Author's response to reviews

Title: A Global Patient Outcomes Registry: Cochlear Paediatric Implanted Recipient Observational Study (Cochlear P-IROS)

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Author's response to reviews: see over
Dear Dr. Morawska,

**MS: 1037763845131478: “A Global Patient Outcomes Registry: Cochlear Paediatric Implant Recipient Observational Study (P-IROS)”**

We sincerely thank the reviewers for their thorough assessment of our manuscript.

Please find below our detailed response to the individual comments and concerns of the two referees (non-bold text). The major amendments made to the revised manuscript were;

- Inclusion of a new section (2.3) detailing Cochlear P-IROS hypothesis,
- Inclusion of a new section (2.4.8) discussing the proposed statistical analysis plan,
- Revisions to Introduction and Discussions sections as per reviewer comments
- Re-formatting of Table 2, and
- Re-formatting of Table 3 and inclusion of text explaining the table in Section 2.4.2 User Access.

Please find enclosed a clean version of the revised manuscript (with no track changes), for your kind perusal.

**Response to Referee 1:**

1. I have some concern for the comparability of the results with other related analysis. Firstly, as the majority of the studies in literature use CAP instead of CAP-II as the evaluation tool, the follow-up data collected by this protocol may not be comparable to previous studies. Yet, longitudinally speaking, CAP-II may become a standard tool in the future, as its nine-point scale provides better insight into the patients’ auditory performance.

The authors’ acknowledge that the majority of the literature to date has used the original 8-point hierarchy rating scale Categories of Auditory Performance (CAP) scale which assesses a child’s functioning in everyday situations. It covers a range of auditory performance and takes into consideration different developmental rates of children. There is evidence of ceiling effects of the CAP, as it does not address the more complicated listening skills now achievable with cochlear implants and other hearing devices, particularly when used in bilateral configurations. Therefore, two new additional categories were added to the original scale to form the CAP-II.

Given that the original eight categories of the CAP are retained in the CAP-II, comparisons with previous studies are possible up to the point of the ceiling effect. However, this is not the point...
of the P-IROS study which is observing the changes in performance of patients recruited to this patient registry.

As suggested by the reviewer, CAP-II therefore provides a more sensitive measure of functional hearing in hearing impaired children. Furthermore, compared with the CAP, CAP-II was deemed more appropriate for use in the Cochlear P-IROS, given one of the key objectives of the Study was to “compare the patient-related benefits arising from the use of hearing implants in unilateral versus bilateral configuration”.

2. Secondly, in order to allow better comparability between different languages, I would suggest that only assessment tools that have been validated in other languages are used. Therefore, the CuHI-QoL may require further validation.

The development of the CuHI-QoL is an ongoing process starting with the definition of the conceptual framework. The concepts, domains and were defined through a literature review and exploratory reviews with health professionals and parents.

The 25 items map to 12 domains. Each item was written for reading comprehension, translatability, and cross-cultural relevance. A four-week recall period was selected for repeated administration at six monthly intervals.

As the CuHIQoL is a self-administered questionnaire it uses a consistent five point Likert scale to assess the level of agreement or disagreement for all items. To reduce data transcription error and optimise response rates, paper and electronic formats are available.

The questionnaire was piloted in multiple cultural and socioeconomic settings with parents and providers. The CuHIQoL has now been translated into more than 15 languages and human ethics committee approval has been granted for evaluation of Reliability, Validity, Responsiveness and Interpretability.

We acknowledge that language and cultural adaptations of the CuHIQoL are important. Each item has been written for reading comprehension, translatability, and cross-cultural relevance. All translations were prepared by a professional translator and then reviewed by a native speaker for accuracy and appropriateness. Cultural validations will only be possible once the questionnaire is being used.

3. The SSQ scale was included in the protocol but only as an optional tool. I would suggest the SSQ evaluation to be conducted compulsorily at least at the time point 24 months post-implant. The data of this scale may better reflect the patients' progress than that of the CAP-II.

The SSQ Parent’s version has been included in the P-IROS as an optional evaluation option.

Many of the patients being observed in the P-IROS study will be implanted at ages well below the recommended age appropriate for the SSQ for Parents.
As noted in Galvin and Noble Adaptation of the SSQ for use with children, parents, and teachers [Cochlear Implants International 2013 VOL. 14 No. 3], the first author’s research team has not applied the SSQ for parents or the SSQ for teachers with parents or teachers of children younger than five years of age.

Given the complexity of the items and of the response format of the SSQ, this suggested age limit of five years is reasonably consistent with the age recommendations in the literature for other parent questionnaires evaluating children’s listening performance. Again, further work is needed to provide evidence-based recommendations for the target age range.

Whilst a within subject comparison indicated a significant increase in pre-operative to 24-month post-operative ratings for all three sections (Arch Otolaryngol Head Neck Surg. 2012;138(2):134-41), the SSQ Parent’s version is likely to be most sensitive for between group comparisons of unilateral and bilaterally implanted groups.

The registry was designed with flexibility to allow investigators to tailor the evaluation tools to their patient populations.

4. Also, aided and unaided hearing thresholds are suggested to be assessed pre-implant (0 month) and post-implant (at least at one of the time points during 6-60 months post-implant) as a reference in evaluating the patients’ post-implant progress.

The authors agree with this comment and as such the platform provide for these evaluations. However, we also note that these evaluations should complement individual investigation site’s clinical practices.
Response to Referee 2:

1. No specific hypotheses have been proposed. Some comments on the objectives are made below. The study design is reasonable to achieve the stated objectives – although information of expected numbers of patients has not been provided.

Participating in the Cochlear P-IROS is voluntary for both clinic and parent/caregiver/patient. The clinic and parent/caregiver/patient are free to electively cease participation in the registry at any time. As such, it is not possible to determine the actual number of patients that may be registered over time. The design of the supporting third party database does not pose a constraint on the number of patients able to be entered. The detailed Registry Protocol for the Cochlear P-IROS outlines the primary, secondary and tertiary hypotheses. These have been included as part of Section 2.3 in the revised manuscript (pages 16-17). These hypotheses are as follows:

“PRIMARY HYPOTHESIS
Post-implant performance for all patients on the Categories of Auditory Performance -II (CAP-II) are superior to pre-implant performance (baseline) and show incremental improvement at each subsequent post implant assessment point (six months, 12 months, 18 months, 24 months, and annually thereafter for up to five years) during the study.

