) The other study with positive, significant findings reported less negative vocal qualities, such as hoarseness (Baudonck et al., 2011), compared with the vocal qualities of children who had unilateral CI. Of the 2 studies without clearly positive findings, 1 study found no difference in scores for young children with bilateral CI, unilateral CI, and a CI plus hearing aid on two scales for assessing auditory comprehension according to linguistic components and the ability to speak the names of objects in pictures (Nittrouer et al., 2009). The other test without clearly positive findings involved videotape analysis and reported findings that favored a bilateral CI group over a unilateral CI group, but quantitative results were reported in such a way that the validity of the comparisons was unclear (Tait et al., 2010). All studies used a cross-sectional (Design A) analysis and were judged to be of very poor quality.

Functional and Quality of Life (QOL) Outcomes

Five studies (total, n=175), including the study involving adolescents and young adults, evaluated the impact of bilateral CI, compared with unilateral CI, on measures of functional, health, and QOL outcomes (Scherf et al., 2009b; Galvin et al., 2010; Lovett et al., 2010; Sparreboom et al., 2012; Kim et al., 2013). Final measurements were made at 1 to 4 years. The 5 studies were somewhat heterogeneous in terms of the measures evaluated. See **Appendix IV-E** evidence table.

Hearing Function in Real Life: Disease-specific measures of function included a question about exclusive use of oral communication, selected questions from the Categories of Auditory Performance (CAP) questionnaire, and the entire Speech, Spatial and Qualities of Hearing (SSQ) and Würzberg questionnaires. All studies reported positive statistically significant results according to at least one analysis. Two poor-quality studies (Scherf et al., 2009; Lovett et al., 2010) each detected no difference according to one measure but positive, significant differences by one or more other measures. The following data exemplify the magnitude of differences where the results were statistically significant (all pertain to the SSQ): 7.55 versus 5.88 (P=0.04) median group scores for speech section and 7.47 versus 4.85 (P=0.000) median group scores for the spatial subscale on 0 to 10 scale(Lovett et al., 2010);

improvement in total score from median 0.49 preoperatively to 0.62 (0.13 difference) on 0 to 1.0 scale (z-score, 4.2; *P*<0.001) (Sparreboom et al., 2012); median 0.62 (95% CI, 0.56 to 0.72) in the bilateral CI group versus 0.50 (95% CI, 0.43 to 0.65; *P*=0.04) in a unilateral CI group (Sparreboom et al.); and improvement from 118 preoperatively to 160 (*P*<0.05) after the second implant on a 0 to 200 scale (Kim et al., 2013).

General Function and Health: The study by Scherf et al. (2009b) found that at 3 years after the second CI, approximately 20% more children were attending mainstream school, compared with school attendance prior to the second CI (*P*=0.031). Assuming that natural developmental factors could lead to increased fitness for mainstream classrooms, maturation bias would seem to be a serious possibility for this study. The study by Sparreboom et al. (2012) showed disease-specific health status to improve from before the second CI to afterward, according to the Glasgow Children's Benefit Inventory (GCBI) *P*<0.001), but found no differences on a generic measure of overall health.

QOL: In the studies by both Lovett et al. (2010) and Sparreboom et al. (2012), five analyses of *generic* QOL were made, using different instruments and different comparators. None of the analyses showed a difference between bilateral and unilateral CI. Sparreboom et al. (2012) showed *disease-specific* QOL according to the Nijmegen Cochlear Implant Questionnaire (NCIG) to improve within the bilateral group from 0.74 before the second implant to 0.78 afterward (*P*=0.02), but when NCIG scores were compared between the bilateral group and a unilateral group, there was no difference.

No studies followed children long enough to measure outcomes such as college attendance or employment. All studies were judged to be of poor quality.

Quality Assessment Issues

Quantity of Evidence: Sample sizes and the total number of children evaluated for each major type of outcome were very small. Some of the positive findings were either statistically nonsignificant, perhaps because of the small sample sizes, or were not reported with significance testing results. Lack of statistical significance in analyses that suggested a substantial effect and that were consistent in direction with other analyses was not counted as a separate factor for downgrading evidence quality.

Individual Study Quality: Five studies were rated as being of good quality for assessing bilateral versus unilateral differences as a primary outcome, while the other studies were of very poor to fair quality. Key study weaknesses other than those inherent in the study designs included loss to follow-up or missing data and lack of blinded evaluation where subjective measures were used. Matched patient selection or analytic control for possible or known confounders was generally absent or incomplete (but this omission was not counted against studies following Design B where patients served as their own controls in nonlongitudinal comparisons of binaural and monaural listening). The studies generally made assessments after individuals had time for adequate training and adjustment of the new device.

Consistency: The studies included in this review addressed a wide variety of tools and measurement strategies. However, the direction of the findings was generally consistent.

Applicability to PICO Statement: There is a theoretical issue of an indirect comparison in studies using Design B (binaural hearing compared with monaural hearing, within subjects and measured after the second implant surgery). This comparison is not the same as comparing measurements made after

bilateral CI with measurements made when the patient only had unilateral CI. If the solo performance of the first implant ear degrades over time as the individual becomes accustomed to binaural hearing, then Design B can exaggerate the bilateral benefit (Smulders et al., 2011). No evidence that this actually occurs was identified; in fact, two good-quality studies showed the performance of the first CI ear to remain stable across longitudinal measurements conducted over 1 to 3 years (Peters et al., 2007; Sparreboom et al., 2011). The binaural-monaural comparison becomes potentially even further removed from the comparison of interest when the comparison is made with the poorer-hearing ear as opposed to the ear that received the first CI in every case. However, only 1 study (Vincent et al., 2012) used this type of comparison. Therefore, where Design B studies were included in a body of evidence, quality was *not downgraded* forlack of applicability to the PICO.

Publication Bias: Searching for unpublished studies was beyond the scope of this review, and mathematical techniques for assessing publication bias were not feasible.

Relevance of Findings to Patients

Study authors provided very little guidance for assessing the implications of improvements in auditory test scores. Three studies reported both auditory test outcomes and more functional outcomes; the findings suggest that small improvements in auditory measures might lead to significant improvements in function or QOL. In one study, bilateral advantage measured as differences in speech reception threshold of 3 to 6 dB and signal-to-noise differences of 6 in one of the noise conditions was accompanied by statistically significant differences favoring bilateral CI on the SSQ and on disease-specific measures of health status and QOL (Sparreboom et al., 2011; Sparreboom et al., 2012). Sparreboom and colleagues also cited evidence showing that the bilateral advantage (difference in speech reception thresholds between binaural and monaural listening) in normal hearing individuals is approximately 5 to 6 dB at comfortable sound levels; in the few studies that reported bilateral advantage in these terms for recipients of bilateral CI, mean differences were in the range of 2 to 4 dB. In another study, bilateral advantages of 6% to 21% on a speech perception test were accompanied by positive findings with respect to several functional and QOL measures, including statistically significant differences in exclusive use of oral communication, ability to have telephone conversations, and attendance at mainstream schools (Scherf et al., 2007; Scherf et al., 2009a; Scherf et al., 2009b). In a third study, a significant benefit in sound localization was accompanied by a modest, although nonsignificant, benefit on one of two generic QOL scales (Lovett et al., 2010). All 3 studies were of poor quality, at least with respect to assessment of functional status and QOL.

ADULTS, KEY QUESTION #1

Study Characteristics

The 19 selected studies (19 publications) are listed in Box 2. Among the publications treated as separate studies, there was likely overlap in patient groups between the studies by Nopp et al. (2004) and by Schleich et al. (2004), likely overlap between the studies by Dunn et al. (2008) and by Dunn et al. (2010), and reported overlap between the studies by Grantham et al. (2007) and Buss et al. (2008). Sample sizes ranged from 20 to 182 adults. The only randomized trial was one in which patients who were eligible for a second CI were randomized to immediate second implantation or second implantation 1 year later;

analysis was according to randomization for evaluation of QOL outcomes (Summerfield et al., 2006), but both arms were treated as a single group for evaluation of speech perception (Ramsden et al., 2005) and sound localization (Verschuur et al., 2005). All four of the study designs described in Table 1 were represented by the 19 publications. Analyses of intrasubject binaural versus monaural listening at a point in time after two implants (Design B) was the most common; several studies used a cross-sectional group comparison (Design A) or a longitudinal intrasubject assessment (Design D). Only 1 study compared change over time between a bilateral CI group and a unilateral CI group (Design C). Where reported, all study participants had postlingual deafness and the severity of deafness was severe to profound or profound. Three studies recorded improvement after bilateral CI in comparison with preoperative performance using bimodal stimulation (CI plus hearing aid) and two other studies made comparisons between a bilateral CI and a bimodal group, while the remaining studies made comparisons only with unilateral CI. However, studies generally required that patients have received minimal or no benefit from a hearing aid (either alone or in combination with the first CI) before bilateral CI. A small number of studies defined inclusion criteria in terms of sound detection levels and/or speech perception performance prior to the second implant, as follows:

- ≥ 30% on the Bamford-Kowal-Bench (BKB) open-set sentence test in quiet (1 study of sequential bilateral CI).
- ≤ 50% on the open set sentence Hearing in Noise Test (HINT) in best-aided condition (1 study of simultaneous bilateral CI).
- ≤ 40% on the open set sentence Hearing in Noise Test (HINT) in best-aided condition (1 study of simultaneous bilateral CI).
- ≤ 40% on the Freiburg monosyllable test in quiet in best aided condition (no detail on whether this is a closed or an open set test) (1 study of sequential bilateral CI).
- Hearing loss at pure tone average (PTA) 80 dB HL and minimal or no benefit from conventional amplification (defined in 1 study as ≤20% on monosyllabic word tests) (2 studies of sequential or sequential and simultaneous bilateral CI).
- ≤ 10% on an open set disyllabic word recognition test in quiet using a hearing aid (1 study of simultaneous bilateral CI).

Mean duration of bilateral deafness prior to the first implant was 3 to 32 years. Mean age at the time of the second implantation procedure was usually not reported but fell in the range of 46 to 57 years in the studies that provided this information. In the studies that reported age at the time of the 1st CI, patients had received their 1st CI as adults with one exception: an unspecified number of patients received their 1st CI as young as 11 years of age (Nopp et al., 2004), One study (Buss et al., 2008) excluded individuals with poor physical or mental health and another excluded patients lacking the cognitive ability to participate in testing or complete questionnaires (Laske et al., 2009). Otherwise, no information on the presence of concomitant disability was provided. Follow-up intervals, i.e. the time between the last implant and final testing, ranged from 1 to 17 months in most studies, with one study following patients for approximately 5 years. Patients were followed for at least 6 months in most studies.

Box 3. Selected Primary Studies of Bilateral Versus Unilateral CI in Adult Populations

Laszig et al. (2004)
Nopp et al. (2004)
Schleich et al. (2004)
Ramsden et al. (2005)
Verschuur et al. (2005)
Litovsky et al. (2006a) (*Simultaneous bilateral cochlear implantation in adults)*
Summerfield et al. (2006)
Grantham et al. (2007)
Buss et al. (2008)
Dunn et al. (2008)
Noble et al. (2008)
Zeitler et al. (2008)
Budenz et al. (2009)
Laske et al. (2009)
Mosnier et al. (2009)
Veekmans et al. (2009)
Dunn et al. (2010)
Cullington et al. (2011)
Olze et al. (2012)

NOTE: In the following discussion, *analyses* refers to the multiple comparisons involving different measures, comparators, and/or listening conditions for the same outcome within some studies. See **Appendix I-B** for descriptions of the measurement tools used in evidence selected for this report.

Sound Detection

No eligible studies evaluated the effect of bilateral CI on sound detection.

Neurocognitive Development

No eligible studies evaluated this type of outcome

Speech Perception

Thirteen studies (total, n=448) used various open set tests to evaluate the effect of a second CI or simultaneous bilateral CI on speech perception. See **Appendix V-A.**

Speech Perception in Quiet: Eleven studies (total, n=342) evaluated speech perception in quiet (Litovsky et al., 2006a; Laszig et al., 2004; Ramsden et al., 2005; Buss et al., 2008; Dunn et al., 2008; Zeitler et al., 2008; Budenz et al., 2009; Laske et al., 2009; Mosnier et al., 2009; Dunn et al., 2010; Olze et al., 2012). One study reported results separately for simultaneous and sequential implantation. All 4 studies reporting results specific to simultaneous CI, and 4 of 7 studies reporting results for sequential or a mix of simultaneous and sequential procedures, presented results that consistently favored bilateral CI and that were statistically significant. The studies of simultaneous implantation showed binaural advantages against the better ear, as well as improvements in comparison with testing conducted before the second implant. In studies that showed a benefit from bilateral CI, percent correct scores ranged from 2% to 95% in comparator groups or conditions and from 59% to 100% in patients with bilateral CI. Mean differences and absolute differences between means ranged from 5% to 77%. Three studies had negative or mixed results for sequential or a mix of sequential and simultaneous bilateral CI. The study by Ramsden et al. demonstrated no improvement on a word test or on a sentence test at 9 months after a second implant, compared with preoperative performance with patients using their first CI and a hearing aid; no binaural-monaural differences were observed at 9 months. The study by Laszig et al. also resulted in generally negative findings: no difference in binaural versus monaural (better ear) performance at 6 months on a word test and either no difference or a very small difference (78% versus

75%; *P*=0.03) on sentence tests. Results reported by Laske et al. were inconclusive: no binaural advantage was demonstrated at > 6 months of follow-up when the monaural listening condition was the better ear CI alone, but when the monaural condition was the *poorer* ear, a significant advantage of 69% (binaural) versus 51% (monaural) (mean difference 18% ± 27%; *P*<0.05) was observed. Laske and colleagues did not identify the type of bilateral CI (sequential or simultaneous). They also did not report how many, if any, patients were found to have poorer performance in the first-implanted ear; for these patients, a second implant would have provided an advantage. The inconsistent findings across studies cannot be explained by differences in study quality, mean duration of deafness before the first implant, mean length of time between implants, type of comparator, specific speech test, or duration of follow-up. As a possible explanation for the lack of observed effects, Ramsden and colleagues and Laszig and colleagues cite ceiling effects associated with the test they used. However, other studies did observe an effect using the same test. Study design also does not explain differences in findings; the 3 studies with negative or mixed findings were intrasubject binaural-monaural comparisons (Design B), but 5 studies with positive findings also included Design B analyses. Study quality was judged to be good (N=5) or fair (N=5).

Speech Perception in Noise: Eight of 11 studies (total, n=350) (Litovsky et al., 2006a; Laszig et al., 2004; Schleich et al., 2004; Ramsden et al., 2005; Buss et al., 2008; Zeitler et al., 2008; Laske et al., 2009; Mosnier et al., 2009; Dunn et al., 2010; Olze et al., 2012; Cullington and Zeng, 2011) reported data that showed bilateral CI to be associated with better performance on speech tests. Seven studies, including 3 good-quality studies, reported statistically significant effects; one fair-quality study reported positive findings but did not report statistical significance (Buss et al.); one fair-quality study reported positive findings with variances that suggested nonsignificance (Schleich et al.); and two studies of fair (Laske et al.) or very poor quality (Cullington and Zeng) reported negative findings. One of the good-quality studies counted in the 7 with significant effects reported these results for a binaural-unilateral comparison (Design B, Table 1) but did not detect effects in the less robust Design D longitudinal intragroup comparison (Ramsden et al.). Percentage of correct scores ranged from 12% to 55% in the comparator groups or conditions and from 42% to 82% with bilateral CI; statistically significant mean or median differences or absolute differences in means ranged from 8% to 37%. Some test results were reported in terms of the signal-to-noise ratio (SNR) at which the participant could score 50% correct (SNR-50%). In analyses reporting SNR-50%, values ranged from to 5.42 to –7 dB in the better ear alone and –0.26 to –18 dB with both CIs activated (smaller, more negative scores denote better performance). Statistically significant mean differences and absolute differences between means for SNR scores ranged from 0.53 to 11 dB. Study quality was judged to be good (N=2), fair (N=6), or very poor (N=2).

Sound Localization (Left-Right Discrimination)

Five studies (total, n=172) evaluated the effect of bilateral CI on sound localization (Laszig et al., 2004; Nopp et al., 2004; Verschuur et al., 2005; Grantham et al., 2007; Dunn et al., 2008). Findings consistently favored bilateral CI and most results were statistically significant. Angle errors ranged from 44° to 87° in comparator groups or conditions and from 5° to 50° under bilateral CI conditions; statistically significant mean differences and absolute differences between means ranged from 8° to 43°. Smaller angle errors denote better performance. Maximum possible errors were generally 90°. Study quality was judged to be good (N=3) or fair (N=2). See the **Appendix V-B** evidence table.

Speech Production and Comprehension Tests
A single very-poor-quality study found no difference between a group of patients with bilateral CI and a group of patients with bimodal stimulation (CI plus hearing aid) in their ability to understand certain nonlinguistic cues in speech or to discriminate between voices (Cullington and Zeng, 2011). No studies evaluated speech production. See the **Appendix V-C** evidence table.