SECONDARY HYPOTHESES:

a. Post-implant hearing ability for patients > 4 years of age as assessed via the standardised Speech Spatial and Qualities scale Parents’ version (SSQ-P) are superior to their pre-implant hearing ability (baseline) and show incremental improvement at each subsequent post-implant assessment point (six months, 12 months, 18 months, 24 months, and annually thereafter for up to five years) during the study.

b. Post-implant auditory performance for patients using binaural hearing/stimulation is superior to that of patients using unilateral hearing/stimulation at each post-implant evaluation point (six months, 12 months, 18 months, 24 months, and annually thereafter for up to five years) during the study as measured by assessments of the:
   i. Categories of Auditory Performance – II (CAP –II) scale for all patients
   ii. Speech Spatial and Hearing Qualities Parents’ version (SSQ-P) scale
   iii. Post-implant, aided hearing-threshold levels

TERTIARY HYPOTHESES:

a. Post-implant assessment of quality of life for the patient and family via the CUHI-QoL questionnaire as assessed by the parent or caregiver are superior to quality of life assessed at baseline (pre-implant) and show incremental improvement at each subsequent post implant evaluation time point (six months, 12 months, 18 months, 24 months, and annually thereafter for up to five years) during the study.

b. Patients who begin mainstream school during the study enter at an age-appropriate time.

c. The proportion of patients who are participating in mainstream school with no additional support is higher than the proportion of patients in other categories of school placement.
2. As noted below, there is information which could be usefully added to the manuscript, including more clarity on the roles of clinicians, investigators etc., predicted number of clinics, patients etc. likely to be registered, and more explanation of the choice of assessment tools.

Please see below for more detailed response to the referee’s concerns.

3. These are minor essential revisions. There are numerous minor issues of writing style, punctuation etc., including
   a. inconsistent use of a comma before the “and” in a list of items

   Corrected in the revised manuscript.

   b. use of semicolons in lists rather than commas

   Corrected in the revised manuscript.

   c. lack of comma usage to set off parenthetical element in a sentence (eg. Comma should be before and after the phrase “which began in January 2010 and ended in December 2012” on pg 4); and to separate adjectives.

   Corrected in the revised manuscript.

   d. beginning a sentence with “however”

   Corrected in the revised manuscript.

   e. inconsistent use of terminology (making it more difficult for the reader to follow the text eg. bone conduction hearing implants versus osseointegrated hearing implants; implantable hearing devices versus implantable hearing solutions versus implantable hearing systems.

   In the revised manuscript the term “bone conduction implants” have been used rather than osseointegrated hearing implants; and the term “implantable hearing devices” have been used to refer to the collective group of hearing implants available in the market.

   f. inconsistent use of capitalization and acronym for “Cochlear Paediatric Implanted Recipient Observational Study” – full term defined as P-IROS on page 6, but then Cochlear P-IROS is used on page 16 and defined in list of abbreviations; P-IROS registry also used.
The term “Cochlear P-IROS” has been used to refer to the study name throughout the revised manuscript.

g. inconsistent use of Cochlear trademark

In line with Cochlear policy Cochlear trademark was used at the first mention of the brand, and not in the remainder of the text.

h. mixed use of “patient”, “child”, and “recipient

We have used the term “patient” consistently throughout the revised manuscript.

i. phrases which are not meaningful or are grammatically incorrect

   i. eg. “9% of this population is represented by children”, “in pediatrics…”, “in the otolaryngology setting…”, “the decision for use of bone conduction hearing implants”, “the auditory performance benefits…”, “the degree of success achieved in children”, “benefits…in hearing impaired children or their families”.

These phrases have been either removed or amended in the revised manuscript.

There are other specific issues which I would also consider minor essential revisions, including:

4. Page 3, para 1

   a. line 3: change “was” to “has been”

Corrected in the revised manuscript.

   b. “various aetiologies that may also be influenced by local factors” is unclear

The phrase was revised to:
“other causes that may also be influenced by regional and geographic factors”.

   c. final line: unclear; does this mean that, in low- and middle-income countries, there is a relationship between hearing loss and regions ?

The sentence was corrected to:
“Prevalence of hearing impairment is positively related to age, male sex; and is greater in regions of low- and middle-income”.

5. Page 3, para 2

   a. line 3-4: implantable hearing devices do not “restore” hearing; in many clinics these devices are not limited to those “unable to successfully use conventional amplification”

Agree with the reviewer on this comment. Line 3-4 has been amended to read as follows in the revised manuscript:
“The gold standard interventions available for treating patients with a permanent hearing impairment include cochlear implants and bone conduction implants.”

b. cochlear implantation is not generally recommended for children with moderate hearing loss.

As per regulatory approved indications for cochlear implants, the statement has been revised to read as follows:
“Currently, intervention by cochlear implantation is the recommended treatment for children presenting with a permanent bilateral sensorineural hearing loss. This impairment may range from moderate in the low frequencies sloping towards severe to profound in the high frequencies.”

6. Page 3, para 3
- text implies commercialization of bone conduction hearing implants occurred 30 years ago?; “large investments into research and development” have not

The sentence has been revised to:

“Large investments into research and development as well as over 30 years of clinical experience, have established that cochlear implants and bone conduction implants are safe and clinically effective. This resulted in the expansion of candidacy criteria to include very young children.”

7. Page 4, para 3
- the “audit” does not “report” results

Corrected in the revised manuscript.

- bilateral implants can be assumed to provide bilateral sound input but this does not equal binaural hearing

Agree with the reviewer on this comment. The paragraph has been amended in the revised manuscript (see page 6, paragraph 1) to:

“In response, a national audit was set up through collaboration of the cochlear implant programmes throughout the United Kingdom (UK). The UK national audit of paediatric bilateral cochlear implantation, which began in January 2010 and ended in December 2012, is one of the largest non-randomised prospective, observational studies exploring hearing outcomes in children with a permanent sensorineural hearing loss treated with cochlear implants [14]. The data collected included: listening, speech recognition, speech production, sound localisation, acquisition of vocabulary, parental perception and information relating to the implant surgery. Although the report from the audit showed encouraging results for bilaterally implanted children when considering hearing gains as well as acceptably low rates of adverse events, the study did not measure quality of life or humanistic measures such as access to services, educational placement, literacy, numeracy or social inclusion, which are of interest to payers and policy makers.”
8. Page 4, para 4  
- first line: missing space after “even” (“Despite...” may be a better term); change “may not be” to “is not”

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

- line 7: is this success with the implant? or success in habilitation? Unclear

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

- line 8: what may be assessed through use of measures of auditory performance?

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

- penultimate sentence refers to assessment of auditory performance and final sentence refers to “hearing-independent benefits” so this is contradictory.

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

- Or perhaps the author is not referring to the same thing in these two sentences? It is unclear

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

- the “Speech Spatial Qualities Index” should be the “Speech, Spatial and Qualities of Hearing Scale” (acronym the SSQ) (as per the original version developed by Noble and Gatehouse). The version for parents should be referred to as the “Speech, Spatial and Qualities of Hearing Scale for Parents” (acronym SSQ-P)

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion (as per reviewer’s comment #30).

9. Page 5, para 2  
- line 7: “to this end” suggests a solution to the previously identified problem is about to be provided, but this is not the case; also, “Bond and colleagues note that...” suggests that the lack of high quality long-term data has a particular effect but the sentence simply ends.

This paragraph was amended in the revised manuscript (page 5, paragraph III), to:

“A recent National Institute of Health and Clinical Excellence (NICE) health technology appraisal into the clinical and cost effectiveness of cochlear implants in adults and children, reviewed the body of evidence on the effectiveness of cochlear implants with the consideration of expert opinion. The final appraisal document was published in February 2009 highlighting recommendations for clinical
practice in the UK [13]. NICE recommendations included the provision of simultaneous bilateral CI to children born deaf, adventitiously deaf, or those newly diagnosed with severe to profound bilateral hearing impairment. The report also highlighted the deficiencies in the available evidence, including the difficulties in making comparisons due to heterogeneity in measures and protocols, the absence of sufficiently long term observation periods, the absence of benefits observed in daily circumstances and in the quality of life for the implanted child. To this end, the authors of the NICE report noted that more large scale studies are needed, that prospectively follow-up patients for longer time periods, using standard measures for outcomes, full information of known covariates of post-implantation speech- and quality of life outcomes.”

- unclear what is meant by the final point in this paragraph

This point was removed from this paragraph in the revised manuscript.

10. Page 6, para 2: aims/objectives are usually specified at the end of the Introduction

Amended in the revised manuscript.

11. Page 7, 2.1 title: acronym already contains the word “study”

Corrected in the revised manuscript.

12. Page 7, Objectives

- Objective 3: hyphenate patient-related; replace semicolon with comma

Corrected in the revised manuscript.

13. Page 7, Population

- line 4: insert “the” before “Cochlear”; “has made available” is incorrect; what is meant by the phrase “to address the trend for intervention....” - it implies intervention only occurs in children showing significant auditory performance benefits?

Corrected in the revised manuscript (page 8, paragraph II) to:

“The Cochlear P-IROS will enrol infants and children up to the age of 10 years, at the time of intervention. Children (who will be referred to as ‘patients’ here forward), may receive any brand of regulatory approved implantable hearing device including any type of cochlear, bone conduction, electroacoustic or other implantable hearing device. If required, the Cochlear P-IROS platform also permits the capture of data from patients implanted at the age of 10 years or above, to address the growing trend for intervention in older children with an acquired or progressive hearing loss. [34]. For this purpose, additional questionnaires appropriate for this age bracket have been included for completion by these individuals. Patients above the age of 10 years may also be entered into the Cochlear IROS, a corresponding registry platform available for adult patients.”

- line 8: Patient Administered Speech, Spatial, and Quality – should be “the SSQ for Children” (SSQ-C)
In Comment 8, the reviewer advises that standard questionnaire (for adults) should be abbreviated as SSQ and the parent’s version (for children) to be abbreviated as SSQ-P. Here the reviewer advises the parent’s version to be abbreviated as SSQ-C. We believe the appropriate abbreviation on line 8, is ‘SSQ’, as it is the adult questionnaire that will be administered to children of age 10 years or above at the time of implantation. The sentence has been amended in the revised manuscript to:

“To this end, additional questionnaires appropriate for this age bracket have been included for completion by these individuals.”

b. line 12: misspelt study

Corrected in the revised manuscript.

- line 15: “prior to first external device activation” is unclear (to readers not familiar with cochlear implant terminology)

This sentence was amended in the revised manuscript (page 9, paragraph II) to:

“...prior to the first time the hearing implant system is switched on by the fitting of the externally worn sound processor”

14. Page 8, Study period
a. line 1: the registry does not “collect” data

Amended in the revised manuscript.

b. line 2: insert “in the” prior to long term

Corrected in the revised manuscript.

c. line 3: insert “at” prior to any

Corrected in the revised manuscript.

d. line 5: the information in brackets is confusing

Amended in the revised manuscript.

e. line 8: comma required after Table 1

Corrected in the revised manuscript.

f. line 10: specify who determines 2 year follow-up is “compulsory”, and how is the family compelled?

The duration of compulsory follow-up was in line with the study protocol, which was developed by Georgina Sanderson, Josephine Wyss and Valerie Looi, who were involved with the design and development of the registry concept. As the registry is entirely investigator-driven, it is at the investigator’s discretion to motivate the family to participate in the study in the long-term.
To make the above points clearer, the paragraph has been amended in the revised manuscript (page 9, paragraph II) to:

“The Cochlear P-IROS registry will be available for clinics on a voluntary basis for monitoring the long term progress of patients and sub-groups of patients using hearing devices. The recruitment of study sites is ongoing; i.e. any implant clinic may join the Cochlear P-IROS at any time to gather data longitudinally for newly implanted and enrolled patients at their discretion. For patients enrolled, baseline registration is scheduled post-implant, which may ideally be at any time after surgery and prior to the first time the hearing implant system is switched on by the fitting of the externally worn sound processor. Typically, activation occurs at two to four weeks post-operation. As illustrated in Table 1, follow-up evaluations suggested may be recorded at six months, 12 months, 18 months, 24 months, and annually thereafter for up to five years, ideally in parallel to routine clinical visits. Patient follow-up for for a minimum of two years following initial enrolment in the registry is mandatory as per the study protocol, while further evaluation remains optional. As the registry is entirely investigator-driven, the clinician is responsible of counselling and ensuring that the patient and their family are sufficiently motivated to participate in the study long-term, while maintaining the decision for participation is entirely voluntary.”