Functional and Quality of Life Outcomes

Seven studies (total, n=432) evaluated functional and/or quality of life (QOL) outcomes (Litovsky et al., 2006a; Summerfield et al., 2006; Noble et al., 2008; Laske et al., 2009; Veekmans et al., 2009; Cullington and Zeng, 2011; Olze et al., 2012). (See the **Appendix V-D** evidence table). Five of these studies reported scores from 3 different disease-specific functional questionnaires; results for disease-specific function consistently favored bilateral CI, and almost all analyses resulted in statistically significant differences (Laske et al. had nonsignificant results). Five studies reported inconsistent results with respect to QOL scales, but the inconsistencies followed a pattern: favorable and statistically significant findings on disease-specific scales but no difference according to generic scales . In analyses using disease-specific functional or QOL scales, the magnitude of benefit was as follows:

- Scores of 3.0 to 4.4 with monaural listening and 4.4 to 5.7 with binaural listening on a 1 to 7 scale; statistically significant absolute differences were 1.3 to 1.4.
- Scores of 4.0 to 5.8 for comparator groups or conditions and 5.7 to 6.9 for bilateral CI on a 0 to 10 scale; statistically significant mean differences and difference between means were 1.0 to 1.8.
- A statistically significant difference of 6 on a 0 to 90 scale.
- 71 versus 64 (statistically significant difference 7) on a 0 to 100 scale.

A meta-analysis of data from studies of *unilateral* CI in adults, conducted by the authors of the 2011 AHRQ report (Raman et al., 2011), likewise demonstrated a significant effect on disease-specific functional and QOL scales, but no effect according to generic scales (Gaylor et al., 2013).

Two studies (both of fair quality) showed conflicting results with respect to improvement in tinnitus annoyance. However, the study showing an average nonsignificant *increase* (worsening) in tinnitus did demonstrate a correlation (r=0.068; P<0.01) between improvement in tinnitus and an increase in generic QOL according to a visual analog scale (VAS) (Summerfield et al., 2006). Summerfield and colleagues also found a nonsignificant improvement in generic QOL after adjustment for change in tinnitus annoyance: VAS QOL, 0.147 (95% CI, –0.150 to 0.444); Health Utilities Index 3 (HUI3), 0.030 (95% CI, –0.045 to 0.104). (NOTE: Based on these findings, some cost-utility studies have assumed a utility gain of 0.03 for bilateral CI; see **Findings, Key Question #4**). Two studies (poor or very poor) using two different scales found music perception to be slightly better with bilateral CI, but differences were generally nonsignificant. No studies evaluated impact on employment status or job performance. Among the 7 studies, quality was judged to be good (N=1), fair (N=2), poor (N=2), or very poor (N=2).

Quality Assessment Issues

Relevant issues were similar to those considered for studies of children and adolescents. Regarding the possibility of an exaggerated effect in a Design B analysis (binaural hearing compared with monaural hearing, within subjects and measured after the second implant surgery), the selected studies, like those

of children and adolescents, provided no evidence of deteriorating performance of the first CI ear between the time of second implant and the time of testing. One study explicitly reported that the performance of the first CI ear remained stable during the 9-month follow-up period (Ramsden et al., 2005). As explained in Table 1, maturation bias was not considered a threat to internal validity in before-and-after studies of adults with patients as their own controls (Design D), whereas this was considered a probable threat to internal validity in most Design D studies of children.

The studies of adult populations tended to make binaural monaural listening comparisons with the better and poorer ear rather than with the first CI and second CI ear, as in the studies of pediatric populations. Most studies provided no information on whether the first implant was placed in the ear considered to be the better or the poorer ear. Ramsey et al. (2005) reported that 16 of 29 study participants received the first implant in the *better* ear although differences between the two ears were not large. In order to form the most conservative conclusions possible, the analysis in this report focused on comparisons with the better ear since the first CI ear was not typically identified.

Relevance of Findings to Patients

As was the case with studies in pediatric populations, authors of studies in adult populations generally officed little guidance on how auditory test scores might translate to hearing-related function in real-life situations. Some authors have estimated that in normal-hearing individuals, bilateral squelch contributes 2 dB improvement to (reduction in) the signal-to-noise ratio required for listening to speech or another signal in the context of background noise and that the head shadow effect contributes about 3 dB improvement in the required signal-to-noise ratio in noisy situations (Ramsden et al., 2005). Thus, the reported improvements of 0.53 to 11 dB for speech perception in noise in the selected studies, with most improvements ≥ 2 dB, suggests that bilateral CI produces clinically relevant improvements in speech perception in noise.

Key Question #2: ***Is bilateral cochlear implantation safe?***

CHILDREN AND ADULTS

The types of adverse events that are common in pediatric and adult populations are the same, and much of the available safety evidence presents combined data for both populations. Therefore, review findings are discussed together for children and adults. None of the studies in pediatric populations that were selected as evidence for Key Question #1 reported any assessment of adverse events. This was also true of most of the adult studies. One clinical study of bilateral CI in adults reported 2 adverse events: 1 patient developed tinnitus and used the 2nd CI inconsistently for a period but then became a consistent user; 1 patient withdrew from the study and discontinued use of the second CI because of a belief that it interfered with the first CI (Ramsden et al., 2005). Another study in adults found that none of 40 patients developed new-onset tinnitus after their first or second CI and that the mean tinnitus annoyance score declined (Olze et al., 2012). However, in another study, the mean score for tinnitus annoyance was greater in the bilateral CI group than in the unilateral CI group (Summerfield et al., 2006).

The health technology assessment conducted by the UK National Institute for Health and Research (NIHR) concluded that cochlear implants are safe and reliable both for children and for adults. The authors did not distinguish between unilateral and bilateral implantation (Bond et al., 2009). Four

uncontrolled studies of CI, focusing on adverse events and complications and published since the 2009 UK report, wereidentified (Stamatiou et al., 2011; Brito et al., 2012; Ciorba et al., 2012; Masterson et al., 2012). These studies involved children, adults, or a mix of children and adults. Findings from studies identified by Bond and colleagues and from the four additional studies are described in Table 2.

Major complications, including surgical complications and device failure, generally required surgical intervention and ranged from a rate of 1.6 per 100 patient-years (incidence density) to an incidence of 8.9% over a mean follow-up of 4 years. (An incidence density rate adjusts for differences in follow-up times for different patients; an incidence density of 1.6 per 100 patient-years is equivalent to an incidence of 1.6% among patients who are all followed for 1 year.) Data specific to device explantation, most often due to device failure, include estimates of 0.9% over 2 years of follow-up to between 5.1% and 10% after 11 years or more. Examples of minor complications included wound infection and tinnitus; estimates have ranged from 1% after a minimum follow-up of 6 months to 7.8% after a mean follow-up of 4 years in 2 studies published since 2009. The 2009 UK health technology assessment reported an incidence density of 35 per 100 patient-years (equivalent to 35% over a 1-year follow-up), based on unpublished data supplied by Med-El to the FDA.

Table 2. Adverse Events Associated with Cochlear Implantation

Source	Rates	Events
Abandoned Operation		
Bond et al. (2009)*	0.12% (1 study, n=844 adults and children) 0.33% (n=300 pediatric patients)	---
Overall Complications		
Stamatiou et al. (2011)	5.7% (n=212 adults)	---
Ciorba et al. (2012)	4.3% in children and adolescents 4.8% in adults (n=438 [all patients], mean follow-up 46 months)	*Early (at ≤3 mos):* Swelling (2.9%), vertigo (1.1%), severe postoperative pain (0.5%), tinnitus (0.2%) *Late (>3 mos):* Device malfunction (2%), infections (1.1%), tinnitus (0.5%), vertigo (0.2%), allergic reaction (0.2%)
Major Complications (defined as those that lead to revision surgery under general anesthesia [including explantation with or without subsequent reimplantation])		
Bond et al. (2009)	6.8 per 100 patient-years (1 study, n=82 pediatric patients)† 1.7 per 100 patient-years (1 study, n=106 adults)† 1.8 per 100 patient-years (1 study, n=100 adults) 1.6 per 100 patient-years (1 study, n=100 adults)	*Examples of reasons:* Uncomfortable stimulation, flap breakdown, cholesteatoma, ear drum perforation, facial nerve damage, persistent infection, meningitis, extrusion of the electrode array, device failure, scalp incisions opened, chronic otorrhea (a patient with a history of recurrent acute otitis media)
Major Complications (defined as requiring subsequent surgery or permanent disability)		
Stamatiou et al. (2011)	4.7% (n=212 adults, minimum follow-up 6 months)	Device failure (2.8%), perioperative subdural hematoma or cerebrospinal fluid leak (1.4%), device extrusion (0.5%)
Major Complications (defined as requiring surgical intervention or hospital admission)		
Brito et al. (2012)	8.9% (n=550 children and adults, mean follow-up 4 years)	Most common: Problems during electrode insertion (3.8%), flap dehiscence (1.4%)
Meningitis		
Bond et al. (2009)	29/100,000 (CI, 9-68) (1 study, n=3630 adults and children), versus 1.3/100,000 in the general population	---
Explantation or Device Failure		
Bond et al. (2009)	5 studies: 8.3% over 11 years (n=192) 10% over 13 years (n=363) 5.1% over 12 years (n=16,427) 0.9% over 2 years (n=118) 7.8% over 5 years (n=8804)	All data apply to device failure.
Ciorba et al. (2012)	2.5% (n=438 adults and children, mean follow-up 46 months)	Device failure (2.3%), otitis media with mastoiditis (0.2%), silicone allergic reaction (0.2%)
Masterson et al. (2012)	4.1% in children (n=345) 4.7% in adults (n=401) (Follow-up not reported)	Medical (n=11, e.g., chronic suppurative otitis media and postauricular mastoid abscess), electrode displacement (n=2), hard device failure (n=15), soft device failure (n=5)

Source	Rates	Events
	33 failures requiring explantation did not actually result in reimplantation. In 80% of reimplantations, audiological performance was stable or improved following reimplantation.	*Hard device failure*=malfunctioning device. *Soft device failure*=unpleasant symptoms, declining performance or intermittent function during which communication between external and internal parts is maintained.
Minor Complications		
Bond et al. (2009)	34.7 per 100 patient-years (1 study, n=82 pediatric patients)†	Post-operation infection, middle ear infections, scalp incisions opened but no resuturing required, erythema at the implant site, facial nerve stimulation, vertigo with tinnitus or nausea, child could only use 5 stimulation channels, skin irritation from cracked coil. Med-El Package Insert states that all complications were resolved (CHRH, 2001).
Bond et al. (2009)	35.3 per 100 patient-years (1 study, n=106 adults)†	Facial nerve stimulation, tinnitus and/or temporary vertigo, dizziness, tickling sensation in the ear, air pocket created over the implant due to vigorous nose blowing, temporary facial weakness, post-operative swelling at the implant site, device case reversed, uncomfortable stimulation, constant buzzing, strong metallic taste. Med-El Package Insert states that all complications were resolved (CHRH, 2001).
Stamatiou et al. (2011)	1.0% (n=212 adults; minimum follow-up 6 months)	Wound infection
Brito et al. (2012)	7.8% (n=550 children and adults, mean follow-up 4 years)	Most frequent: Temporary facial palsy (2.2%), canal-wall lesion (2.2%), tympanic membrane lesion (1.8%).
Permanent Nonuse		
Bond et al. (2009)	Of 110 explantations, 7 resulted in permanent nonuse (6 studies, follow-up 2-18 years where reported; study sizes not reported)	---

*Systematic review/technology assessment

†Unpublished data supplied by a Med-El to the FDA. Dated 2001.

The Manufacturer and User Facility Device Experience (MAUDE) database of the FDA includes 176 instances of an adverse event following implantation of CIs from all 3 manufacturers with FDA-approved devices. The most recent 10 reports (all having to do with Nucleus devices by Cochlear Americas, which appears to be the most commonly implanted device in the U.S.) included loss of connection and "intermittencies" with plans for explantation unknown; pain and/or infection leading to explantation; and nonauditory stimulation occurring with electrodes found to be outside the cochlea and leading to explantation (MAUDE, 2013). A search of the Food and Drug Administration (FDA) database revealed that in 2010, Advanced Bionics voluntarily recalled any unimplanted HiRes 90K cochlear implant devices because of two instances where product malfunction required explantation. The reasons for explantation were severe pain, overly loud sounds, and/or shocking sensations at 8 to 10 days after initial activation (FDA, 2010).

In patients who have had to have a CI device removed because of major infection, the choice has sometimes been made to reimplant the new device in the contralateral ear (Masterson et al., 2012); this would not be possible in patients who have bilateral CIs. Some studies have compared the safety of simultaneous bilateral implantation with that of sequential implantation. This evidence is discussed in relation to Key Question #3.

Key Question #3: ***Does the effectiveness or safety of bilateral cochlear implantation vary according to age at implantation, prelingual versus postlingual onset of hearing loss, duration or degree of deafness, choice of implanted ear, time interval between implantations, specific device, or provider characteristics?***

CHILDREN, KEY QUESTION #3

Study Characteristics

Seven of the bilateral-unilateral comparative studies included analyses of effect modifiers and/or success predictors (Steffens et al., 2008; Zeitler et al., 2008; Scherf et al., 2009a; Gordon et al., 2011; Sparreboom et al., 2011; Boons et al., 2012; Strøm-Roum et al., 2012). *Effect modifiers* would be factors that change the comparative effect of bilateral CI compared with unilateral CI, that is, that alter the bilateral advantage. *Success predictors* would be factors that are simply associated with the absolute value of outcome measures following bilateral CI, without taking into account any comparison with unilateral CI. Two studies that did not provide any bilateral-unilateral comparative data but that analyzed success predictors in children were identified (Van Deun et al., 2010; Asp et al., 2011). Lastly, 2 studies comparing safety data between children undergoing sequential and simultaneous bilateral CI were identified (Ramsey et al., 2009; Grainter et al., 2012). The entire body of evidence from the 21 studies evaluating bilateral versus unilateral CI in pediatric populations was also reviewed for patterns related to the factors of interest that were not directly studied. See the **Appendix IV-F** evidence table.

Effectiveness According to Age and Time Between Implants

Factors for which > 1 study provided data were age at deafness onset, age at the time of the first CI, age at the time of the second CI, and the time interval between implants. Two studies (total, n=70) could find no correlation between age at deafness onset and auditory testing results (speech perception in

noise and lateralization) (Steffens et al., 2008; Van Deun et al., 2010). Six studies (7 publications; total, n=247) evaluated age at first implant with variable findings (Steffens et al., 2008; Gordon et al., 2009; Scherf et al., 2009a; ; Van Deun et al., 2010 Asp et al., 2011; Sparreboom et al., 2011; Sparreboom et al., 2010). Six analyses of the correlation between age at first implant and bilateral advantage in speech perception (quiet and noise) and lateralization were all negative (no correlation). Four analyses of this factor as an absolute success predictor had mixed results: younger age was related to better speech perception in noise (statistical testing not reported) and with better lateralization (significant after adjustment for other factors) in two studies but no association with speech perception in quiet or noise or with functional status was found in two other studies. Five studies (total, n=197) reported mixed results for age at second implant (Steffens et al., 2008; Zeitler et al., 2008; Van Deun et al., 2010; Asp et al., 2011; Sparreboom et al., 2011). Two studies suggested that younger age may be associated with a greater bilateral advantage with respect to speech perception in noise or with sound localization, while another study found no correlation between bilateral advantage and either speech perception or localization. The remaining 2 studies reported conflicting results for an association between age and absolute lateralization outcomes. The overall findings regarding age did not confirm authors' expectations concerning the effect of age at the time of the second implant. It has been theorized that older children and adolescents may have less central auditory plasticity, may have more ingrained preference for using the first CI implant ear, and may also be more resistant to a second implant because of more social and emotional distractions (Peters et al., 2007). However, given the very poor quality of the available evidence, future findings could alter the conclusions that are possible at this time.

Six studies (total, n=249) evaluated time between implants (Steffens et al., 2008; Zeitler et al., 2008; Gordon et al., 2009; Van Deun et al., 2010; Strøm-Roum et al., 2012; Boons et al., 2012). The results were somewhat mixed with respect to both effect modification and success prediction, but the better-quality studies found no relationship with speech perception or lateralization.

Effectiveness According to Hearing Aid Use

A single noncomparative study reported a positive relationship between duration of prior hearing aid use and absolute lateralization scores, after adjustment for other factors (Van Deun et al., 2010). No pattern was discernible across the 21 comparative studies with regard to differences in the results between comparisons with unilateral CI and comparisons with CI plus hearing aid, and no studies adjusted for prior hearing aid use in their analyses. Two studies reported both types of comparisons in speech perception tests for the same patients. In both studies, the results were positive for both comparators, but statistical significance for testing in quiet was demonstrated only in the comparison with preoperative CI plus hearing aid, while the comparison in quiet between binaural and monaural listening after the second implant yielded results that favored bilateral CI but were statistically nonsignificant (Peters et al., 2007; Zeitler et al., 2008).

Effectiveness According to Other Factors

Single studies reported no relationship between effectiveness and etiology of deafness (Steffens et al., 2008), an inverse relationship with duration of deafness (Zeitler et al., 2008), and a positive relationship with attendance at a mainstream school (Van Deun et al., 2010). However, these small studies provide insufficient data to allow any conclusion for these particular factors. Baseline data for these factors was not sufficient to allow any inferences from the overall body of 21 comparative studies. No data on

differential effectiveness according to device or provider were identified. Almost all of the studies evaluated for Key Question #1 involved devices that have received Food and Drug Administration (FDA) approval, with the Nucleus (Cochlear Ltd.) being the most common. No patterns according to device were noted in the results across studies. There were also no data on effectiveness according to sex, ethnicity, race, or disability other than hearing loss.

Safety

The only data identified concerning the differential safety of bilateral implantation in pediatric populations came from a study comparing the first 50 consecutive children undergoing simultaneous bilateral CI with a historical control group of 55 children who had undergone sequential bilateral implantation (Ramsden et al., 2009) and from another similarly designed study (n=25 and n=25) (Grainger et al., 2012). As shown in **Appendix IV-F**, evidence regarding differences in analgesic requirements and complications between children undergoing simultaneous and sequential bilateral CI was conflicting, and no differences in nausea were detected. The study by Grainger et al. recorded fewer minor complications with simultaneous bilateral CI, but the difference was nonsignificant, while no difference in extended stay for complications was found in the study by Ramsden et al.

No analyses of differential safety according to device or provider were available. Almost all of the studies evaluated for Key Question #1 involved devices that have received FDA approval, with the Nucleus (Cochlear Ltd.) being the most common. No patterns according to device were noted in the results across studies. A case series of primarily unilateral procedures (in children and adults) reported very small differences in the rate of reimplantation for devices from the 3 manufacturers with FDA approval (Masterson et al., 2012). Masterson and colleagues did observe, however, a large difference in the rates of device failure between early models and new generation devices.

The authors of one of the case series selected for safety data reported that a disproportionate number of children requiring reimplantation (12 of 345 procedures) had a structural deformity or had been affected by bacterial meningitis or a congenital infection, but no statistical analysis was performed (Masterson et al., 2012). Many of the studies selected for a comparison of bilateral and unilateral CI excluded patients with structural abnormalities.

Quality Issues

Since data pertaining to the differences between bilateral and unilateral CI were most germane to the PICO statement for this report, the same study quality ratings that were assigned with respect to Key Question #1 were also applied to Key Question #3. For evaluating bodies of evidence, data pertaining to effect modification were considered of higher quality than the more indirect data pertaining to success predictors.

The vast majority of analyses, whether they were designed to measure effect modifiers or success predictors, were some form of correlation analysis, which does not provide any information on the magnitude of differences in effect or differences in outcome. Among the few analyses where authors specified a cutoff value and treated the factor of interest as a binary variable (e.g., age < or ≥ 4 years), there was no consistency in cutoff values. Thus, even positive findings would be difficult to translate to clinical policy.

ADULTS, KEY QUESTION #3

A small number of studies investigated patient- or treatment-related factors that might affect whether bilateral CI improves outcomes but analyses were not replicated in multiple studies. See **Appendix V-E** for a display of studies that evaluated effect modifiers.

Analyses of Effect Modifiers (factors associated with differential effectiveness)

- Two studies evaluated binaural advantage in speech perception, comparing bilateral stimulation with the better ear CI alone, and looked at outcomes in subgroups defined by the relative performance of the two ears. Both studies found a binaural advantage only in patients with ear symmetry, i.e., patients in whom there was not more than a small difference in speech perception performance between the two ears *after* bilateral implantation (Litovsky et al., 2006a; Mosnier et al., 2009). In patients with a substantial difference in performance between the two ears, no binaural advantage over the better ear was observed. However, the authors did not define a threshold of relative or absolute performance in the better ear at which no binaural advantage was observed. Furthermore, the relative performance of the two ears was determined *after* the second implant; thus, these findings do not help define patient selection criteria for a second implant.
- A single study found that a reduction in tinnitus annoyance occurred only in patients who were decompensated, i.e., who had a score > 46 on a scale of 1 (minimum annoyance) to 84 (maximum annoyance), prior to the second implant (Olze et al., 2012).
- Another study found no relationship between the effect of bilateral implantation on speech perception in quiet and time between implants, age at second implant, or deafness duration in either ear (Zeitler et al., 2008).

Analyses of Success Predictors (no consideration of differences between bilateral and unilateral CI):

- One study found no relationship between sound localization in the binaural listening condition and duration of deafness (prior to first implant) or duration of unilateral CI use (Nopp et al., 2004). However, the study showed a negative correlation between poorer sound location (greater deviation from correct location) and age at onset of deafness, as well as a positive correlation between poorer sound localization and duration of deafness *as a fraction of age*. In other words, older age at the onset of deafness, which means longer binaural hearing experience before deafness, is a *predictor* of better sound localization with bilateral CI.

The study by Laske et al. (2009) reported that outcomes were *not* correlated with duration of deafness or length of follow-up. The authors did find significant negative correlation between the interimplant interval and binaural speech perception in quiet.

No studies explored the relationship between effectiveness and sex, ethnicity, race, concomitant disability, age at first implantation, prelingual versus postlingual deafness, choice of first-implanted ear, specific device, or provider characteristics. No studies explored differential safety between bilateral and unilateral CI according to any factor. However, a case series of primarily unilateral procedures (in children and adults) reported very small differences in the rate of reimplantation for devices from the 3 manufacturers with FDA approval (Masterson et al., 2012). Masterson and colleagues did observe,

however, a large difference in the rates of device failure between early models and new generation devices.

Key Question #4: *What are the cost implications, including cost-effectiveness, of bilateral cochlear implantation?*

CHILDREN AND ADULTS

Since cost-effectiveness data for both children and adults came from a single source, Key Question #4 findings for the two populations are discussed together. A good-quality systematic review (Lammers et al., 2011), which includes all economic evaluations that have been published as of the date of the current report, was used for cost-utility data. See the **Appendix VI** evidence table for detail from the individual cost-utility studies. No other studies with additional cost or utilization data were identified other than two very-poor-quality studies of children (total, n=155) showing shorter hospital stay in the simultaneous group compared with cumulative stay in the sequential group (mean, 1.1 versus 2.13 days; *P*<0.0001 [Ramsden et al., 2009]; mean, 1.24 versus 3.00 days; *P*<0.001 [Grainger et al., 2012]).

The selected systematic review was based on a search of the PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, and Web of Science databases spanning inception to December 7, 2010 (Lammers et al., 2011). The authors imposed no language restrictions and used dual screening of abstracts and titles. In order to make the results of the studies comparable, Lammers and colleagues adjusted cost data for inflation, citing the Organisation for Economic Co-operation and Development as the source for this adjustment and using 2009 as the base year. They also converted prices to USD using the exchange rate on December 31, 2009. The authors did not discuss the validity of these adjustments. Lammers and colleagues referred to a commonly used checklist for economic evaluations (Drummond and Jefferson, 1996) for quality assessment.

Lammers and colleagues (2011) selected five cost-utility studies, including a modeling study that was part of the NIHR UK technology assessment (Bond et al., 2009) cited elsewhere in the present report. Two studies, including the NIHR report, provided analyses for adult and pediatric populations, 1 study dealt only with children, and 2 studies conducted analyses only for adult populations. All of the studies involved simulation modeling of QOL and cost data from different sources or extrapolation to a long-term time horizon from data collected as part of clinical studies. Utilities (scores on QOL scales) were derived from surveys of small groups of bilateral CI patients in a clinical research setting, or from healthy volunteers who ascribed utilities to a set of vignettes. QOL results from a randomized wait list study (Summerfield et al., 2006) (see findings for adults, Key Question #1) served as the utility estimate for the cost-utility analysis by the same authors as well as for both adults *and* children in the NIHR report. All of the studies assumed a payer perspective (U.S., 1 study; UK, 4 studies); an additional analysis of cost-utility in children from a societal perspective was also conducted for the NIHR report. Time horizons of 30 years to lifetime were assumed. Lammers and colleagues did not provide information on sensitivity analyses conducted within individual studies. Only the analyses of bilateral CI versus unilateral CI are discussed here.

In the following discussion, *utility gains* refers to increases in scores on generic QOL scales of 0 (equivalent to death) to 1.00 (equivalent to perfect health). Quality-adjusted life-years (QALYs) were derived by multiplying utility gains by the number of years represented by the time horizon of each study.

Findings Pertaining to Pediatric Populations

Two studies computed incremental cost-utility ratios (ICERs) for *sequential* bilateral CI. After conversion by Lammers et al. (2010), ICERs rangied from $39,115/QALY (Bichey and Miyamoto, 2008) to $94,340/QALY (Bond et al., 2009) for *sequential* bilateral CI. This wide range reflects small differences in time horizons, some differences in cost assumptions, and large differences in assumed utility gains (0.09 versus 0.03). A different two studies computed ICERS for *simultaneous* bilateral CI; after conversion by Lammers and colleagues, the ICERs ranged from $30,973 or $37,100 per QALY depending on instrument (Summerfield et al., 2010) to $70,470/QALY ($70,078 with a societal perspective) (Bond et al., 2009) . These estimates also primarily reflect differences in assumed utility gains (0.063 and 0.076 versus 0.03).

Findings Pertaining to Adult Populations

Four studies computed ICERs that after conversion by Lammers and colleagues ranged from $38,189/QALY to $127,767/QALY for *sequential* bilateral CI (Summerfield et al., 2002; Summerfield et al., 2006; Bichey and Miyamoto, 2008; Bond et al., 2009). As with the analyses for pediatric populations, this wide range reflects large differences in assumed utility gains (0.11 in the study by Bichey and Miyamoto versus 0.03 from a single source for the other 3 studies). ICERs of $86,425/QALY (Bond et al.) and $118,387/QALY (Summerfield et al., 2002) were computed for *simultaneous* implantation.

Summary Statistics Reported by Lammers et al. (2011)

The systematic review authors conducted global sensitivity analyses *at the study level* and reported the following (Lammers et al., 2011):

- Plotting ICERs against assumed gains in QALYs demonstrated that ICERs greatly diminished (improved) as the assumed QALY gains increased.
- Assuming a willingness-to-pay threshold of $48,300/QALY, there would need to be a QALY gain of at least 1.5 over the long term, and given the results from the 5 studies, there is a 50% probability that QALY gains would meet or exceed 1.5.
- Plotting ICERs against a range of possible discounts offered for second CI devices demonstrated that ICERs declined as discounts increased.

NOTE: Conversion of the 2009 dollar figures reported by the systematic review authors to 2013 U.S. dollars, following best practice, would entail adjustment for inflation according to the Gross Domestic Product deflator (GDPD) index. Such a conversion, using an online calculator (http://eppi.ioe.ac.uk/costconversion/default.aspx), results in ICERs ranging from $32,074/QALY to $136,179/QALY. However, these 2013 numbers have a very approximate correspondence to the original calculations of the individual studies since the 2009-based ICERs calculated by Lammers and colleagues were themselves conversions involving inflation adjustment (presumably according to GDPD index) and currency conversions. Lammers and colleagues used exchange rates for the currency conversions. It should also be noted that best practice for currency conversion would dictate using Purchasing Power Parity (PPP) values.

PRACTICE GUIDELINES

Three potentially relevant practice guidelines were identified from a search of several systematic review and guidelines databases, MEDLINE, and the websites of American Academy of Neurology (AAN), American Academy of Pediatrics (AAP), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), the American Auditory Society, the American Speech-Language-Hearing Association, and the International Hearing Society.

Guidelines with Relevant Recommendations

Cincinnati Children's Hospital Medical Center: A 2011 Best Evidence Statement from Cincinnati Children's Hospital states that there is insufficient evidence and a lack of consensus to allow a recommendation regarding sequential bilateral cochlear implantation (CI) rather than unilateral CI *for purposes of improving quality of life (QOL)* in children with hearing loss (CCHMC, 2011). This guideline was considered to be of poor quality because of a lack of detail about how evidence was identified and selected and a lack of detail on study findings and quality. Although conclusions are consistent with the conclusions of the present report, this statement is based on a somewhat different evidence base. Four studies are cited: 2 cost-utility studies (Bichey and Miyamoto, 2008; Summerfield et al., 2010), a study included in the present report for evidence pertaining to Key Question #1 (Lovett et al., 2010), and a study excluded from the present report because of small sample size (Beijen et al., 2007).

National Institute for Health and Clinical Excellence (NICE): Guidance on *Cochlear implants for children and adults with severe to profound deafness* was issued in 2009 (NICE, 2009) following a systematic review and technology assessment conducted by the National Institute for Health and Research (NIHR) (Bond et al., 2009). This guideline was considered to be of good quality, when considered in combination with the supporting technology assessment, the only deficiency being the lack of a clear characterization of the strength of recommendations. However, this guidance does not reflect evidence published after 2009, which is substantial. The document includes this guidance regarding bilateral implantation:

- Simultaneous bilateral implantation is recommended as an option for (a) children with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids (based on expert testimony, no distinction is made between prelingual and postlingual hearing loss) and (b) adults with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids *and* who are also blind or have other disabilities that increase their reliance on auditory stimuli as a primary sensory mechanism for spatial awareness.
- Sequential bilateral cochlear implantation is not recommended as an option for people with severe to profound deafness.
- For individuals who received a unilateral implant before publication of the 2009 guidance, a contralateral implant should be offered only if this is considered to provide sufficient benefit by the responsible clinician after an informed discussion with the individual and his or her caregivers.

The document also provides these definitions:

- Severe to profound deafness: Hearing only sounds that are louder than 90 decibels hearing level (dB HL) at frequencies of 2000 and 4000 hertz (Hz) without hearing aids.
- Adequate benefit from acoustic hearing aids: For children, speech, language, and listening skills appropriate to age, developmental stage, and cognitive ability. For adults, ≥ 50% score on

Bamford-Kowal-Bench (BKC) sentence testing at a sound intensity of 70 dB sound pressure level (SPL).

In response to the 2009 guidance, 13 cochlear implant centers in the UK formed a consortium and created a multicenter audit program to collect outcomes data on children receiving simultaneous and sequential bilateral CI (Cullington et al., 2011). Plans are to collect test results for speech perception, sound localization, and vocabulary tests, as well as speech intelligibility ratings and parent-reported data regarding hearing-related behavior. Data are collected preoperatively and at 1 and 2 years following the last implant. However, no data have yet been published.

Guidelines Without Relevant Recommendations (No Quality Assessment)

American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS): A 2012 practice guideline on *Sudden Hearing Loss*, which focused on managing sudden sensorineural hearing loss (sudden SNHL) advises clinicians to counsel patients about amplification and hearing-assistive technology when there is residual hearing loss after treatment, but the only comment on CIs is that research is ongoing on the utility of CI for single-sided deafness (Stachler et al., 2012). The authors note that bilateral sudden SNHL is relatively rare. (The guideline defines sudden SNHL as occuring over a 72-hour period and indicating an abnormality of the cochlea, auditory nerve, or higher aspects of central auditory perception or processing.) This guideline was not assessed for quality since it entails no recommendations regarding bilateral CI.

SELECTED PAYER POLICIES

At the direction of Washington State Health Care Authority (HCA), the coverage policies for the following organizations were reviewed:

Centers for Medicare & Medicaid Services (CMS)

A technology assessment of cochlear implants (CIs) in adults that was recently published by the Agency for Healthcare Research and Quality (AHRQ) (Raman et al., 2011) reported having been commissioned by CMS since additional studies had been published following the 2009 National Institute for Health and Clinical Excellence (NICE) guidelines (NICE, 2009). The AHRQ report concludes with the following finding:

> Bilateral cochlear implantation provides added improvements in speech perception outcomes in noisy environments over unilateral cochlear implantation. Bilateral cochlear implants show significant binaural head-shadow benefit, small benefits in binaural summation, binaural squelch effects, and better sound localization (Raman et al., 2011, p. 45).

The authors of the AHRQ report recommended additional research to determine whether demonstrated improvements in perceptual abilities following bilateral CI translate into quality of life (QOL) outcomes. They recommended the development of more disease-specific QOL instruments for individuals with severe to profound hearing loss. However, no new decision memo has been published since the AHRQ report was issued.

The currently effective National Coverage Determination (NCD) allows coverage of CI for the treatment of bilateral pre- or postlinguistic, sensorineural, moderate-to-profound hearing loss in individuals who demonstrate limited benefit from amplification. Limited benefit from amplification is defined by test scores ≤ 40% correct in the best-aided listening condition on tape-recorded tests of open-set sentence cognition. Coverage is additionally approved for individuals who have test scores ≤ 60% on such tests when the provider is participating in, and patients are enrolled in, either a Food and Drug Administration (FDA)-approved category B investigational device exemption (IDE) clinical trial, a trial under the CMS Clinical Trial Policy, or a prospective controlled comparative trial approved by CMS (CMS, 2005).

In addition to these hearing loss parameters, CMS stipulates that recipients of CIs have the cognitive ability to use auditory clues and a willingness to undergo an extended program of rehabilitation. Implanted devices must also be used in accordance with FDA-approved labeling.

CMS policy does not currently differentiate between unilateral and bilateral CI.

> *Link to full policy statement:*
> https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=14792&searchStore=%24search_type%3Dall%24icd%3D%24keywords%3D%24status%3Dall%24page%3D1%24from_date%3D%24to_date%3D%24report_type_options%3DDirectoryReport%24technology_type_options%3D%24organ_system_options%3D%24specialty_options%3D%24order%3Ddtransformdatesort&sectionSelector=SourcesOfInformation.