15. Page 8-9, Ethical Considerations
   a. line 2: either delete “as” and comma after Helsinki, or insert comma before “as”;

Corrected in the revised manuscript.

b. “obligations” cannot be implemented; they are “met” or “fulfilled”

The wording has been corrected to “fulfilled” in the revised manuscript.

c. ISO 14155: the author must briefly explain what this ISO standard is for the reader (in addition to providing the reference); also, the relevant year for the standard should be included in the text; there is a 2011 standard so why is the 2003 standard referred to here?

Agree with the reviewer. This paragraph has been amended in the revised manuscript (page 9, paragraph III) to:

“The Cochlear P-IROS will be conducted according to the guidelines established in the Declaration of Helsinki (Fortaleza, 2013) [35]. All study investigators, as well as the sponsor are obliged to follow obligations outlined in the Declaration of Helsinki and the ISO 14155:2011, the international standard regarding good clinical practice for clinical investigations of medical devices for human subjects. The guidance includes the design, conduct, record and report including protection of privacy for all clinical investigations performed in human subjects [35, 36]. According to the standard, an investigator is defined as an individual member of the investigation site team designated and supervised by the principal investigator (referred to as the ‘chief investigator’ in the Cochlear P-IROS) at an investigation site, to perform critical procedures or to make important decisions relating to the clinical study. The sponsor is defined as the organisation taking responsibility and liability for the initiation or implementation of the clinical study. Cochlear Limited is the sponsor for the Cochlear P-IROS (refer to Table 3 for details).”

Furthermore, reference 36 has been updated to:
d. the reader needs to know what is meant exactly by the terms “Sponsor” (why the capital?) and "investigator"

In the revised manuscript (page 9, paragraph II), definitions of the terms have been included as follows:

“According to the standard, an investigator is defined as an individual member of the investigation site team designated and supervised by the principal investigator (referred to as the ‘chief investigator’ in the Cochlear P-IROS) at an investigation site, to perform critical procedures or to make important decisions relating to the clinical study. The sponsor is defined as the organisation taking responsibility and liability for the initiation or implementation of the clinical study. Cochlear Limited is the sponsor for the Cochlear P-IROS (refer to Table 3 for details).”

e. one or two examples of the obligations and how they will be fulfilled would be informative

We have referenced the link to the ISO 141455: 2011, which highlights in detail, examples of obligations to be fulfilled.

f. para 2, line 1: what does “favourable opinion” mean?

The phrase “favourable opinion” meant “has obtained approval”. However, we acknowledge that this may be unclear. In the revised manuscript the sentence was changed to:

“Presently, the Cochlear P-IROS has gained approval from the Human Research Ethics (HREC) Advisory Committees of Hear and Say (Brisbane, Australia), Peking University Third Hospital (Beijing, China) and the Istanbul University, Faculty of Medicine, (Istanbul, Turkey).”

g. para, line 2: inconsistent capitalization of ethics committee; again, meaning of “opinion” unclear; explain why requirement was waived – or do the authors mean these were jurisdictions in which approval was not required (as discussed on pg 8)

We acknowledge the term “favourable opinion” may be unclear, and an explanation was required as to why Ethics Committee Approval was not obtained/ or waived. Some study sites did not have an Ethics Committee at the time of registering with the study but have since formed a Human Research Ethics Committee, and are currently on the process of gaining ethical approval. As such, this paragraph in the revised manuscript (page 10, paragraph III) has been amended to:

“Presently, the Cochlear P-IROS has gained approval from the Human Research Ethics (HREC) Advisory Committees of Hear and Say (Brisbane, Australia), Peking University Third Hospital (Beijing, China) and the Istanbul University, Faculty of Medicine, (Istanbul, Turkey). In Turkey, specifically, one HREC approval from a clinic was acceptable, nationally. Therefore ethics approval was waived at the following centres; Marmara University Hospital (Istanbul, Turkey) and Osmangazi University Hospital (Eskisehir, Turkey). Ethics Committee Approval was not required at the following study sites, at the time of registration with the Cochlear P-IROS: First Affiliated University of Anhui Medical University (Hefei, China), Peking Union Medical College Hospital (Beijing, China), Saket City Hospital (New Delhi, India), Shruti ENT Hospital and Cochlear Implant Centre (Surat, India), Salemba Satu Medika (Jakarta, Indonesia) and Shandong Provincial Hospital (Jinan, China).”
h. para 2, line 7: capital required for “city”

Corrected in the revised manuscript.

16. Page 9, Consent
   a. vital that consent is “voluntary” so this should be specified

We acknowledge reviewer’s comment above, however, we must clarify that whilst participation in the study is voluntary, patient informed consent is compulsory for a patient to enrol in the Cochlear P-IROS.

   b. given that a Human Research Ethics Committee would usually require that the person obtaining consent was sufficiently informed about the project (actually this would usually need to be an investigator named on the ethics application) to ensure that the person giving consent understood the implications of participation the authors should explain how this issue will be dealt with or why it is not deemed necessary for an investigator to obtain consent

We acknowledge this comment, and have amended the section on the revised manuscript (page 10, paragraph IV) to include the role of the investigator, as follows:

“A Cochlear P-IROS Patient Information Sheet will be provided to each participating family in their local language by the authorised investigators (refer to Table 3) who are responsible for obtaining patient consent and explaining the purpose of the study, why they have been chosen to take part in the study, potential advantages and disadvantages of participation and what happens once the research study ends. Authorised investigators are also advised to review their local Patient Consent Forms to ensure that the information collected through the registry is covered under their current terms and conditions.”

   c. line 2: consent is required from the person with legal responsibility for the child, i.e., parent or guardian; the “caregiver” looks after the child (e.g. grandparent or nanny).