Aetna

Adults

Aetna considers unilateral and bilateral CI to be medically necessary for adults who have bilateral, pre- or postlingual sensorineural hearing loss (SNHL) and who meet both of the following criteria (Aetna, 2013):

- Severe-to-profound bilateral SNHL determined by a pure tone average (PTA) ≥ 70 decibels (dB) hearing loss (HL) at 500, 1000, and 2000 hertz (Hz).
- Limited benefit from appropriately fitted binaural hearing aids. Limited benefit from amplification is defined by test scores ≤ 40% correct in best-aided listening condition on open-set sentence recognition.

Children

Aetna considers unilateral and bilateral CI to be medically necessary for children ≥ 12 months of age who have bilateral SNHL and who meet the following criteria (Aetna, 2012):

- Profound, bilateral SNHL defined as a PTA ≥ 90 dB HL at 500, 1000, and 2000 Hz.
- Limited benefit from appropriately fitted bilateral hearing aids, defined as performance below a certain level on age-appropriate tests. (A specific test for infants and toddlers and specific open-set word recognition tests for children able to complete them, as well as maximum eligible scores, are provided in the full policy.)
- Completion of 3- to 6-month hearing aid trial if there is no previous experience with hearing aids (possible waiver of this requirement when there is radiological evidence of cochlear ossification).

Adults and Children

Enrollment in an educational program that supports listening and speaking with aided hearing, assessment by an audiologist and by an otolaryngologist confirming the likely success of CI, and arrangements for follow-up care and long-term speech therapy are required.

Link to full policy: http://www.aetna.com/cpb/medical/data/1_99/0013.html

Regence BCBS

Regence Group covers both unilateral and bilateral CI with FDA-approved devices for individuals age ≥ 12 months of age who have bilateral severe-to-profoundSNHL, which is defined as PTA ≥ 70 dB HL at 500, 1000, and 2000 Hz, as well as limited to no benefit from hearing aids unless hearing aids are unreasonable. Both prelingual and postlingual SNHL are covered. Adults must score < 50% correct on open-set sentence recognition. Children must have a PTA ≥ 90 dB HL and either show a failure to develop basic auditory skills, or, in the case of older children, score < 30% correct on open-set tests (Regence Group, 2012).

Link to full policy: http://blue.regence.com/trgmedpol/surgery/sur08.pdf

GroupHealth

Adults (≥ 18 Years of Age)

GroupHealth covers unilateral and bilateral CI in adults with moderate-to-profound postlingual SNHL (the following definition actually corresponds to severe SNHL), defined as a PTA ≥ 70 dB HL at 500, 1000, and 2000 Hz, as well as limited benefit from appropriate hearing (or vibrotactile) aids. Postlingually deaf recipients of CI must have a score ≤40% on sentence recognition tests under best listening condition. Unilateral and bilateral CI are also covered in adults with prelingual deafness and a score ≤ 40% on sentence recognition tests under best listening condition. All recipients should also have appropriate cognitive abilities, expectations, and motivation (GroupHealth, 20120).

Children

Unilateral and bilateral CI are covered for children ages 12 months through 17 years who have profound SNHL, defined as a PTA ≥ 90 dB HL at 500, 1000, and 2000 Hz. Eligible candidates may have pre- or postlingual deafness. The child must have worn appropriately fitted high-power hearing aids and received intensive aural rehabilitation ≥ 3 to 6 months (exception: infants with a documented profound hearing loss following bacterial meningitis), have reached a plateau in auditory development, and have minimal to no useful aided benefit (failure to develop auditory skills [age 18 months to 5 years] or minimal open-set word recognition [age ≥ 5 years]). Families should be willing to put children in a rehabilitative or educational setting for development of listening and speaking skills, be able to provide a positive family environment, and have realistic expectations (GroupHealth, 2012).

Requirements at the Time of Second CI

Individuals who have already received a unilateral CI may qualify for a second CI (sequential bilateral CI) without having to be retested if medical records document that criteria were met at the time of the first CI (GroupHealth, 2012).

Link to full policy: https://provider.ghc.org/all-sites/clinical/criteria/pdf/cochlear.pdf

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APPENDICES

APPENDIX I-A. Outcome Measurement Tools Used in Included Studies of Pediatric Populations

Speech Perception Tests

Closed-Set (Predefined Response Choices)

- Auditory Toy Discrimination Test (ATT): As used in 1 study, each trial consisted of a set of 4 monosyllabic word pairs. Scores were expressed as the speech response threshold (in decibels [dB]) at which 71% of trials lead to a correct response (Sparreboom et al., 2011).
- Children's Realistic Index of Speech Perception (CRISP): The child's familiarity with a set of target words is first confirmed and then the ability to recognize those spoken words is tested. The child points to the picture of the spoken word, which may be included in a leading phrase such as "Point to the…" In noise interference condition, an opposite sex speaker is speaking while the first speaker announces the word (Litovsky et al., 2006b; Peters et al., 2007).
- Dutch Audiology Society List (also referred to as NVA list): Similar to the Göttinger lists. The test for children age 6 to 10 years has 5 lists and the test for adults or children with an extensive vocabulary has 10 lists; there are 12 words per list. Scoring is expressed as a percentage of correctly identified words or phonemes (Scherf et al., 2009a).
- Early Speech Perception (ESP) test: This test evaluates pattern perception (differentiating syllable number and stress pattern), spondaic word (2-syllable words with equal stress on each syllable) identification, and monosyllable identification. The test involves 4 categories: (1) detection, (2) pattern perception, (3) some word identification, and (4) consistent word identification. The standard version, which tests syllabic patterns and word targets known by most hearing-impaired children by the age of 6 years, involves picture plates of 12 items. The low-verbal version uses objects and fewer items (Eisenberg et al., 2006). After hearing the spoken word, the child responds by selecting the appropriate picture or object representing that word (Eisenberg et al., 2006; Gordon and Papsin, 2009).
- Göttinger Lists I (age 3 to 4 years) and II (age 5 to 6 years): Each test has 10 lists of 10 words each. The words have different vowel and consonant combinations. Scoring is per correctly identified word (Scherf et al., 2009a).
- Oldenburger Kinder Reimtest (OLKI): As used by Steffens et al. (2008), this test was modified for use in noise conditions and involved bisyllabic spoken words and 4 response choices for each word.
- Word Inventory Picture Index (WIPI): This test is appropriate for children at a slightly higher language level than that required for the ESP test. The child hears a monosyllabic word and points to 1 of 6 pictures. Scoring is expressed as a percentage of correct choices (Gordon and Papsin, 2009).

Open-Set (Unlimited Choices)

- Adaptive Spondee Discrimination Test (AdSpon): This test consists of 4 lists, each with 10 sets of 4 spondees. Lists are continuously presented, and the child responds to what is heard by using a

touch-screen computer with pictures of the spoken spondees and additional "foils." Speech perception is measured in terms of the signal-to-noise ratio (SNR) at which the child identifies a prespecified percentage of words correctly (Galvin et al., 2010).

- Bamford-Kowal-Bench (BKB) sentences Speech in Noise: This test consists of sentence lists with 50 key words per list and is scored as a percentage of key words or total sentences correctly repeated (Waltzman et al., 2002).
- Consonant Nucleus Consonant (CNC) test: This measure involves monosyllabic words consisting of a consonant, a nucleus of vowels, and another consonant. The test score is based on the percentage of correct responses (Ruffin et al., 2007).
- Expressive One-Word Picture Vocabulary Test (EOWPVT): The experimenter elicits the child's vocabulary by showing pictures and giving nonverbal instructions for the child to provide lexical labels (Nittrouer and Chapman, 2009).
- Glendonald Auditory Screening Procedure (GASP): The GASP word recognition task involves 10 sentences and/or 12 words, which the child is asked to repeat. It uses mostly multisyllabic words familiar to young children (Zeitler et al., 2008; Gordon and Papsin, 2009).
- Hearing in Noise Test for Children (HINT-C): This test comprises 250 sentences divided into 25 phonetically balanced lists of 10 sentences each. It can be administered in quiet or in noise. There is also an adult version (Zeitler et al., 2008).
- Lexical Neighborhood Test (LNT): This is a word recognition test for children age ≥ 5 years (Staller et al., 2002). It consists of 25 monosyllabic words and is scored as either the percentage of correct words or the percentage of correct phonemes (Zeitler et al., 2008). Tests involving monosyllabic words are more difficult because the words provide fewer phonetic cues. The LNT also uses more difficult vocabulary words than those in the GASP or MLNT test (Gordon and Papsin, 2009).
- Multisyllabic Lexical Neighborhood Test (MLNT): This is a word recognition test for young children. It consists of 15 bisyllabic and trisyllabic words and is scored as a percentage of correct words or phonemes (Zeitler et al., 2008).
- Phonetically Balanced-Kindergarten test (PB-K): The PB-K test consists of phonetically balanced lists of up to 50 monosyllabic words that the child is required to repeat verbally (Zeitler et al., 2008). The test is scored by the percentage of correct words or phonemes (Strøm-Roum et al., 2012). Tests involving monosyllabic words are more difficult because the words provide fewer phonetic cues. The PB-K also uses more difficult vocabulary words than those in the GASP or MLNT test (Gordon and Papsin, 2009).
- Preschool Language Scales-4: To evaluate how well children understand language components such as prepositions, word order, and inflectional morphemes; responses are generally elicited by the experimenter (Nittrouer and Chapman, 2009).

Speech Comprehension and Speech Production Tests

- Expressive One-Word Picture Vocabulary Test (EOWPVT): In this test, the child views pictures and, in response to nonverbal cues from the experimenter, provides lexical labels. Scores reflect the number of correct responses (Nittrouer and Chapman, 2009).
- Preschool Language Scales – 4 (PLS-4), Auditory Comprehension Subscale: This tests children's understanding of language elements such as prepositions, word, order, and inflectional morphemes. Scores reflect the number of correct responses elicited by the experimenter (Nittrouer and Chapman, 2009).

- Reynell Developmental Language Scales (RDLS): This measure evaluates expressive and receptive (comprehension) language separately. Tests entail object manipulation and description based on questions of varying length and complexity to reflect real-world communication. Responses are graded as age-equivalent scores (Holt and Svirsky, 2008). It is designed for children from 1 to 6 years of age and measures comprehension at gradually increasing levels of difficulty. Examples of questions/instructions include "Where is the ball?" (easy) and "Put the spoon in the cup." (more difficult). Scores are expressed as a standardized mean with a standard deviation (SD) of 100 (Boons et al., 2012).
- Schlicting Expressive Language Test (SELT): This test measures expressive (spoken) language capabilities in children age 1 to 6 years. The Word Development Subtest asks children to name objects or pictures. The Sentence Development Subtest asks the child to repeat given sentences. Scores are expressed as a standardized mean with a standard deviation (SD) of 100 (Boons et al., 2012).
- Speech Intelligibility Rating (SIR): This is a global measure of speech production in "real-life" situations. In 1 study, audiologists evaluated children's global speech production and categorized it on a 6-point scale ranging from 0 = preverbal communication to 6 = intelligible speech for all listeners (Scherf et al., 2009b). Another study used a scale described as analogous to the SIR scale to evaluate children's naming of a set of pictures, repetition of seven sentences based on a picture, and repetition of a short story based on four consecutive illustrations. Five-point scoring included the following categories: 1 = totally unintelligible speech; 2 = nearly unintelligible speech (some single words are intelligible while lip-reading and using a known context); 3 = intelligible speech if the listener is concentrated and reads the child's lips; 4 = intelligible for listeners with little experience with deaf speech; and 5 = intelligible speech for all listeners in daily situations (Baudonck et al., 2011). In another study (Vincent et al., 2012), speech therapists used a 5-point SIR scale, with score definitions very closely matching those reported by Baudonck et al.

Disease-Specific Functional Scales (Actual Performance in Real Life)

All of the following are questionnaires that are completed by parents or teachers.

- Categories of Auditory Performance (CAP): This is a global measure of speech perception in real-life situations. Auditory ability is scored on an 8-point scale, ranging from 0 (no awareness of environmental sounds) to 4 (discrimination of some speech sounds without lip-reading) to 7 (telephone use with a familiar speaker) (Scherf et al., 2009b; Vincent et al., 2012).
- Speech, Spatial and Qualities of Hearing (SSQ) Scale: This questionnaire was originally designed for adults. Investigators have created modified versions for completion by parents of young children, by older children, and by teachers, but these versions have not been validated. If completed by parents, ratings range from 0 = my child can do this not at all to 10 = my child can do this perfectly. There are three sections pertaining to speech perception (in quiet and/or noise), spatial hearing (location, direction, and distance of sounds), and quality of hearing (segregating and identifying sounds and listening effort). The six questions having to do with spatial issues ask whether the child can immediately identify the direction of sound in these situations: there is a constant unseen source of noise, such as a lawnmower, in an unfamiliar place; another person starts to speak in a group sitting around a table; one of two people sitting on either side of the child starts to speak; the child is outside and a dog starts to bark; an unseen bus or truck is coming (Van Deun et al., 2010; Galvin et al., 2010).

- Würzberg Questionnaire: Applied to parents of children who had received a second implant in one of the selected studies (Scherf et al., 2009b). There are a total of 12 questions, with 11 questions regarding child behavior with respect to different aspects of hearing such as complex listening situations or directional hearing. Each question is scored on 51-point scale (0 = the most negative behavior; 50 = the most positive behavior). The 12th question is a yes/no question regarding whether the parent would choose a second cochlear implant (CI) if given the choice again.

Disease-Specific Health Status and Quality of Life (QOL)

- Glasgow Children's Benefit Inventory (GCBI): This measure was developed to assess the benefit of otorhinolaryngological interventions to health status (Sparreboom et al., 2012).
- Nijmegen Cochlear Implant Questionnaire (NCIQ): This validated test comprises three domains comprising six subdomains: (1) physical domain (basic sound perception, advanced sound perception, and speech production); (2) psychological domain (self-esteem); and (3) social domain (activity limitations and social interactions). Patients apply a 5-point Likert scale corresponding to *never to always* or *no to good* to each item, or indicate *not applicable* response. The total possible score ranges from 0 = very poor to 100 = optimal. The test has been used in both children and adults (Olze et al., 2012; Sparreboom et al., 2012).

Generic QOL Assessment

See the corresponding section in **Appendix I-B**.

APPENDIX I-B. Outcome Measurement Tools Used in Included Studies of Adult Populations

Speech Perception Tests

Open-Set Tests (Predefined Response Choices)

- AzBio: This sentence test was developed to avoid the ceiling effect often seen with other tests. It has been shown to correlate highly with the more commonly used Consonant-Nucleus-Consonant (CNC) Test (Budenz et al., 2009).
- Aprosodia Battery: This has five subtests evaluating aspects of affective prosody and recognition of sarcasm, devised to measure functioning in brain-damaged patients; it is a standardized test for prosody identification (Cunnington et al., 2011).
- Bamford-Kowal-Bench-Sentence in Noise (BKB-SIN) test: This test consists of 36 lists of sentences that are divided into 18 equally difficult pairs of sentence lists. Each sentence list contains 8 to 10 sentences; each has 3 or 4 key words. Hearing level is assessed as the so-called speech recognition threshold, defined as the correct repetition of at least 50% of these words (Zeitler et al., 2008).
- City University of New York (CUNY) sentence test: The test consists of 72 lists of 12 sentences that vary in length from 3 to 14 words, for a total of 102 words per list. It is scored as the percentage of words correctly repeated, may be applied in quiet or in noise, and uses a signal-to-noise ratio (SNR) of 10 when applied in noise (Waltzman et al., 2002; Ramsden et al., 2005).
- Cognitive Load: This test assesses a listener's ability to divert attention between two tasks, such as listening to a speech signal while simultaneously engaged in a different task, e.g., with a different modality such as vision. An array of 8 loudspeakers spanning a horizontal arc of 108° is used. The loudspeaker location of the target words is selected randomly on each trial, and the background of competing speech noise (one talker repeating one of several randomly selected sentences) is presented from one loudspeaker that is four loudspeakers from the location where the target word is played. At the same time, a brief visual display is presented on a touch screen with varying numbers of three sets of colored shapes. The arrangement and number of the shapes varies from trial to trial. The listener has to judge which set of colors is more numerous or if they are equal while at the same time identifying the target word that is played. The visual display is turned on simultaneously with the background noise and turned off simultaneously with the target word being spoken. The subject has to make a judgment on the visual display first and then choose the target word they hear (Dunn et al., 2010).
- Consonant Nucleus Consonant (CNC) test: This measure involves monosyllabic words consisting of a consonant, a nucleus of vowels, and another consonant. The test score is based on the percentage of correct responses (Ruffin et al., 2007).
- Consonant-Nucleus-Consonant (CNC) word test: The test consists of 10 lists of 50 monosyllabic words, with each list representing phonemic balance in the English language. It may be scored by the percentage of words correct or the percentage of phonemes correct (Zeitler et al., 2008; Budenz et al., 2009).
- Cueing the Listener Test: This test represents a situation where a listener might hear a talker, turn to face them, and then recognize their message. An auditory cue ("hey I'm over here") is played in quiet (at the same level as the target word) to orient the listener to the location of the

loudspeaker from where the target word is be played. After the auditory cue is played, there is a 1-second delay, followed by initiation of the background noise and 0.8 second after the target word is played. The loudspeaker location of the target words is selected randomly on each trial, and the background of competing speech noise (a male and a female each repeating a different sentence from the same loudspeaker) is presented from one loudspeaker that is four loudspeakers from the location where the target word is played (Dunn et al., 2010).

- Freiburger test (sometimes referred to as Freiburg test): This is a monosyllabic, open-set word test (Laszig et al., 2004).
- Hearing in Noise Test (HINT): The test consists of 250 sentences divided into 25 phonetically balanced lists of 10 sentences each (Zeitler et al., 2008). Sentences vary from 3 to 7 words, and the test is scored based on the total number of correctly identified words in the sentences (Parkinson et al., 2002). This test may be performed in quiet (HINT-Q) or with competing noise (HINT-N) (Zeitler et al., 2008).
- Hochmair-Schulz-Moser (HSM): This is an open-set sentence test (Laszig et al., 2004).
- The Montreal Battery of Evaluation of Amusia (MBEA) is a standardized test of music abilities; it is sensitive, normally distributed, and reliable on test-retest (Cullington et al., 2011).
- Multiple-Jammers test: In everyday settings, listeners are often faced with competing sounds in the form of several other voices at spatially discrete locations. To represent this situation with this test, the target spondee word is presented from one of two loudspeakers placed at 8° from 0° azimuth. In addition, two separate loudspeaker combinations are used to play randomly selected male and female sentences (jammers) simultaneously. The jammers are located either at 54° and 38° or at 38° and 54° azimuth. The sentences and the location of the male and female talkers saying the sentences vary from trial to trial (Dunn et al., 2010).
- Oldenburg Sentence (OLSA) test: This open-set sentence test consists of 40 lists of 30 (5-word) sentences. Sentences are generated from a pool of 50 words. Sound level is adaptively altered to identify a patient-specific SNR at which 50% correct speech perception is achieved (Laszig et al., 2004; Schleich et al., 2004; Olze et al., 2012).

Disease-Specific Functional (Real-Life Experience)

- Abbreviated Profile of Hearing Aid Benefit (APHAB) (disease-specific): This is a disease-specific functional scale. Its four subscales are ease of communication (EC), reverberant listening conditions (RV), background noise (BN), and aversion to sounds (AV). Responses are on a 7-point scale ranging from “never” to “always” (Litovsky et al., 2006a).
- Oldenburg Inventory (OI): This disease-specific functional scale comprises 12 questions about different standard hearing situations. The questions are organized according to four domains: hearing in quiet, hearing with background noise, and localization. Responses are made on a 5-point Likert scale (1 = never to 5 = always). Scores can be converted to percentages, with higher percentages representing better performance (Olze et al., 2012).
- Speech, Spatial and Qualities of Hearing (SSQ) Scale: There are three sections to this disease-specific functional test. Spatial Hearing includes 17 questions such as: “Can you tell from the sound which direction a bus or truck is moving, for example, from your left to your right or right to left?” Quality of Hearing includes 19 questions such as: “When you listen to music, does it sound clear and natural?’’ Hearing for Speech is designed to measure the ability to direct attention to a specific source and includes 14 questions such as: ‘‘You are in a group of about five people in a busy restaurant. You cannot see everyone else in the group. Can you follow the

conversation?'' Each item may be rated on a 0 to 10 scale to indicate the frequency with which the respondent can perform as specified by the question (Summerfield et al., 2006).

Disease-Specific Health Status, Quality of Life (QOL), and Symptom Scales

- Glasgow Health Status Inventory (GHSI) (semi-generic): This instrument assesses the social, emotional, and psychological aspects of QOL that may be affected by impaired hearing and interventions to treat impaired hearing. Examples include optimism and self-confidence. There are 18 questions, which are ranked on a 5-point Likert scale corresponding to increasing impact of hearing-related disabilities on the aspect of QOL described in the question (Summerfield et al., 2006).
- Nijmegen Cochlear Implant Questionnaire (NCIQ): This validated test comprises three domains comprising six subdomains: (1) physical domain (basic sound perception, advanced sound perception, and speech production); (2) psychological domain (self-esteem); and (3) social domain (activity limitations and social interactions). Patients apply a 5-point Likert scale corresponding to *never to always* or *no to good* to each item, or indicate *not applicable* response. The total possible score ranges from 0 = very poor to 100 = optimal. The test has been used in both children and adults (Olze et al., 2012; Sparreboom et al., 2012).
- Tinnitus Questionnaire: This symptom-specific instrument measures tinnitus-related annoyance with 52 items in 6 subscales: emotional distress, cognitive distress, intrusiveness, sleep disturbance, auditory perceptual difficulties, and somatic complaints. Emotional distress and cognitive distress can be combined to create a psychological distress score. Total possible score ranges from 1 to 87 and the following severity levels have been defined: low (1-30), moderate (31-46), severe (47-59), and very severe (60-84). A score ≤ 46 is interpreted to signify *compensated* tinnitus (Olze et al., 2012).

Generic Health Status and QOL

- *EuroQol EQ-5D* (E*Q-5D) (gen*eric): This utility instrume*nt first establ*ishes functional status relative to five attributes: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Combinations of scores for the five attributes are mapped to health states for which member of the British public have assigned a utility, or preference. The scale is 0 = death to 1 = full health (Summerfield et al., 2006).
- Health Utilities Index Mark III (HUI 3) (generic): This utility instrument first establishes functional status relative to eight attributes: hearing, vision, the capacity to be understood when speaking, mobility, dexterity, cognition, feelings, and pain. Developers of the HUI 3 have devised formulas to weight the eight attributes of the HUI instrument and to map any combination of scores to a particular health state. The utility value (preference) for each health state is assumed to be equal to utility values that have been assigned in surveys of members of the Canadian public. Values range from zero = death to 1 = full health. This approach is preferred when the objective is to set priorities for expenditure in publicly funded systems of healthcare but generic instruments may not have sufficient sensitivity to measuring disease-specific QOL (Summerfield et al., 2006).

APPENDIX II. Search Strategy

Search for Systematic Reviews and Practice Guidelines (October 5, 2012)

Core Sources

Initially, evidence for this report was obtained by searching for relevant systematic reviews in the following databases: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (York University), Cochrane Library, Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Services Health Technology Assessment (NIHR HTA) Program (UK), National Guidelines Clearinghouse, TRIP Database, VA/Department of Defense Clinical Practice Guidelines, and VA Technology Assessment Program (VA TAP).

MEDLINE

Additional systematic reviews were selected from a search of the MEDLINE database spanning July 2007 to October 5, 2012, using various limits:

- Limited to Practice Types: meta-analysis, practice guideline, consensus development conference, NIH
- Limited to Journal Groups: systematic review

(two separate searches, connected by "OR")

Searches for Primary Studies Published After the Systematic Reviews (November 28, 2012; Update Search February 17, 2013)

Databases Searched: MEDLINE, Embase

Search Terms: (cochlear implant) or (cochlear prosthesis)*

Limits: Humans; published July 2009 to current

In addition to the July 2009 to present literature search, registry analyses and large case series published prior to July 2009 were identified from systematic reviews; the articles were retrieved and reviewed for data specific to bilateral implantation.

Searches for Cost Studies or Economic Evaluations (October 5, 2012; Update Search February 17, 2013)

The National Health Service Economic Evaluation Database (NHSEED) was searched for the years 2002 through 2012 with the keyword *cochlear implant*. In addition, MEDLINE was searched for the same time frame using this search string, combined with *cochlear implant*:

((((economic analysis) OR (economic evaluation)))) OR (((((cost AND (analysis OR benefit OR effective* OR consequence OR minimization)))) OR (("Costs and Cost Analysis"[MeSH] OR "Cost-Benefit Analysis"[MeSH]))))

Additional Searches for Practice Guidelines (October 5, 2012)

In addition to the sources searched for systematic reviews, the following websites were searched: American Academy of Neurology (AAN), American Academy of Pediatrics (AAP), and American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), American Auditory Society, American Speech-Language Association, and International Hearing Society.

APPENDIX III. Overview of Evidence Quality Assessment Methods

The tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

Step 1	Individual study appraisal a. Initial rating according to study design *Good:* Randomized Controlled Trials *Fair:* Nonrandomized Trial (controlled, parallel group, quasi-randomized) *Poor:* Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) *Very Poor:* Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study
Step 2	Evaluation of each body of evidence by outcome, key question, or application a. Initial quality designation according to *best* study design in a body of evidence b. Downgrade/upgrade *Downgrade factors:* Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias *Possible upgrade factors:* Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Very Low d. Repeat for each outcome/question/application
Step 3	Evaluation of overall evidence a. Rank outcomes by clinical importance b. Consider overall quality of evidence for each *critical* outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low
Step 4	Evidence-Based Conclusion Overall quality of evidence + Balance of benefits and harms

APPENDIX IV. Evidence Tables (Children)

NOTES: See **Appendix I** for more detail on specific testing strategies. See **Table 1** in **METHODS** for a description of study designs and their inherent weaknesses. Briefly, studies are categorized as:

Treatment and outcomes data collected at the same time		Change in outcome measures is assessed	
A – Two or more groups (starting quality very poor)	B – Patients are their own controls (starting quality good)	C – Two or more groups (starting quality poor)	D – Patients are their own controls (starting quality poor)

Appendix IV-A. Sound Detection (Children)

✓ **= Significant results favoring bilateral CI.**

✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported (and often small in magnitude).

Authors, Design, Type of Bilateral CI	n	Age at Last CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	PTA Threshold	Quality/Comments
Scherf et al. (2007); Scherf et al. (2009a) Design B Sequential	18	Younger grp (<6 yrs at 2nd CI): Mean 3.5 yrs Mean 24 mos 3 yrs	Monaural hearing (1st CI alone)	✓Significantly favored bilateral CI, starting at 1 yr. Box plots suggest difference <5 dB at 3 yrs.	Poor. Substantial missing data at 2 yrs and later for testing in unilateral condition. Manufacturer funding.
	17	Older grp: Mean 8.8 yrs Mean 4.7 yrs 3 yrs	Monaural hearing (1st CI alone)	✓?Favored bilateral CI, but significant only up until 2 yrs. Box plots suggest difference <5 dB at 3 yrs.	

Appendix IV-B. Speech Perception (Children)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported (and often small in magnitude).
0 = Results suggest no difference.
* = Open-set word or sentence recognition test.
Key: AdSpon, Adaptive Spondee Discrimination Test; ATT, Auditory Toy Discrimination Test; BKB-SIN, Bamford-Kowal-Bench Signals in Noise (test); CI, cochlear implantation; CNC, Consonant-Nucleus-Consonant (word test); CRISP, Children's Realistic Index of Speech Perception; dB, decibel(s); EOWPVT, Expressive One-Word Picture Vocabulary Test; ESP, Early Speech Perception; f/u, follow-up; GASP, Glendonald Auditory Screening Procedure; grp(s), group(s); HA(s), hearing aid(s); HINT-C, Hearing in Noise Test for Children; LNT, Lexical Neighborhood Test; MLNT, Multi-syllabic Lexical Neighborhood Test; N/A, not applicable; NR, not reported; OKLI (Oldenburger Kinder Reimtest); PB-K, Phonetically Balanced Kindergarten (test); pt(s), patient(s); preop, preoperative(ly); SNR, signal-to-noise ratio; SRTs, speech reception thresholds; WIPI, Word Inventory by Picture Index

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results in Quiet[1]	Results in Noise[1,2,3]	Quality/Comments
Litovsky et al. (2006b) Design A Sequential	20 *Bilateral* *10* *CI+HA* *10*	NR Mean 13.5 mos ≥1 yr	CI+HA	CRISP: Binaural advantage (reduction in SRT for 79.4% correct; positive value favors binaural advantage) was 4 vs –3 dB.	CRISP: Binaural advantage was 4 vs 0, 2 vs 0, and 2 vs –2, depending on noise condition.	Very poor. No control for confounders. Wide variability across individuals.
				✓Global *P*<0.005 across all quiet and noise conditions. (dB values for speech reception thresholds were estimated from bar graphs)		
Schafer et al. (2006) Design A Sequential	22 *Bilateral* *12* *CI+HA* *10*	Mean 6 yrs 6-9 mos ≥6 mos	CI+HA	---	0Modified BKB-SIN*: No overall grp effect when controlling for binaural vs monaural listening mode and whether a speaker enhancement system was used.	Very poor. Differences in time using the 2nd device favored CI+HA grp. No control for confounders.

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results in Quiet[1]	Results in Noise[1,2,3]	Quality/Comments
Peters et al. (2007) Designs D and B Sequential	30	3-13 yrs NR 12 mos (quiet) or 9 mos (noise)	Monaural hearing (1st CI alone)	✓?MNLT* and/or LNT*: Small (4%-8%) NS absolute differences favoring binaural hearing.	✓CRISP: 69% vs 62% (*P*=0.018), ✓69% vs 55% (*P*<0.001), and ✓79% vs 72% (P=0.018) correct, depending on noise condition (7%-14% absolute differences, all significant).	Good. Manufacturer funding and author-manufacturer affiliation. All children used HA before 2nd CI.
			Preop CI+HA	MNLT* and/or LNT* (depending on age grp): ✓92% vs 67% (*P*=0.003); ✓?81% vs 71% (NS); ✓86% vs 69% (*P*=0.004) (LNT scores estimated from bar graphs)	---	
Scherf et al. (2007); Scherf et al. (2009a) Design B Sequential	18	<u>Younger grp (<6 yrs at 2nd CI)</u>: Mean 3.5 yrs Mean 24 mos 3 yrs	Monaural hearing (1st CI alone)	✓?Göttinger Test: Binaural (89%) vs 1st CI alone (83%) (6% absolute difference; NS).	✓Göttinger Test: Significant bilateral advantage starting at 18 mos; 68% vs 58% (10% absolute difference; *P*=0.042).	Fair. Some in younger grp could not perform the tests in noise; substantial missing data at 2 yrs and later for testing in unilateral condition.
	17	<u>Older grp</u>: Mean 8.8 yrs Mean 4.7 yrs 3 yrs	Monaural hearing (1st CI alone)	✓Dutch Audiology Society Test: Significant bilateral advantage beginning at 18 mos; 81% vs 60% (21% absolute score difference) (*P*=0.001) at 3 yrs.	✓Dutch Audiology Society Test: Significant bilateral advantage beginning at 24 mos; 56% vs 37% (19% absolute difference) (*P*=0.001) at 3 yrs.	
Steffens et al. (2008) Design B Sequential	20	Mean 5.6 yrs Mean 3.6 yrs Mean 1.4 yrs	Monaural hearing (1st CI alone)	---	✓OLKI Test: 73% vs 36% correct (37% absolute difference; *P*<0.001)	Good
Zeitler et al. (2008) Designs B and D Sequential	43	Mean 7.8 yrs Mean 5.2 yrs	Monaural hearing (1st CI alone)	✓?GASP*word, CNC, PB-K*, MLNT*, LNT*, and/or HINT-C*: Very small differences favoring bilateral CI;	NR	Poor. Short f/u. Incomplete results reporting.

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results in Quiet[1]	Results in Noise[1,2,3]	Quality/Comments
		3 mos		significance testing NR.		1 author-manufacturer affiliation.
			Preop CI+HA	✓MLNT* (n=15): Differences favored bilateral CI (*P*=0.017), mean scores and other tests NR.	✓HINT-C*: Favored bilateral CI (*P*<0.05); scores NR.	
Gordon and Papsin (2009) Design B Sequential (n=52); simultaneous (n=6)	58	Mean 21 mos (simultaneous), mean 3-11 yrs (sequential, by subgrps defined by interimplant time) 0 to mean 6 yrs 6 mos to 3 yrs (6-18 mos for most participants)	Monaural hearing (either CI alone)	✓?GASP*, MLNT*, LNT*, PB-K*, ESP, and/or WIPI: In 3 of 4 subgrps most (55%-88%) children had a bilateral advantage ≥1%; in 1 subgrp w/ 1st CI at >3 yrs and 2nd CI at ≥2 yrs after 1st CI, 33% of children had bilateral advantage ≥1%. Significance testing w/in subgrps NR.	✓?GASP*, MLNT*, LNT*, PB-K*, ESP, and/or WIPI: Differences described as "significant" but quantitative results and *P*=NR.	Poor Study was designed primarily to explore factors affecting bilateral advantage rather than to demonstrate a bilateral advantage. Significance testing NR Rationale for threshold of improvement (≥1%) not given Score values were estimated from bar graphs;
			Monaural hearing (1st CI alone)	✓GASP*, MLNT*, LNT*, PB-K*, ESP, and/or WIPI: Small significant advantage (~10%-14% absolute differences in mean scores) in subgrps w/ 0 to mean 21 mos between 1st CI and 2nd CI. No advantage in other subgrps.	✓GASP*, MLNT*, LNT*, PB-K*, ESP, and/or, WIPI: Small significant advantage (~6% absolute differences in mean scores) in the subgrps w/ 0 to mean 21 mos between 1st CI and 2nd CI. No advantage in other subgrps.	
Galvin et al. (2010) Design B Sequential	9	10-20 yrs 6-17 yrs ~1 yr	Monaural listening (1st CI alone)	---	0AdSpon* Noise ipsilateral to 1st CI: Differences very small (<0.5 dB); NS Noise contralateral: NS in grp; quantitative data NR	Poor Considerable variability in results. Extremely small . (Study included because no other studies focused on analysts.)
Sparreboom et al. (2011) Designs B and C Sequential	38 *Bilateral 29* *Unilateral 9*	5.3 yrs NR 2 yrs	Monaural listening (1st CI alone)	✓ATT: Speech reception threshold for 71% correct: ~42 vs 48 dB (*P*<0.001)	✓?ATT: NS differences in mean scores (SNR –4 dB vs 2 dB favoring bilateral), but 76% children w/bilateral CI had better scores (by 1-11 dB) in binaural listening than in best ear alone.	Good. Possibly underpowered (speech perception in noise) Matched analysis of the 2 grps. Variability in results. dB values estimated from bar graphs Manufacturer funding.
			Unilateral	✓?ATT: Speech reception threshold	✓ATT: Noise next to 1st/only CI: SNR	

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results in Quiet[1]	Results in Noise[1,2,3]	Quality/Comments
			CI grp	for 71% correct: 42 vs 45 dB (NS)	–4 vs 2 dB (*P*<0.01) ONoise and speech from front: SNR 2 vs 2 dB (no difference)	
Strøm-Roum et al. (2012) Design B Sequential	73	Mean 8 yrs Mean 5 yrs 2 yrs	Monaural listening (1st CI alone)	✓PB-K*: Mean difference 4.39% (CI, 1.2-7.49; *P* value unclear; reported as >0.006).	---	Good
Vincent et al. (2012) Design B Simultaneous (n=12); sequential (n=11)	23	Simultaneous, mean 4 yrs; sequential, mean 1.9 yrs NR Mean 4.3 yrs	Monaural listening (better side alone)	✓Boorsma word lists (% correct): 83% vs 73% (*P*=0.036)	✓Boorsma word lists (% correct): 70% vs 57% (*P*<0.001)	Fair Blinded evaluation NR. No analysis w/ control for confounders

[1]"And/or" or "or" signifies that tests were assigned according to age subgroup.