The sentence has been amended in the revised manuscript (page 10, paragraph IV) to:

“Patient informed consent is compulsory, and must be obtained in writing from a person with legal responsibility for the implanted child, i.e., parent, guardian or the caregiver who looks after the patient (e.g. grandparents or nanny), prior to the child’s enrolment in the registry.”

   d. line 4: explain what the decision should be independent of

The sentence has been amended in the revised manuscript (page 10, paragraph IV) to:

“This is intended to occur after the patient is implanted, when the decision for device type and configuration has been made to ensure the decision to participate in the registry remains independent of the type and brand of the device implanted.”

17. Page 9-10, Evaluation Measures
   a. para 2, line 1: the study does not “administer”; a “customized questionnaire” is a standard questionnaire which has been altered to fit a purpose; I don’t think this is what the authors mean
The word “administer” has been replaced with “includes” and “customised” has been replaced with “non-standardised”, in the revised manuscript.

b. para 2, line 3: delete space before “caregivers”; why “in particular”
Corrected in the revised manuscript.

c. para 2, line 4: “leading industry experts” requires explanation
In the revised manuscript this term has been amended to “published researchers in hearing implant field”.

d. para 2, line 6: change “into” to “in”; “questionnaires’ is plural - relevant variables were included in all questionnaires?
The word “into” was amended to “in” in the revised manuscript.
The relevant variables were incorporated in all non-standardised forms (more than one) that are being used to collect clinical and demographic data in the Cochlear P-IROS.

18. Page 10-11, Evaluation forms for the clinician

a. para 1, line 2: delete “specific” (and in line 3); “it was developed with the aim to collect” is wordy – more straightforward just to list the information which is collected.
Corrected in the revised manuscript.

b. para1, line 7: unclear what is meant by the term “and other comorbidities/syndromes” – assume “other comorbidities, and syndromes”
Corrected in the revised manuscript.

c. para 2, line 6: insert ‘the” before “patient’s”
Corrected in the revised manuscript.

d. para 3, line 1: hyphenate 10-points
Corrected in the revised manuscript.

e. para 3, line 4: delete “progressive”; cross cultural would usually be hyphenated
Corrected in the revised manuscript.

f. para 3, line 2: clarify is meant by “binaural hearing state and skills”
In the revised manuscript, this paragraph has been amended to:

“The CAP-II when compared to CAP, adds two additional higher-level auditory skill categories to the original scale. As such, the CAP-II is a more sensitive measure of the range of auditory skills in hearing impaired children, compared with the CAP. Hence the CAP-II was selected for use in the Cochlear P-IROS, to assess and compare the patient-related auditory benefits arising from the use of hearing implants in unilateral and bilateral configuration to the pre-operative listening condition [8,14].”

g. para 4 & 5: the form does not “capture” or “provide”; multiple rather inappropriate terms (hearing capability, hearing performance, are used here to describe what is simply sound detection or threshold measurement).

These words have been removed in the revised manuscript.

h. para 4, line 3: “detailed summary” is something of an oxymoron; in any case, it is simply the standard hearing thresholds

This term has been removed in the revised manuscript.

i. Para 4, line 4; delete colon; are these thresholds all “routinely measured” in all clinics

These thresholds “may” be routinely measured at clinics. The word “may” therefore has been inserted into the sentence in the revised manuscript.

j. Para 4, line 6-10: wordy and difficult to follow sentence – perhaps it is missing commas? Or a word after “or later”?

The sentence has been amended in the revised manuscript. Commas have been inserted and the words “post-implantation intervals” were inserted after “or later”.

k. Para 4, line11: delete “measurements”

Corrected in the revised manuscript.

19. Page 12, Evaluation forms for the parent
   a. para 1, line 3: delete “and”

Corrected in the revised manuscript.

b. para 2, line 3: “family wellbeing” or “the wellbeing of the family”

Corrected in the revised manuscript.
c. para 2, line 6: again, “industry experts” is unclear – experienced paediatric cochlear implant clinicians? experienced teachers-of-the deaf?

The term “industry experts” has been amended to “published researchers in the hearing implant field” in the revised manuscript.

d. para 2, line 8: the meaning of the term “four-week-recall is unclear here

The term “four-week-recall” has been removed in the revised manuscript.

e. para 4 & 5: as above, the acronyms around the SSQ are confusing

In the revised manuscript, SSQ-P has been used to distinguish the SSQ Parent’s Version questionnaire.

f. para 4, line 1: given the citation of reference 51, assume this is the SSQ for Children?; what is meant by “standardized”

The citation has been changed to:


g. para 5, final line: “William Noble (University of New England), the co-developer of the original SSQ” would be more informative; it is correct practice in scientific writing to include personal communications (including date) in the reference list (or a separate list, depending upon journal requirements) rather than in the text

Corrected in the revised manuscript (page 16, paragraph III) to:

“William Noble (University of New England, NSW, Australia), the co-developer of the original SSQ”.

20. Page 13, Data Management

a. line 3: insert “the” before “international”

Corrected in the revised manuscript.

b. line 8: has Hindi been left off this list?

The Cochlear P-IROS electronic web-based platform is not available in Hindi; however, all recipient case report forms have been translated to Hindi.

21. Page 14, Data Privacy

- the information about the registration of the adult registry does not seem relevant
We acknowledge this comment from the reviewer. Information about the registration of the adult registry has been removed from the revised manuscript.

- line 9: change “by the study” to “as part of the study”; should “questionnaires” be “evaluation forms”?

This line and paragraph have been amended in the revised manuscript (page 18, paragraph III) to:

“All clinics will have ownership rights for their site’s data and the flexibility to operate under their own local processes or regulations around data collection, privacy and maintenance of patient records. In Australia, all participating clinics must obtain ethical approval for the Cochlear P-IROS via a legislated Human Research Ethics Committee (HREC), who will assess the study’s protocol and documents for breach of privacy standards. Under the Australian Privacy Act, the data collected and stored by the Cochlear P-IROS registry is not classed as “personal information”, as a patient’s identity is not apparent, nor can it be reasonably ascertained from the information collected via the evaluation forms administered as part of the study. The Cochlear P-IROS registry is also listed on the Australia New Zealand Clinical Trials Registry, a public database for clinical research in humans [55].”