[2]Results expressed as *% correct* refer to the percentage of all responses across repetitions and/or lists that were correct. Results expressed as speech reception thresholds (*SRTs*) are in decibels (dB) and refer to the lowest sound intensity of speech or other signal at which a certain % correct was possible. Results expressed as signal to noise ratios (*SNRs*) are in dB and were adaptively identified for each patient so that the patient achieved a 50% correct score on the test. Since the dB scale is a logarithmic scale, a mean SNR of –4 implies that on average, respondents achieved 50% correct performance when the signal intensity was 4 dB lower than the noise intensity.

Appendix IV-C. Sound or Speech Localization (Right-Left Discrimination) (Children)

✓ **= Significant results favoring bilateral CI.**

✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported (and often small in magnitude).

? = Unclear results

0 = Results suggest no difference.

* = Open-set tests

Key: CI, cochlear implantation; dB, decibel(s); f/u, follow-up; grp(s), group(s); HA(s), hearing aid(s); MAA, minimum audible angle; N/A, not applicable; NR, not reported; pt(s), patient(s); preop, preoperative(ly); SNR, signal-to-noise ratio; SRTs, speech reception thresholds

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results with Fixed Sound Intensity	Results with Roving (Variable) Sound Intensity	Quality/Comments
Steffens et al. (2008) Design B Sequential	20	Mean 5.6 yrs Mean 3.6 yrs Mean 1.4 yrs	Monaural hearing (1st CI alone)	✓ 75% vs 58% correct choice of source loudspeaker (mean intrasubject absolute difference 18%; *P*=0.009)	---	Good
Lovett et al. (2010) Design A Sequential	50 *Bilateral 30* *Unilateral 20*	NR NR Mean 47-50 mos	Unilateral CI Grp	<u>Quiet</u> ✓Observation of eye-head movement, ✓objective localization test, ✓video recording of eye-head movementsall grp differences statistically significant (*P*<0.025). 50% [where chance level was 25%)-100% correct scores vs 25%-50%. Absolute score differences 15%-30%. <u>Noise</u> Relative SNR for 71% correct score when hearing speech w/ background noise at side vs noise at front (higher score denotes greater binaural benefit for spatially separated noise and signal): NS difference between grps, as expected, w/noise	---	Poor. Commercial funding; authors had other financial ties to manufacturers. Parents had higher-than-average incomes.

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Results with Fixed Sound Intensity	Results with Roving (Variable) Sound Intensity	Quality/Comments
				contralateral to 1st CI) and ✓ 4.75 vs –0.48 (*P*<0.02) (noise ipsilateral to 1st CI).		
Sparreboom et al. (2011) Designs B and C Sequential	38 *Bilateral 29* *Unilateral 9*	5.3 yrs NR 2 yrs	Monaural listening (1st CI alone)	✓Minimum audible angle ±42° vs ±78° (*P*<0.01), favoring bilateral CI. (83% of children could lateralize significantly better than chance performance in binaural condition vs 41% in monaural; 42% absolute difference)	---	Good. Analysis by 2 designs and matched selection of Unilateral Grp help control for the different potential biases inherent in each design. Manufacturer funding.
Grieco-Calub and Litovsky (2012) Designs A and B Sequential	39 *Bilateral 27* *Unilateral 12*	<3 yrs <2 yrs 9-29 mos	Monaural listening (1st CI alone)	✓Mean performance better than chance (*P*<0.001) in binaural condition vs no better than chance in monaural; significant advantage w/in individuals (*P*<0.001). Quantitative results NR.		Fair. Substantial missing data due to inability of children to complete tests. Young age may have created floor effects.
			Unilateral CI Grp	✓Mean performance better than chance (*P*<0.001) in Bilateral Grp vs no better than chance in Unilateral Grp. Quantitative results NR.	**?** 10 of 19 children w/ better than chance performance under fixed intensity performed better than chance. Performance at chance levels in unilateral grp, but data available for only 2 children.	
Vincent et al. (2012) Design B Simultaneous (n=12;) sequential (n=11)	23	Simultaneous, 4 yrs; sequential, 1.9 yrs NR Mean 4.3 yrs	Monaural listening (1st and 2nd CI alone)	---	✓36% absolute difference: 86% correct (*P*<0.001 for difference from chance alone) vs 50% correct (chance score) for either single CI.	Fair

Appendix IV-D. Speech Comprehension and Speech Production Tests (Children)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference.
? = Unclear findings.
Key: CI, cochlear implantation; f/u, follow-up; grp(s), group(s); HA(s), hearing aid(s); N/A, not applicable; NR, not reported; PLS-4, Preschool Language Scales-4; pt(s), patient(s); RDLS, Reynell Developmental Language Scales; SELT, Schlichting Expressive Language Test; SIR, Speech Intelligibility Rating

Authors, Design, Type of Bilateral CI	n	Age at Last CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Quiet[1]	Noise[1]	Quality/Comments
Nittrouer et al. (2009) Design A Sequential (n=19); simultaneous (n=7)	58 *CI+CI* 26 *CI+HA* 17 *CI* 15	Mean 32 mos NR ~2 yrs	Unilateral CI and CI+HA Grps	0PLS-4 (comprehension) 0EOWPVT (speech production) Similar scores across grps	---	Very poor. No control for confounders.
Tait et al. (2010) Design A Simultaneous (n=27); sequential (n=9)	53 *Bilateral* *27* *Unilateral* *26*	NR 0 or 1-7 mos 1 yr	Unilateral CI Grp	**?**Structured videotape analysis of instances of predefined conversational turns, turn-taking autonomy, and auditory awareness: Results favored bilateral CI in some measures but not others.		Very poor Unclear validity of comparisons (# instances of responsive behavior reported; no information on comparability of opportunities between grps) Limited control for confounders
Baudonck et al. (2011) Design A Sequential	27 *Bilateral* *13* *Unilateral* *14*	NR NR NR	Unilateral CI Grp	✓?<u>Intelligibility (assessed in a manner analogous to SIR)</u>: 92% of children w/ score 5 (highest possible) vs 69% (NS) ✓<u>Perceptual voice (0-3 scale for negative vocal qualities, 3 = severe)</u>: CI, 0.00-0.31 (depending on quality evaluated) vs CI, 0.18-1.04 (significant differences for 3 of 6 qualities) ✓?<u>Articulation</u>: Absolute differences in % correct were 6%-7%, favoring bilateral CI; differences significant for 3 of 8 measures.		Very poor. No control for confounders. Subjective evaluation and no blinding reported.

Authors, Design, Type of Bilateral CI	n	Age at Last CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Quiet[1]	Noise[1]	Quality/Comments
Boons et al. (2012) Design A Simultaneous (n=8); sequential (n=17)	50 *Bilateral 25* *Unilateral 25*	1 yr (simultaneous); 1-5 yrs (sequential) ≤3 yrs ≥3 mos	Unilateral CI Grp	✓RDLS (comprehension): 85.6 vs 76.2 (mean intrasubject difference 9.4 [confidence interval, 0.3-18.6]) ✓SELT, spoken words: 86.1 vs 70.4 (mean intrasubject difference 15.7 [confidence interval, 15.9-25.4]) ✓SELT, spoken sentences: 86.8 vs 77.0 (mean intrasubject difference 9.7 [CI, 1.5-17.9]) Best possible score for all tests is 100.		Very poor. No control for confounders. Short f/u (may have created bias in favor of unilateral CI).

Appendix IV-E. Functional and Quality of Life Outcomes (Children)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference.
? = Unclear findings.
Key: CAP, Categories of Auditory Performance; CI, cochlear implantation; f/u, follow-up; GCBI, Glasgow Children's Benefit Inventory; grp(s), group(s); HA(s), hearing aid(s); HUI, health utilities index; NCIQ, Nijmegen Cochlear Implant Questionnaire; NR, not reported; pt(s), patient(s); preop, preoperative(ly); QOL, quality of life; SSQ, Speech, Spatial, and Quality of Hearing Scale; VAS, visual analog scale

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Hearing Function in Real Life	General Function and Health	Quality of Life	Quality/Comments
Scherf et al. (2009b) Design D Sequential	18	Younger grp (<6 yrs at 2nd CI): Mean 3.5 yrs Mean 24 mos 3 yrs	Prior to 2nd CI (11 of 18 w/ HA)	✓Used oral communication exclusively (% children): Younger, 100% vs 59%; older, 77% vs 71% (*P*=0.016 for entire study grp) ✓?Ability to understand common phrases (CAP): Younger, 100% vs 81%; older, NR vs 96% ✓?Have conversation w/ familiar person w/o lip-reading (CAP): Younger, 90% vs 50%, older, 76% vs 38% ✓Have telephone conversation w/ familiar talker) (CAP): Younger, 72% vs 3%; older, 35% vs 7% (*P*=0.034 for entire study grp) Würzberg Questionnaire, positive experiences (median score on 0-51 scale of increasingly positive behavior): ✓?Younger, 40 vs 33.1; 0older, 33.5 vs 33.1 Würzberg Questionnaire, negative experiences: ✓?Younger, 18.6 vs 20.3; older, 26.7 vs 23.7	✓Attendance at mainstream school**:** Younger, 79% vs 59% (absolute difference 20%); older, 69% vs 47% (absolute difference 22%) (*P*=0.031 for entire study grp)	---	Poor. High rate of dropouts/missing data. Possible maturation bias.
	17	Older grp: Mean 8.8 yrs Mean 4.7 yrs 3 yrs	Prior to 2nd CI (10 of 17 w/ HA)				

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Hearing Function in Real Life	General Function and Health	Quality of Life	Quality/Comments
Galvin et al. (2010) Design D Sequential	9	10-20 yrs 6-17 yrs ~1 yr	Prior to 2nd CI (2 of 9 w/ HA)	✓?SSQ (0-10 scale) (n=8): For 6 participants, median before-and-after improvement 1-7.5 points for each of the 3 sections. For 2 participants, positive change in 2 sections, no change in 1 section.	---	---	Poor SSQ results may be biased by child/parent expectations. Inconsistency in parent vs child completion of SSQ. Extremely small . (Study included because no other studies focused on analysts.)
Lovett et al. (2010) Design A Sequential	50 *Bilateral* 30 *Unilateral* 20	NR NR Mean 47-50 mos	Unilateral CI Grp	✓SSQ, speech section (0-10 scale): Median 7.53 vs 5.88 (*P*=0.04)✓SSQ, spatial section: Mmedian 7.47 vs 4.85 (*P*=0.00) 0SSQ, qualities section: Median 7.60 vs 7.16 (NS)	0Parent-rated, generic visual analog scale (VAS): NS	✓? Parent-rated generic health utilities index (HUI): 0.83 vs 0.78 (0-1.0 scale)(NS)	Poor. Commercial funding; authors had other financial ties to manufacturers. Parents had higher-than-average incomes.
Sparreboom et al. (2012) Designs B and C Sequential	39 *Bilateral* 30 *Unilateral* 9	Mean 5 yrs Mean 3.3 yrs 2 yrs	Preop 1st CI alone	✓Disease-specific hearing function (SSQ) (0-1.0): Favored bilateral, 0.49 preoperatively vs 0.62 at 2 yrs (*P*<0.001)	0Generic parent-rated overall health (VAS): Very similar scores; NS differences ✓Parent-rated disease-specific health status (GCBI) (–100 to 100): Results favored bilatera (*P*<0.001) (assessment time unclear; absolute improvement NR)	0Parent-rated generic QOL (HUI for age ≥4 yrs only): Very similar scores; NS differences 0Parent- and child-rated PedsQOL: Very similar scores; NS differences ✓Parent-rated disease-specific QOL (NCIQ): 0.78 vs 0.74 (*P*=0.02)	Poor

Authors, Design, Type of Bilateral CI	n	Age at 2nd CI, 1st-2nd CI Interval, F/u Since 2nd CI	Comparator	Hearing Function in Real Life	General Function and Health	Quality of Life	Quality/Comments
			Unilateral CI Grp	✓ Disease-specific hearing function (SSQ) (0-1.0 scale): Median difference favored bilateral, 0.62 (CI, 0.56-0.72) vs 0.50 (CI, 0.43-0.65; *P*=0.04)	0Generic parent-rated overall health (VAS): Very similar scores; NS differences	0Parent-rated generic QOL (HUI for age ≥4 yrs only): Very similar scores and NS differences 0Parent- and child-rated PedsQOL: Very similar scores; NS differences 0Parent-rated disease-specific NCIQ: : Very similar scores and NS differences	
Kim et al. (2013) Design D Sequential	42	Mean 9.7 yrs Mean 5.5 yrs 6 mos	Preop CI+HA	✓SSQ (0-200 scale): 160 vs 118 (*P*=0.018). Significant improvement on each subscale.	---	---	Poor No control for confounders other than interimplant delay

Appendix IV-F. Differential Effectiveness of Bilateral CI (Children)

✓ **= Significant effect modifier or success predictor.**
✓? = Differences shown, but were nonsignificant or significance testing was not reported.