22. Page 15, Electronic Case Report Forms
   a. para 1, line 6: what are “patient side forms”

By “patient side forms” we meant “case report forms for patients”. Therefore the sentence has been changed in the revised manuscript (page 19, paragraph II) to:

“To date all of the case report forms for patients have been translated into 22 languages spoken in China, Japan, Korea, India, Middle East, Taiwan, Turkey, South Africa, South East Asia, Europe and South America.”

b. para 1, line 7: languages are not “applicable to” countries; extra space after India

Changed in the revised manuscript from “applicable to” to “spoken in”.

c. para 2, line 3: how does the registry “complement” routine follow-up?; the second half of this sentence is an incomplete phrase

In the revised manuscript, paragraph 2 has been amended and presented as a new section, “2.4.5 Data Entry” (pages 19-20), as follows:

“2.4.5 Data Entry

The Cochlear P-IROS registry may complement management of patients at clinics including their routine clinical follow up. A clinician or another approved person at the clinic could enter the data into the Cochlear P-IROS platform. Investigators participating in the registry will have access to real time patient data updates as well as automated summary reports through the use of their confidential system allocated password.

For investigators, automated email reminders notifying of follow-up times for individual patients will be sent two months before the evaluation is due. Should families wish to opt-out of the study, completion of an End of Study form is required.
For parents who have elected and agreed via signature on the patient informed consent form to respond directly on-line, an automated email reminder will be sent two months prior to the next follow-up time for their child and on the day of the scheduled follow-up. Should the parent not respond and complete the recommended evaluations for that time-point, the clinician will be subsequently notified by email. Equally, a notification will be sent to the clinician, once the parent has completed their data entry for that time-point.”

23. Page 15, Data Outputs
   a. line 2: what is meant by “recruitment age at implantation”?

   Changed in the revised manuscript (page 20, paragraph II) to:

   “Cochlear P-IROS web interface facilitates centre-specific automated summary reports on the number of patients’ recruited to-date, their age at implantation, number and types of implants and outcomes (i.e. mean CAP-II, mean SSQ, and mean CuHI-QoL).”

24. Page 16-17, Discussion
   a. para 2, line 2: what is meant by “who are presented to routine clinical practice”?

   The phrase means patients who are presented for “routine intervention”. Line 2 in the revised manuscript (page 22, paragraph I) has been amended in the revised manuscript, as follows:

   “The registry is designed to collect clinical, demographic, and patient-related outcomes data from newly implanted children who are presented for routine intervention.”

   b. para 2, line 3: “translated into” or “translated to”

   Changed in the revised manuscript from “translated in to” to “translated into”.

   c. para 2, line 5: grammatically incorrect

   Line 5 has been amended in the revised manuscript (page 22, paragraph II), as follows:

   “However, the authors acknowledge that there may be a risk of emotional bias for the baseline evaluation time point. This is because the evaluation takes place part way through the two-part fitting of an implantable hearing device. That is, after the surgical placement of the internal implant but before activation of sound, with the fitting of the external sound processor.”

   d. para 2, penultimate line: change “a” to “the”

   Changed in the revised manuscript from “a” to “the”.

   e. para 3, line 4: insert “the” before “development”

   Corrected in the revised manuscript.

   f. para 5, line 2: why “in the meantime”? – suggests the P-IROS will be relevant only for a period of time until there is local development of a registry?
The word “in the meantime” has been removed in the revised manuscript.

g. para 5, final line: “using .....longitudinally” is awkward

Changed in the revised manuscript from “longitudinally” to “in the long term”.

25. Page 25, Table 1
   a. “evaluation tools” used in table title, versus “electronic case report form” in column heading

The title of Table 1 (see page 31 in the revised manuscript) has been changed in the revised manuscript to:

“Cochlear P-IROS evaluation schedule illustrating electronic case report forms used against the recommended evaluation time-point”.

b. footnote 1: “resemble”

The word has been changed in the revised manuscript to “represent” instead.

26. Page 26, Table 2
   a. insufficient detail in title

The title of Table 2 has been changed in the revised manuscript to:

“A description of evaluation tools used in the Cochlear P-IROS for longitudinal assessment of speech perception, language development, auditory disability, educational placement, quality of life, device use and associated clinical and demographic covariates.”

27. Page 30, Table 3
   a. are there maximum numbers of permitted users for any role apart from Chief Investigator?

There is no upper limit for the number of permitted users for any other role apart from that of the Chief/Principal Investigator.

b. users who may obtain consent seems contradictory with statement in first line of section 2.1.6 row 8: who is the request made of?

Patient consent may obtained only by authorised investigators as outlined by Table 3. As such, section 2.1.6 (section 2.1.5, page 10, paragraph IV in the revised manuscript) has been amended to read:

“A Cochlear P-IROS Patient Information Sheet will be provided to each participating family in their local language by the authorised investigators (refer to Table 3) who are responsible for obtaining patient consent and explaining the purpose of the study, why they have been chosen to take part in the study, potential advantages and disadvantages of participation and what happens once the research study ends. Authorised investigators are also advised to review their local Patient Consent Forms to ensure that the information collected through the registry is covered under their current terms and conditions.”
28. Page 3, para 3
   a. line 3: both safety and clinical efficacy are referred to here, but the authors provide very limited detail regarding efficacy

In the revised manuscript, we have changed the term “efficacy” to “effectiveness”, which would be more relevant, as the purpose of the Cochlear P-IROS is to assess the benefit gained from implantable hearing solutions in a real-world setting.

In line with this change, we have inserted reference to the NICE evaluation by Bond and colleagues (2009) and have dedicated a paragraph to the UK National Audit of bilateral cochlear implantation in children (page 4, paragraph III of the revised manuscript), which was developed in response to recommendations by the authors.

The NICE review by Bond and colleagues (2009) examined the body of literature on effectiveness of cochlear implants and reported that the available evidence was heterogeneous, and were not supported by large-scale prospective observational studies. Therefore, we have not presented the results from these studies in detail as this would deviate from the purpose of this manuscript, which is to describe the concept, design and methodology of the Cochlear P-IROS registry.