Study	n	Study Quality*, Follow-up	Outcome	Versus Unilateral CI (Effect Modifiers)	Bilateral CI Patients Only (Success Predictors)
Etiology of Deafness					
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Speech perception in noise	No correlation	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Lateralization	No correlation	---
Age at Deafness Onset					
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Speech perception in noise	No correlation	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Lateralization	No correlation	---
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	No association (analysis adjusted for duration of HA use prior to CI, age at 1st CI, age at 2nd CI, 1st CI-2nd CI interval, time using 2nd CI, mainstream school)
Deafness Duration in 1st Ear					
Zeitler et al. (2008)	43	Poor, 3 mos	Speech perception in quiet	✓? Shorter duration, better score (r=–0.456; P=0.05); ✓ Shorter duration, better score (r=–0.794; P<0.001)	---
Zeitler et al. (2008)	43	Poor, 3 mos	Speech perception in noise	✓ Shorter duration, better score (r=–0.858; P<0.001)	---
Deafness Duration in 2nd Ear					
Zeitler et al. (2008)	43	Poor, 3 mos	Speech perception in noise	✓r=–0.554, P<0.05	---

Study	n	Study Quality*, Follow-up	Outcome	Versus Unilateral CI (Effect Modifiers)	Bilateral CI Patients Only (Success Predictors)
Duration HA Use Prior to 1st CI					
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	✓ >18 mos, smaller (better) angle (24° vs 34°; *P*=0.010) (analysis adjusted for age at deafness onset, age at 1st CI, age at 2nd CI, 1st CI-2nd CI interval, time using 2nd CI, mainstream school)
Age at 1st CI					
Sparreboom et al. (2011)	38	Good, 2 yrs	Speech perception in quiet	No correlation	---
Gordon et al. (2009)	58	Good, 6 mos-3 yrs	Speech perception in quiet	---	No association in stepwise regression
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Speech perception in noise	No correlation	---
Gordon et al. (2009)	58	Good, 6 mos-3 yrs	Speech perception in noise	---	No association in stepwise regression
Scherf et al. (2009a)	35	Fair, 3 yrs	Speech perception in noise	---	✓? Younger age correlated w/ better performance; statistical testing NR
Sparreboom et al. (2011)	38	Good, 2 yrs	Speech perception in noise	No correlation	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Lateralization	No correlation	---
Asp et al. (2011)	66	Very poor (no unilateral control), multiple measurements up to 3 yrs	Lateralization	---	No association
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	✓ Age <2 yrs, smaller (better) angle (25° vs 35°; *P*=0.018) (analysis adjusted for age at deafness onset, duration HA use prior to CI, age at 2nd CI, 1st CI-2nd CI interval, time using 2nd CI, mainstream school)
Sparreboom et al. (2011) (same study as Sparreboom et al., 2012)	38	Good, 2 yrs	Lateralization	No correlation	---

Study	n	Study Quality*, Follow-up	Outcome	Versus Unilateral CI (Effect Modifiers)	Bilateral CI Patients Only (Success Predictors)
Sparreboom et al. (2012) (same study as Sparreboom et al., 2011)	30	Poor, 2 yrs	1 generic and 2 disease-specific hearing-related functional scales	---	No correlation
Age at 2nd CI					
Sparreboom et al. (2011)	38	Good, 2 yrs	Speech perception in quiet	No correlation	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Speech perception in noise	No correlation	---
Zeitler et al. (2008)	43	Poor, 3 mos	Speech perception in noise	✓Younger age, better score (r=–0.545; P<0.05)	---
Sparreboom et al. (2011)	38	Good, 2 yrs	Speech perception in noise	No correlation	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Lateralization	✓Younger age, better score (r=–0.0562; P=0.015)	---
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	No association (analysis adjusted for age at deafness onset, duration of HA use prior to CI, age at 1st CI, 1st CI-2nd CI interval, time using 2nd CI, mainstream school)
Asp et al. (2011)	66	Very poor (no unilateral control), multiple measurements up to 3 yrs	Lateralization	---	✓?Younger age (≤4 yrs), greater improvement (change in error index –0.31 vs –0.16 or –0.23 vs –0.17, depending on frequency of testing)---
Sparreboom et al. (2011)	38	Good, 2 yrs	Lateralization	No correlation	---
Time between 1st and 2nd CI					
Gordon et al. (2009)	58	Good (but see comment on effect modifier analysis), 6 mos-3 yrs	Speech perception in quiet	Bilateral benefit was demonstrated in simultaneous and short-delay (≤2 yrs) subgrps but not in long-delay subgrps (numerous methodological and sample size issues w/ this analysis)	---

Study	n	Study Quality*, Follow-up	Outcome	Versus Unilateral CI (Effect Modifiers)	Bilateral CI Patients Only (Success Predictors)
Strøm-Roum et al. (2012)	73	Good, 2 yrs	Speech perception in quiet	---	No correlation
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Speech perception in noise	No correlation	---
Zeitler et al. (2008)	43	Poor, 3 mos	Speech perception in noise or quiet	No correlation	---
Gordon et al. (2009)	58	Good (but see comment on effect modifier analysis), 6 mos-3 yrs	Speech perception in noise	Bilateral benefit was demonstrated in simultaneous and short-delay (≤2 yrs) subgrps but not in long-delay subgrps (numerous methodological and sample size issues w/ this analysis)	---
Steffens et al. (2008)	20	Good, mean 1.4 yrs	Lateralization	No correlation	---
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	No association (analysis adjusted for age at deafness onset, duration of HA use prior to CI, age at 1st CI, age at 2nd CI, time using 2nd CI, mainstream school)
Boons et al. (2012)†	25	Very poor, ≥3 mos	Speech comprehension	---	✓Shorter interval, better scores (r=0.40; P=0.04)
Boons et al. (2012)†	25	Very poor, ≥3 mos	Speech expression, sentences	---	✓Shorter interval, better scores (r=0.53; P=0.006)
Boons et al. (2012)†	25	Very poor, ≥3 mos	Speech expression, words	---	✓Shorter interval, better scores (r=0.50; P=0.01)
Boons et al. (2012)‡	22	Very poor, ≥3 mos	Speech comprehension, sentences	---	No difference between simultaneous and sequential
Boons et al. (2012)‡	22	Very poor, ≥3 mos	Speech expression, sentences	---	No difference between simultaneous and sequential
Boons et al. (2012)‡	22	Very poor, ≥3 mos	Speech comprehension, words	---	No difference between simultaneous and sequential
Boons et al. (2012)‡	22	Very poor, ≥3 mos	Speech expression, words	---	✓Significantly better performance in simultaneous subgrp
Ramsden et al. (2009)	105	Very poor (no unilateral	Safety	---	No difference in acetaminophen or antiemetic

Study	n	Study Quality*, Follow-up	Outcome	Versus Unilateral CI (Effect Modifiers)	Bilateral CI Patients Only (Success Predictors)
		CI control), peri- and postop			use between simultaneous and short-delay (6-12 mos) sequential bilateral CI. (Simultaneous vs long-delay sequential CI comparison confounded by age differences; age associated w/ medication use.) No difference in rate of extended stay due to complications.
Grainger et al. (2012)	50	Very poor (no unilateral CI control), median 1.2 yrs (simultaneous) and 0.6 yrs (sequential)	Safety	---	✓Less pain medication in simultaneous grp (mean 4.04 doses paracetamol vs 6.74; *P*<0.001; 1.60 doses NSAIDs vs 2.96; *P*<0.001). No difference in antiemetic use. No major complications. ✓?Minor complications lower in simultaneous grp (4.0% vs 17.4; NS)
Time using 2nd CI					
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	No association (analysis adjusted for age at deafness onset, duration of HA use prior to CI, age at 1st CI, age at 2nd CI, 1st CI-2nd CI interval, mainstream school)
Attendance of Mainstream School					
Van Deun et al. (2010)	30	Very poor (no unilateral control), 11 mos-3.5 yrs	Lateralization	---	✓(26° vs 38°; *P*=0.003) (analysis adjusted for age at deafness onset, duration of HA use prior to CI, age at 1st CI, age at 2nd CI, 1st CI-2nd CI interval, time using 2nd CI)

*Quality refers to bias with respect to the study's assessment of overall bilateral effect, not its assessment of differential effect.

†Eight of the 25 bilateral CI group underwent simultaneous implantation and were included in these analyses.

‡Fourteen of the 17 sequential implant participants were matched to the 8 simultaneous implant participants according to age at second implant of <2 years.

APPENDIX V. Evidence Tables (Adults)

NOTES: See **Appendix I-B** for more detail on specific testing strategies. See **Table 1** in **METHODS** for a description of study designs and their inherent weaknesses. Briefly, the studies are categorized as:

Treatment and outcomes data collected at the same time		Change in outcome measures is assessed	
A – Two or more groups (starting quality very poor)	B – Patients are their own controls (starting quality good)	C – Two or more groups (starting quality poor)	D – Patients are their own controls (starting quality fair)

Appendix V-A. Speech Perception, Open-Set Tests (Adults)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference.
? = Unclear findings.
Key: BKB-SIN, Bamford-Kowal-Bench Signals in Noise; CI, cochlear implant(ation); CNC, Consonant-Nucleus-Consonant; dB, decibel(s); f/u, follow-up; NR, not reported; pt(s), patient(s); preop, preoperative(ly); OLSA, Oldenburger test; SNR, signal-to-noise ratio; SRT, speech reception threshold

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator*	Results in Quiet*†‡ (Variance Is SD)	Results in Noise*†‡§ (Variance Is SD)	Quality/Comments
Simultaneous Bilateral CI						
Litovsky 2006a Designs B and D	37	Mean 6 yrs 6 mos	Preop CI+HA	✓CNC word: 59% vs 7% (reported as significant but w/o *P* value) ✓HINT sentence: 90% vs 13% (*P*<0.008)	---	Good Values estimated from bar graphs
			Monaural (better ear; see additional detail on poorer ear)	✓CNC word: 59% vs 48% (*P*<0.001) (64% pts had better binaural than monaural score) ✓HINT sentence: 90% vs 83% (reported as significant but w/o *P* value) (58% of pts had better binaural than monaural score)	BKB-SIN (SNR-50% in dB): ✓?10 vs 12 (*P*<0.017 for left, NS for right); other differences favoring bilateral were ✓2 (*P*≤0.002) (5 vs poorer), ✓2 (*P*≤0.002) (6 vs poorer); all binaural-monaural differences were significant (*P*≤0.002).	
Buss 2008 Design B	26	>15 yrs 1 yr	Monaural listening (better ear)	✓CNC word: Mean difference 5.8% at 1 mo to 11% mean difference (*P*<0.001) at 1 yr for binaural vs both monaural conditions)	CUNY Sentence: Median difference ✓?5.7%, ✓?10.6%	Fair . Lack of statistical testing in noise condition.
Budenz 2009 Design D (results for	23	18-32 yrs 1 yr	Preop Unilateral CI or no CI	✓CNC word: 58% vs 2% (mean difference 53.25%±22.68%; *P*=0.0078)	---	Fair. Prior use of HA NR.

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator*	Results in Quiet*†‡ (Variance Is SD)	Results in Noise*†‡§ (Variance Is SD)	Quality/Comments
sequential subgrp [n=8] not reported here)						
Mosnier 2009 Design B	27	Mean 3 yrs 1 yr	Monaural listening (better ear)	✓Fournier word test: 77% vs 67% (mean difference 10±0.3%; *P*<0.005)	Fournier word test: ✓63% vs 55% (mean difference 8±3.4%; *P*<0.05); ✓?53% vs 48% (NS); ✓42% vs 33% (mean difference 9±3.8%; *P*<0.05) Different results correspond to different intensities of signal.	Good. 19 pts had used unilateral or bilateral HA for mean 18 yrs.
Dunn 2010 Design A	60 *Bilateral* 30 *Unilateral* 30	Mean 7 yrs ≥6 mos	Unilateral CI grp w/o HA	---	✓Cueing the listener (SNR-50%): –10 vs –1 dB (difference in means 9; *P*<0.00001) ✓Multiple jammer test (SNR-50%): –2.5 vs 2.5 dB (difference in means 5; *P<0.05)* ✓Cognitive load test: –18 vs –7 (difference in means 11; *P*<0.00001)	Very poor. The only known confounder (time between implants) favored Unilateral Grp
Primarily Sequential CI						
Ramsden 2005 Designs B and D	28	Mean 6-8 yrs 9 mos	Preop CI+HA	0CNC word: Negligible change 0CUNY sentence: Negligible change	0CUNY sentence, coincident: No change ✓?CUNY sentence, spatially separate noise: 58% vs 47%	Good. 2nd CI remained poorer performing than 1st at 9 mos, which may mean f/u was too short to show maximum benefit. Possible ceiling effects, CUNY in quiet The stronger analysis (binaural vs monaural listening) had significant results for most noise conditions
			Monaural listening (1st CI)	**0**CNC word: Negligible difference **0**CUNY sentence: Negligible difference	CUNY sentence (different noise conditions): ✓58% vs 46% (mean difference 12.6±5.4%; *P*<0.001); ✓mean difference 7.7%±5.3%; *P*=0.002; ✓69% vs 48% (mean difference 21±6%; *P*<0001); 0Negligible difference	
Zeitler 2008	22	Mean 32	Preop CI+HA	✓Improvements in CNC word:	✓Improvements in BKB-SIN: 6.6	Fair.

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator*	Results in Quiet*†‡ (Variance Is SD)	Results in Noise*†‡§ (Variance Is SD)	Quality/Comments
Design D		yrs 3 mos		P<0.005 ✓Improvements in HINT sentence: *P*=0.010 (test scores , score differences NR)	(*P*<0.001), 5.0 (*P*<0.01), 5.1, (*P*<0.05)	Substantial missing data for BKB test. Short f/u may not have allowed maximum performance of 2nd CI.
Laske 2009 Design B	29	>6 mos	Monaural listening (better ear)	**?**OLSA sentence: No difference (Compared w/ poorer ear, 69% vs 51%, mean difference 18±27%; *P*<0.05)	0OLSA sentence: No difference vs better ear (SNR 50% vs poorer ear: –3.4 vs –0.4, mean difference 3; *P*<0.05)	Fair. Substantial missing data for OLSA in noise. Values estimated from bar graphs
Olze 2012 Designs D	40	Mean 9 yrs ≥6 mos	Monaural listening (better ear)	Freiburg word: ✓81.8±14.2% vs 74.4±16.8% (*P*<0.0001)	HSM sentence: ✓81.2±16.1% vs 72.1±23.1% (*P*<0.001), ✓81.2±16.1% vs 72.1±23.1% (*P*<0.001), ✓82.2±24.7% vs 45.0±25.6% (*P*<0.0001) OLSA sentence (SNR-50%): ✓–0.26±1.53 vs 0.74±1.83 (*P*<0.0001), ✓–5.29±2.61 vs –4.76±2.32 (*P*<0.05), ✓–3.78±4.00 vs 5.42±2.12 (*P*<0.0001)	Good
Mixed Simultaneous and Sequential Bilateral CI or Type not Reported						
Laszig 2004 Design B	37	Mean 10-11 yrs 6 mos	Monaural (better ear)	0Freiburger Word: No difference ✓OLSA sentence: 78% vs 75% (*P*=0.03) 0HSM sentence: No difference	OLSA sentence (SNR -50% in dB): ✓–3, –1 (mean difference –1.4; *P*=0.01); 0No difference; ✓–3 vs 5 (mean difference –10; *P*<0.00001) HSM sentence: 0No difference; 0no difference; ✓60% vs 12% (mean difference 42% (*P*<0.00005)	Fair. Possible ceiling effects in monaural conditions.
Schleich 2004 Design B	20	Mean 13 yrs	Monaural listening (better ear)	---	OLSA sentence (mean SRT relative to noise level of 60 dB): ✓?–3.6±4.1 vs –2.9±5.9, ✓?–4.8±4.6, –3.7±5.2, ✓?–	Fair. Short f/u in some participants may have

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator*	Results in Quiet*†‡ (Variance Is SD)	Results in Noise*†‡§ (Variance Is SD)	Quality/Comments
		≥1 mo			1.2 vs 0.9±4.0 (variance suggests lack of significance)	masked tx effect.
Dunn 2008 Designs B and C	73	Mean 8 yrs Mean 59 mos	Monaural listening (better ear)	✓CNC word: 70% vs 65% (*P*<0.01) ✓HINT sentence: 100% vs 95% (*P*<0.05)	---	Good. Ceiling effects on HINT may have diminished observed difference. Values estimated from bar graphs.
			Unilateral CI Grp	✓CNC word: 70% vs 46% (difference in means 24%; *P*<0.001) ✓HINT-Q: 100% vs 81% (difference in means 19%; *P*<0.01)	---	
Budenz 2009 Design D (results for simultaneous subgrp [n=8] not reported here)	23	18-32 yrs 1 yr	Preop Unilateral CI or no CI	CNC word: ✓If 2nd implant differed from 1st, 73% vs 51% (mean difference 18.4%±17.5%; *P*=0.0006). ✓?If identical, 34% vs 27% (mean difference NR).	---	Fair Prior use of HA NR.
Cullington and Zeng 2011 Design A	26 *Bilateral* 13 *Bimodal* 13	Mean 8 yrs, bilateral; 17 yrs, bimodal Mean 3.5 yrs, bilateral; mean 2.6 yrs, bimodal	CI+HA Grp	---	0Modified HINT: Very small and NS difference	Very poor. No control for confounders.

*Additional detail on binaural versus poorer ear is presented if results for that comparison are substantially different from the comparison with the better ear.

†Results expressed as *% correct* refer to the percentage of all responses across repetitions and/or lists that were correct. Results expressed as speech reception thresholds (*SRTs*) are in decibels (dB) and refer to the lowest sound intensity of speech or other signal at which a certain % correct was possible. Results expressed as signal to noise ratios (*SNRs*) are in dB and were adaptively identified for each patient so that the patient achieved a 50% correct score on the test. Since the dB scale is a logarithmic scale, a mean SNR of –4 implies that on average, respondents achieved 50% correct performance when the signal intensity was 4 dB lower than the noise intensity.

‡Some absolute values have been approximated from bar graphs.

§Multiple results for a single test correspond to varying spatial arrangements of signal and noise.

Appendix V-B. Sound Localization (Left-Right Discrimination) (Adults)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference.
? = Unclear findings.
Key: CI, cochlear implant(ation); dB, decibel(s); f/u, follow-up; NR, not reported; pt(s), patient(s); preop, preoperative(ly); RMS, root mean square; SD, standard deviation

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Results*	Quality/Comments
Simultaneous Bilateral CI					
Grantham (2007) Design B	22	Mean 4.8 yrs	Monaural listening (better ear)	✓Noise signal: Mean adjusted constant error 24.1° vs 50.5° (*P*<0.001) ✓Speech signal: 21.1° vs 47.9° (*P*<0.001)	Good
Primarily Sequential					
Verschuur 2005 Design B	20	3-9 mos	Monaural (better ear)	✓24±10° vs 67±9° (*P*<005); front signal advantage over side ✓signal 5° (NS) vs 13° (*P*<0.001)	Good
Mixed Simultaneous and Sequential or not Reported					
Laszig 2004 Design B	37	Mean 10-11 yrs 6 mos	Monaural listening (left ear)	✓RMS 50° (range 16.0-99) vs 87° (range 70-102) (*P*<0.05)	Fair. Possible ceiling effects in monaural conditions. Short f/u in some participants may have masked tx effect.
			Monaural listening (right ear)	✓RMS 50° (range 16.0-99) vs 89° (range 64-103) (*P*<0.05)	

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Results*	Quality/Comments
Nopp 2004 Design B	20	Mean 14 yrs ≥1 mo	Monaural listening (better ear)	✓RMS 28.9° vs 45.0° (*P*<0.05) (absolute condition difference 15.1°)	Good
Dunn 2008 Designs B and C	73	Mean 8 yrs 59 mos	Unilateral CI Grp w/out HA	✓RMS 19° vs 44° (difference in means 25.4°; *P*<0.001)	Fair. Matched pair analysis (by age at implant and duration of profound deafness).

*Smaller values for all measures denote better performance. *In quiet* describes a condition where there was no *competing* noise in addition to the signal, which could be speech or another type of sound.

Appendix V-C. Speech Production and Comprehension Tests (Adults)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference or possible difference favoring unilateral CI.
? = Unclear findings.

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Results*	Quality/Comments
Cullington and Zeng 2011 Design A	26 *Bilateral* 13 *Bimodal* 13	Mean 8 yrs, bilateral; 17 yrs, bimodal Mean 3.5 yrs, bilateral; mean 2.6 yrs, bimodal	CI+HA Grp	0Affective prosody section of Aprosodia Battery (understanding nonlinguistic includes regarding emotion and attitude): Very small NS differences 0Voice discrimination: Very small NS differences	Very poor. No control for confounders.

Appendix V-D. Functional and Quality of Life Outcomes (Adults)

✓ **= Significant results favoring bilateral CI.**
✓? = Results favor bilateral CI, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference or possible difference favoring unilateral CI.
? = Unclear findings.

Key: APHAB; Abbreviated Profile of Hearing Aid Benefit; CI, cochlear implant(ation); EQ-5D, EuroQol; f/u, follow-up; HUI, Health Utilities Index; MBEA, Montreal Battery of Evaluation of Amusia; MUMU, Munich Music Questionnaire; OI, Oldenburg Inventory; NCIQ Nijmegen Cochlear Implant Questionnaire; NR, not reported; pt(s), patient(s); preop, preoperative(ly); QOL, quality of life; SSQ, Speech, Spatial, and Quality of Hearing Scale

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Hearing-Related Function in Real Life, (Variance Is SD)	QOL, Including Tinnitus (Variance Is SD)	Quality/Comments
Simultaneous Bilateral CI						
Litovsky 2006a Designs B and D	37	Mean 6 yrs 6 mos	Monaural listening	APHAB (scale 1-7): ✓Ease of communication: 5.7 vs 4.4 (grp difference 1.3; *P*<0.0001) (83% pts had binaural superiority). ✓Background noise: 4.4 vs 3.1 (grp difference 1.3; *P*<0.0001) (87% pts had binaural superiority). ✓Reverberant listening: 4.4 vs 3.0 (grp difference 1.4; *P*<0.0001) (97% pts had binaural superiority). ✓?Aversion to sounds: 3.0 vs 3.3 (NS) 57% pts had binaural superiority).	---	Good
Noble 2008 Design A	182 *Bilateral* 36 *Unilateral* 70 *Bimodal* 39	NR >6 mos	Unilateral CI grp	SSQ (0-10 scale) ✓Localization: 5.8±2.3 vs 4.1±2.5 (difference in means 1.7; *P*=0.002). ✓Distance and movement: 5.7±1.9 vs 4.0±2.2 (difference in means 1.7; *P*<0.001). ✓Sound quality and naturalness: 6.9±2.0 vs 5.6±2.6 (difference in means 1.3; *P*=0.02). ✓Identification of sound and objects: 6.6±2.1 vs 5.2±2.5 (difference in	---	Very poor. No control for confounders.

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Hearing-Related Function in Real Life, (Variance Is SD)	QOL, Including Tinnitus (Variance Is SD)	Quality/Comments
				means 1.3; *P*=0.008), 5.8±2.0. ✓Listening effort: 6.1±1.8 vs 5.1±2.4 (difference in means 1.0; *P*=0.04), 4.3±2.1 (*P*=0.001 vs bilateral)		
			CI+HA Grp	SSQ (0-10 scale) ✓Localization: 5.8±2.3 vs 4.6±2.0 (*P*<0.05). ✓Distance and movement: 5.7±1.9 vs 4.3±1.9 (difference in means 1.4; *P*=0.01). ✓Sound quality and naturalness: 6.9±2.0 vs 5.8±1.7 (difference in means 1.1; *P*=0.02**).** ✓**?**Identification of sound and objects: 6.6±2.1 vs 5.8±2.0 (NS). ✓Listening effort: 6.1±1.8 vs 4.3±2.1 (difference in means 1.7; *P*=0.001).	---	
Primarily Sequential						
Summerfield 2006 RCT (randomized wait list design)	24		Wait list (waiting for 2nd CI)	Improvement in SSQ score (0-10 scale) ✓Spatial Hearing: Difference in grp means 1.68 (confidence interval, 0.62-2.75). ✓Qualities of Hearing: Difference in grp means 1.8 (*P*<0.01) (other data NR). ✓?Speech: Difference in grp means 2.0 (NS) (other data NR).	✓GHSI (semi-generic, 0-90): Difference in grp mean, 6 (*P*<0.05, effect size 0.3). 0EQ-5D (generic): Difference in grp mean, 0.3 *favoring unilateral* (*P*<0.05, effect size 0.4). 0HUI3 (generic), 0QOL VAS (generic): Very small and NS difference 0Tinnitus Annoyance (0-100 scale): Difference in means 12 *favoring unilateral* (NS). All differences reflect control of values prior to latest CI.	Fair-Good. Study grp may not have been representative w/ respect to prevalence of tinnitus or may have been too small to allow a reliable estimate. Study likely underpowered to detect effect on generic QOL (no power analysis).
Laske 2009 Design A	54	>6 mos	Unilateral grp	SSQ (0-10 scale): ✓?Spatial Hearing 5.8 vs 4.5 (NS). ✓?Speech Hearing: 6.3 vs 4.8 (NS).✓?Hearing Quality: 6.7 vs 6.2 (NS).	---	Poor. No control for confounders.

Authors, Design	n	Duration Deafness, F/u Since 2nd CI	Comparator	Hearing-Related Function in Real Life, (Variance Is SD)	QOL, Including Tinnitus (Variance Is SD)	Quality/Comments
Veekmans 2009 Designs A and D	69 *Bilateral* 23 *Unilateral* 23	NR 1 yr	Preop single CI (Bilateral grp only)	---	✓?MUSA: Music sounded better (95.5%), more natural (90%), and more pleasant (85%). ✓# categories of music listened to increased significantly (*P*=0.001).	Poor. No correction for multiple testing. Unilateral grp matched to bilateral grp according to music-related variables after 1st CI.
			Unilateral grp	---	✓?MUSA: All 6 subscales substantially favored bilateral; only 1 was statistically significant	
Olze 2012 Designs D	40	Mean 9 yrs ≥6 mos	Unilateral CI (after 1st CI)	✓OI: 3.7±0.65 vs 3.13±0.84 (difference in means 0.57; *P*<0.0001) (total possible score unclear)	✓NCIQ (disease-specific, 0-100): 71.3±12.7 vs 64.5±12.7 (difference in means 5; *P*<0.01) ✓Tinnitus annoyance (1-84): 8.7±12.2 vs 12.8±12.5 (difference in means 4.1; *P*<0.05).	Fair. Significance in NCIQ and OI results was maintained after adjustment for score obtained just after 1st CI.
Mixed Simultaneous and Sequential or not Reported						
Cullington and Zeng 2011 Design A	26 *Bilateral* 13 *Bimodal* 13	Mean 8 yrs, bilateral; 17 yrs, bimodal Mean 3.5 yrs, bilateral; mean 2.6 yrs, bimodal Mean 2.6 yrs	CI+HA grp	---	0MBEA (music perception): Very small NS differences	Very poor. No control for confounders.

Appendix V-E. Differential Effectiveness of Bilateral CI (Adults)

✓ **= Significant effect modifier or success predictor.**
✓? = Differences shown, but were nonsignificant or significance testing was not reported.
0 = Results suggest no difference.
? = Unclear findings.

Study	n	Study Quality*, Follow-up	Outcome	Patient Factor	Versus Unilateral CI (Effect Modifiers)
Nopp et al. (2004)	20	Good, ≥1 mo	Sound localization	Age of deafness onset	0No change in direction of findings and similar magnitude of differences in subgrp w/ age of onset >6 yrs
Mosnier et al. (2009)	27	Good, 1 yr	Speech perception in quiet	Ear symmetry	✓Binaural advantage (vs better ear) in pts w/ ear symmetry; none in pts w/ asymmetry
Litovsky et al. (2006a)	37	Good, 6 mos	Speech perception in noise	Ear symmetry	✓? Binaural advantage (vs better ear) in pts w/ ear symmetry; none in pts w/ asymmetry
Mosnier et al. (2009)	27	Good, 1 yr	Sound localization in noise	Ear symmetry	0Binaural advantage in both subgrps
Zeitler et al. (2008)	22	Fair, 3 mos	Speech perception in quiet	Time between implants, age at 2nd CI, or deafness duration	0No correlation with improvement by any factor.
Olze et al. (2012)	40	Fair, ≥6 mos	Tinnitus annoyance	Decompensated tinnitus (baseline score >46 (1-84 scale)	✓Improvement only in pts w/ decompensated tinnitus

*Quality refers to bias with respect to the study's assessment of overall bilateral effect, not its assessment of differential effect.

APPENDIX VI. Economic Evaluations

The following data were abstracted primarily from a systematic review (Lammers et al., 2011). Individual studies were reviewed where clarification was needed. In the systematic review, cost data were adjusted for inflation, according to the Organisation for Economic Co-operation and Development, using 2009 as the base year. The authors also converted prices to U.S. dollars using the exchange rate on December 31, 2009. Cost data as reported in the systematic review are presented here. Lammers and colleagues did not provide information on sensitivity analyses conducted within individual studies.

Key: CI, cochlear implant; HUI 3, Health Utilities Index 3; ICER, incremental cost-effectiveness ratio; NH, normal hearing; NR, not reported; QALY, quality-adjusted life-year; QOL, quality of life; TTO, time-tradeoff; VAS, visual analog scale

Authors Study Design	Perspective Time Horizon Discounting*	Source of Utility Estimates	Utility Method (Scale)	Source of Costs	Costs Included	Findings, Bilateral vs Unilateral CI			Study Quality According to Lammers et al. Comments
						Utility Gain	Total QALY Gain	ICER (Probability of Cost-Effectiveness)	
Children									
Bichey 2008 (U.S.) Survey, retrospective data collection, and extrapolation	Payer Age ≤76 yrs 5%	All bilateral CI users from a single clinic (n=10 children); 0.5-3.2 yrs experience w/ 2nd CI	HUI 3 (0-1.0)	Retrospective data collection	Direct† Collected from clinic records	Sequential: 0.09 at 0.5-3.2 yrs	1.80	$39,115/QALY (NR)	Poor
Bond 2009 (UK) Simulation modeling	Payer Lifetime 3.5%	Summerfield 2006	HUI 3 (0-1.0)	Published sources and expert opinion; extrapolation from 6-8 yrs of data	Direct† Indirect‡	Simultaneous: 0.03 w/ indirect costs Sequential: 0.03	0.67 0.67 0.60	$70,470/QALY (34.9%) $70,078/QALY (NR) $94,340/QALY (21.3%)	Good. Adult utility values were used for children since no QOL studies in children had been conducted at the time.

Authors Study Design	Perspective Time Horizon Discounting*	Source of Utility Estimates	Utility Method (Scale)	Source of Costs	Costs Included	Findings, Bilateral vs Unilateral CI			Study Quality According to Lammers et al. Comments
						Utility Gain	Total QALY Gain	ICER (Probability of Cost-Effectiveness)	
Summerfield 2010 (UK) Survey and extrapolation	Payer Lifetime 3.5%	All bilateral CI users from a single clinic (n=10 children); 0.5-3.2 yrs experience w/ 2nd CI	Convenience sample of 180 NH volunteers responding to hypothetical vignettes depicting children before and after CI	Bond et al. (2009)	Direct†	Simultaneous, TTO: 0.063 Simultaneous, VAS: 0.076 (time point unclear)	1.57 1.87	$37,100 (48.0%) $30,973 (53.9%)	Good. Assumed benefit of CI based on nonsystematic literature search and expert opinion. Model assumes 1 major or minor complication in 1st yr
Adults									
Bichey 2008 (U.S.) Survey, retrospective data collection, and extrapolation data collection, and extrapolation	Payer ≤76 yrs 5%	All bilateral CI users from a single clinic (n=10 children); 0.5-3.2 yrs experience w/ 2nd CI	HUI 3 (0-1.0)	Retrospective data collection	Direct†	Sequential: 0.11	1.98	$38,189/QALY (NR)	Poor
Summerfield 2002 (UK) Survey and extrapolation	Payer Lifetime 6%	70 NH volunteers responding to hypothetical vignettes depicting adults before and after CI implants	TTO (0-1.0)	Expert opinion	Direct†	Simultaneous: 0.03. Sequential: 0.03 (time point unclear)	0.44 0.44	$118,387/QALY (NR) $132,160/QALY (NR)	Good. A convenience sample of 202 adults who had undergone sequential bilateral CI and completed 9-mo QOL questionnaires provided data against which to check volunteer utilities.

Authors Study Design	Perspective Time Horizon Discounting*	Source of Utility Estimates	Utility Method (Scale)	Source of Costs	Costs Included	Findings, Bilateral vs Unilateral CI			Study Quality According to Lammers et al. Comments
						Utility Gain	Total QALY Gain	ICER (Probability of Cost-Effectiveness)	
Summerfield 2006 (UK) Randomized wait list study and extrapolation	Payer 30 yrs 6%	28 adults eligible for bilateral CI; utilities measured at 9 mos	HUI 3 (0-1.0)	Summerfield 2002	Direct†	Sequential: 0.03 (at 9 mos)		$127,767/QALY (NR)	Fair
Bond 2009 (UK) Simulation modeling	Payer Lifetime 3.5%	Summerfield 2006	HUI 3 (0-1.0)	Published sources and expert opinion; extrapolation from 6-8 yrs of data	Direct†	Adults, simultaneous: 0.03 Adults, sequential: 0.03	0.38 0.38	$86,425 (20.7%) $105,157 (8.9%)	Good

*All studies reported discounting both costs and benefits (QALYs).

†Preoperative assessment, cochlear implant devices, costs of implantation, postoperative tuning and maintenance. The Bond (2009) and Summerfield (2010) studies included the cost of processor upgrades and the cost of treating complications; the Summerfield (2002) (and thus the Summerfield [2006]) study included the cost of processor upgrades but did not mention complication costs; the Bichey (2008) study did not explicitly include processor upgrades or costs associated with complications.

‡Sick leave, schooling, and associated costs.

APPENDIX VII. Studies Included in Systematic Reviews of CI in Adults (Relevant to Key Question #1)

A shaded cell with asterisk signifies inclusion.

	Crathorne et al. (2012) (18 Publications)	Raman et al. (2011) (16 Studies, 20 Publications)	Berrettini et al. (2011) (12 Publications)	Bond et al. (2009b) (NIHR) (4 Publications)	Hayes (2009) (9 Publications)	Included in the Present Review (17 Studies, 19 Publications)
Search Dates	Inception to January 2012	Jan. 2004 – Feb. 2011	2000 – May 2010	Inception – July 2007	1999 – July 2007	Other review bibliographies and a new search: July 2009 – November 28, 2012
Gantz 2002					*	n=10
Laszig 2004	*	*	*	*	*	*
Nopp 2004		*	*			*
Litovsky 2004		*			*	n=17 adults
Schleich 2004		*	*			*
Ramsden 2005	*	*	*	*	*	*
Schoen 2005					*	No comparison w/ unilateral CI
Vershuur 2005	*	*	*	*		*
Litovsky 2006a	*	*	*		*	*
Ricketts 2006		*	*			n=16
Summerfield 2006	*	*		*	*	*
Grantham 2007		*			*	*
Neuman 2007	*		*			n=8
Tyler 2007	*		*			n=7
Wackym 2007			*			n=9
Buss 2008	*	*				*
Dunn 2008	*	*				*
Gifford 2008		*				Irrelevant study design and objectives
Noble 2008	*	*				*
Zeitler 2008	*	*			*	*
Budenz 2009						*
Eapen 2009			*			n=9

	Crathorne et al. (2012) (18 Publications)	Raman et al. (2011) (16 Studies, 20 Publications)	Berrettini et al. (2011) (12 Publications)	Bond et al. (2009b) (NIHR) (4 Publications)	Hayes (2009) (9 Publications)	Included in the Present Review (17 Studies, 19 Publications)
Laske 2009	*	*				*
Litovsky 2009	*	*				n=17
Mosnier 2009	*	*	*			*
Noble 2009	*					Not designed for bilateral-unilateral comparison
Veekmans 2009						*
Dunn 2010	*	*	*			*
Koch 2010 (listed as Koch 2009 in AHRQ report)	*	*				n=15
Cullington 2011	*	*				*
Olze 2012						*