29. Page 4, para 3
   a. this paragraph lacks detail; the outcomes of the UK audit are not described sufficiently; some gaps in the data collected are referred to, but the importance of this type of data is not explained; the final sentence is to sudden a change from the lack of broad outcomes data to the lack of any outcomes data for subgroups; additional explanatory sentences are required if this paragraph is to contribute to the understanding of the reader

In the revised manuscript, two paragraphs in the revised manuscript (see pages 5-6) have been dedicated to discussing the NICE review by Bond and colleagues (2009) and the UK national audit of paediatric bilateral cochlear implantation, in detail, as follows:

“A recent National Institute of Health and Clinical Excellence (NICE) health technology appraisal into the clinical and cost effectiveness of cochlear implants in adults and children, reviewed the body of evidence on the effectiveness of cochlear implants with the consideration of expert opinion. The final appraisal document was published in February 2009 highlighting recommendations for clinical practice in the UK [13]. NICE recommendations included the provision of simultaneous bilateral CI to children born deaf, adventitiously deaf, or those newly diagnosed with severe to profound bilateral hearing impairment. The report also highlighted the deficiencies in the available evidence, including the difficulties in making comparisons due to heterogeneity in measures and protocols, the absence of sufficiently long term observation periods, the absence of benefits observed in daily circumstances and in the quality of life for the implanted child. To this end, the authors of the NICE report noted that more large scale studies are needed, that prospectively follow-up patients for longer time periods, using standard measures for outcomes, full information of known covariates of post-implantation speech- and quality of life outcomes.

In response, a national audit was set up through collaboration of the cochlear implant programmes throughout the United Kingdom (UK). The UK national audit of paediatric bilateral cochlear implantation, which began in January 2010 and ended in December 2012, is one of the largest non-randomised prospective, observational studies exploring hearing outcomes in children.
with a permanent sensorinerual hearing loss treated with cochlear implants [14]. The data collected included: listening, speech recognition, speech production, sound localisation, acquisition of vocabulary, parental perception and information relating to the implant surgery. Although the report from the audit showed encouraging results for bilaterally implanted children when considering hearing gains as well as acceptably low rates of adverse events, the study did not measure quality of life or humanistic measures such as access to services, educational placement, literacy, numeracy or social inclusion, which are of interest to payers and policy makers.”

30. Page 4, para 4
   a. this paragraph needs more coherence and depth the first few sentences skim over language, literacy and education, and then moves to habilitation; more detail is required to link these ideas together or the authors should consider if it is worthwhile commenting on these areas.

This paragraph was removed in the revised manuscript as the authors felt that it did not add value to the discussion.

   b. lines 10-11: why these measures and not other measures? It would be valuable for the reader to have an explanation of the choice of measures
   As per above.

31. Page 7, Objectives
   a. Some reference to the types of benefits here would be useful
   b. Objective 2: what is meant here by statistically valid? how is this validity to be achieved?
   c. Objective 3: explain what is meant here by patient related benefits (as distinct from “benefit” in objective 1)

The three objectives have been revised as follows:

“a) To evaluate the longitudinal improvements in auditory performance with implantable hearing devices in children using standardised questionnaires

b) To provide statistically significant data to support patient management decisions at the clinical, regulatory, payer and policy level.

c) To compare the patient related or humanistic benefits such as educational attainment, quality of life and patient satisfaction resulting from use of hearing implants in unilateral, bilateral and bimodal configurations.”

32. Page 9, Consent
   a. line 1: it should be made clearer that obtaining consent is the responsibility of the local clinician working directly with the child; it would be helpful to have a section earlier in the paper which describes the roles of those involved (clinician, sponsor, investigator, global administrators) to benefit the reader’s comprehension.

It would be the responsibility of the local Cochlear P-IROS investigator to obtain patient consent. This is further explained in Section 2.4.2 User Access (page 16, paragraph III of the revised manuscript).
33. Page 9-10, Evaluation Measures
   a. para 1: the second sentence is too long and is difficult to read. The points need to be broken up into a number of sentence and the relevance of the points made clear.

In the revised manuscript, the paragraph has been amended to:

“The Cochlear P-IROS registry addresses the stated need for representative and uniform data concerning the clinical and humanistic benefits of children using implantable hearing devices. Given the age at the time of implantation of patients to be recruited, spans from less than 12 months through to 10 years, careful consideration was given to the selection of evaluation measures and their administration. Specific factors considered included: achieving a balance between subjective and objective measures, assessments of auditory performance that catered for the development as well as the listening and communication skills of the children, suitable for administration via investigator and parental proxies and suitable for translation and cultural adaptation [37].”

34. Page 10-11, Evaluation forms for the clinician
   a. para 1, line 6: “physical and mental handicap” are old-fashioned terms which should no longer be used.

In the revised manuscript, the term has been revised to “physical and mental impairment”.

35. Page 15, Data Monitoring
   a. Random spot checks may be undertaken? The authors should specify is they will occur or not? If they are to occur, some indication of frequency is required so the reader has an idea of the likely reliability of the data to be collected.

We acknowledge this comment from the referee, as such have amended this section in the revised manuscript (pages 20) to:

“There will be no routine onsite monitoring undertaken of the data entered. Participating clinics are not asked to store paper documents as source documents for data entered online, hence no cross checks between data entered and source data is possible. Online random spot-checks will be conducted on five percent of of the data entered at every quarter year at each participating Cochlear P-IROS clinic.

The platform has been designed with inherent checks of response fields filled on eCRFs and automatically pending the response types. The vast majority of responses on all forms are multiple choice, check box, radio buttons, or pull down response options to facilitate entry and reduce entry error with minimal free text fields. Furthermore, the e-platform operating the Cochlear P-IROS contains an inherent audit trail to trace all amendments made with each form, the investigator making the change and when changes are made. To avoid unnecessary changes, eCRFs are automatically locked upon access and data entry into the corresponding form at a subsequent assessment interval. Manual unlocking of these forms can be requested by the clinician to the Cochlear P-IROS global administrator.”

36. Page 16-17, Discussion
a. The discussion primarily repeats information provided previously. Some discussion of anticipated numbers of clinics, countries, and patients, and predicted timelines would add depth. As would more links between the actual data collected and the potential uses of this data.

The Cochlear P-IROS registry is an on-going study, and will be open for any clinic wanting to join the study from anywhere in the world. Therefore, we believe it is not appropriate to comment on the anticipated number of clinics, countries, who will join the study over a particular period of time. The time taken for a hearing implant clinic to register with the Cochlear P-IROS registry varies with each site, depending on the requirement of ethical committee approval and other constraints, such as, training required for investigators, time involved with obtaining ethics approval etc. Thus, the recruitment of study sites for the Cochlear P-IROS will be a staggered, rather than a stepwise process. The names of clinics currently participating in the Cochlear P-IROS registry, and their corresponding city/country is highlighted in “Section 2.1.4. Ethical Considerations”.

The revised manuscript includes a new section (Section 2.4.8, page 20, paragraph IV) which discusses the proposed statistical plan, anticipated number of patients and the limitations with regard to power calculations.

As per reviewer suggestions, the discussions section of the revised manuscript (pages 22-23) includes four new/amended paragraphs as follows:

“The registry addresses industry-wide concerns around a lack of language-independent, standardised outcome measures for paediatric recipients of implantable hearing devices. To date, the wide variety of language-based, auditory-related outcome measures utilised in this patient population hinders effective meta-analysis [19]. Through the development of a new quality of life instrument, the CuHI-QoL, and the use of a range of standardised outcome measures (SSQ-P and CAP-II), Cochlear P-IROS aims to provide a homogeneous set of data for the comparison of benefit of implantable hearing devices for considerably larger numbers of patients that are more representative of the treatment group at large.

The advantages of using questionnaires for subjective assessment is that it allows for a view to the benefits obtained post-implantation through the patient’s eyes or in the eyes of their parents in the real world, specifically demonstrating hearing benefits and additional hearing-related benefits. A further advantage, not specifically addressed in these papers is the ability to use validated translations of such questionnaires for collection and collation of qualitative patient-reported benefits across different languages, both pre- and post-implant, longitudinally [19],[9],[39]. Comparison of auditory benefit data assessed and reported using local speech audiometry measures is both challenging, in view of the differences in materials and methods, and not recommended where equivalency in materials and measurements is unknown. The Cochlear P-IROS approach could foster not only consistency of data collected but also encourage the reporting of consistent evaluation methods. This therefore makes it one step closer to the possible availability of published meta-analyses of collective standardised outcomes from patients using implantable hearing devices, which could potentially be used by regulators, health technology assessors and health service provision decision makers, as needed.

The Cochlear P-IROS may preclude the need for large local capital investment to design and implement a multi-centre web-based registry. The study therefore provides the grounds for various hearing implant clinics to develop and own their own set of patient profiles, outcomes data and accordingly pursue their own research interests which may lead to scientific publications. Collaborative, multi-centre publications are especially encouraged to combine data collection efforts
from different investigators, which may strengthen the potential power of the data reported and the interpretation of the conclusions drawn. The Cochlear P-IROS registry, therefore, may provide a cost-effective method for interested parties to establish and invest in the outcomes of patients using implantable hearing devices in the long term in a clinically feasible, broadly consistent and practically sustainable manner.”

37. Page 16-17, Discussion
   a. para 4: clarify what is meant by ‘statistically validated evidence”; statistical analysis has not been discussed prior to this point.

This phrase has been removed from the Discussion section of the revised manuscript. Cochlear P-IROS has elaborate plan for statistical analysis around the study hypotheses, which may be provided to investigators on request. In the revised manuscript, a new section has been inserted to discuss statistical analysis (Section 2.4.8, page 20, paragraph IV):

“A proposal for the statistical methods and data analysis plan for the assessment of Cochlear P-IROS hypotheses created by a consultant statistician is available as a separate report upon investigator’s request. Prospective, longitudinal studies, such as the Cochlear P-IROS, are especially powerful due to the repeated measures on participants; as such, relatively low numbers of observations may be adequate for most tests. A sample size of n=50 was considered sufficiently sensitive to measure implant treatment effects assessed via the CAP-II, based on published literature. Current publications on paediatric cochlear implants lack sufficient detail on the SSQ-P or SSQ to generate an accurate power calculation for the sample sizes needed to find significant differences or changes; whilst CuHI-Qol is a completely novel outcome measure and, therefore, a sample size calculation is not currently possible for that outcome. Moreover, it is not possible to determine the actual number of patients that will be registered with the Cochlear P-IROS over time, as participation in the Cochlear P-IROS is voluntary for the clinic and the parent/caregiver/patient. Additionally, the parent/caregiver/patient may also cease to participate in the registry at any time. Nevertheless, the design of the database does not pose any constraint on the number of patients that may be enrolled overtime, as it was developed with the aim to sustain data collection in the long-term with the intent of large-scale enrolment of patients in the range from 100 to 1000 on an annual basis.”

   b. para 4, final two sentences: a list of points; wording and meaning could be improved by putting relevant points together. eg. “or” suggests implantable hearing solution or bimodal – even though bimodal also includes an implantable solution; first sentence refers to unilateral versus CI+HA and second sentence refers to unilateral versus CI+CI – why not have these two together in one sentence. Particularly difficult to understand the point of the second half of second sentence.

These two sentences have been removed in the revised manuscript.

38. Page 26, Table 2
   a. column 4: far too much text in this column to make this a useful table

Table 2 has been amended in the revised manuscript (pages 32-34) to a more user-friendly format.
b. typos/errors in the text eg. pot-surgery; educational placement, educational placement of child

As per above.

c. information often repetitive with manuscript text eg. frequencies for hearing testing, use of objective tests for infants

As per above.

39. Page 30, Table 3
a. there is no mention in the text of some of these users, so it is not meaningful to have them simply listed in the table eg. cochlear country project leader, study nurse; where is the “clinician” referred to in the text column 2 contains a lot of repeated text; if the information was presented differently (eg. a couple of columns to replace column 2) the amount of text would be reduced and the accessibility of the information would be increased

The format of Table 3 has been amended in the revised manuscript (page 35) as per reviewer recommendations, and explained in Section 2.4.2 (page 18, paragraph II).

Kind regards,

Ms. Thathya Ariyaratne