

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation: a cross-sectional retrospective study
AUTHORS	Ramakers, Geerte; van Zanten, Gijsbert; Thomeer, Hans; Stokroos, Robert; Heymans, Martijn; Stegeman, Inge

VERSION 1 – REVIEW

REVIEWER	Angel Ramos-Macias Las Palmas University, SPAIN
REVIEW RETURNED	04-Jan-2018

GENERAL COMMENTS	<p>The authors present a good hypothesis, but its development presents a series of elements that must be clarified before their final publication.</p> <ol style="list-style-type: none"> 1. The indication for a cochlear implant in cases of profound hearing loss should be differentiated from those patients whose priority is the treatment of tinnitus, as it is a different situation to be evaluated and to differentiate in the prognosis. 2. The duration of tinnitus was missing in 45% and severity of tinnitus was missing in 28% , it is not clear if the authors exclude these patients in the final evaluation 3. Not data related to programming method, adjustment and strategy used in patients or rehabilitation data are presented. All these factors have been considered as important factors related to prognosis. <p>I recommend to include these comments before publication.</p>
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REVIEWER	Elisabeth Wallhausser-Franke Senior Researcher Medical Faculty Mannheim Heidelberg University Otorhinolaryngology Phoniatrics and Audiology Germany
REVIEW RETURNED	11-Jan-2018

GENERAL COMMENTS	<p>Moderate Revision</p> <p>In a retrospective study, the authors aim to identify predictors for future complete tinnitus remission (= recovery) following unilateral CI implantation in a sample of 87 with severe to profound hearing impairment in both ears.</p> <p>Lower preoperative CVC score, unilateral localization of tinnitus (ipsi- or contralateral to CI-ear?) and larger deterioration of residual</p>
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	<p>hearing at 250Hz (CI-ear pre- vs post-surgery?) were significant predictors of recovery.</p> <p>This is an interesting and timely approach but validity of the model should have been checked in a second independent sample. Furthermore, significance of own findings for counselling of prospective CI patients with tinnitus should be discussed in more detail.</p> <p>According to Table 3, 2 predictors reach statistical significance ($p < 0.05$), but their ORs are close to 1, while a third predictor (bilaterality of tinnitus) does not reach statistical significance, but has an OR which implies a potentially clinical significant effect (OR 0.412). Please explain the relevance of this finding for the clinician / patient.</p> <p>Appropriateness of statistical procedures should be checked by a statistician.</p> <p>It would be helpful to the reader to explain the consequences of the TRIPOD statement and Akaike's information criterion and why this criterion was used instead of others.</p> <p>Esp. choice of predictors for final model based on p-values and not on OR or a combination of both. Is this the best choice? OR are close to 1 for two (preoperative CVC, Difference 250Hz threshold; Table2) of the 3 final predictors, while other ORs deviate much more from 1 indicating higher potential relevance although p values are higher.</p> <p>Specify tinnitus recovery: Does recovery mean absence of the tinnitus while the CI is switched on (which appears to be more common) or also when CI is not in use?</p> <p>More information on the self-developed questionnaire would be helpful, esp. which potential predictors were interviewed, which information was dropped and why it was dropped.</p> <p>Table 2/3: It should be stated in the legend that ORs > 1 are in favor of tinnitus recovery.</p> <p>It should be stated more clearly at the beginning that deterioration at 250Hz means deterioration of residual hearing in the CI-ear after surgery.</p> <p>How does deterioration of residual hearing relate to the interval between surgery and conducting of the survey? In recent years surgery became less invasive, therefore it can be expected that more recent CI-implantation leads to more residual low-frequency hearing. In line, the time between surgery and the survey is longer (median 5 years) for the group with recovery as opposed to the group without recovery (median 3 years), although follow-up duration in itself does not reach statistical significance. Together, these factors could suggest that it takes time until the tinnitus vanishes which is in line with the unpublished assumptions of some clinicians and patients.</p> <p>Report percentage of those with worsening of the tinnitus and percentage of those who developed tinnitus after surgery. It would be helpful to know if you found predictors for this group.</p>
REVIEWER	<p>Agnieszka J. Szczepak Department of ORL, Head and Neck Surgery Charite University Hospital</p>

	Berlin, Germany
REVIEW RETURNED	16-Jan-2018

GENERAL COMMENTS	<p>The authors of „The development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation” posed an important and timely question and offered a method to address it. Creation and validation of a prediction model could prove to be a very important tool in dealing with CI candidates who are also affected by tinnitus. The paper is written very clearly and reads well.</p> <p>There are; however, few minor points that should be addressed to make this paper even better.</p> <ol style="list-style-type: none"> 1. In the very first sentence of the Introduction, the authors cite a recent systematic review of McCormack and colleagues to support their statement about tinnitus prevalence. However, that particular review examined what and how was reported world-wide in terms of tinnitus prevalence. The prevalence range the authors refer to (5 – 49%) is not a real tinnitus prevalence but rather, it reflects the inclusion and exclusion criteria used by individual authors of publications included in the review. Please revise. 2. The mysterious “self-developed questionnaire”. You refer to it eight times in the text but you do not show what it actually is. Please provide the questionnaire in form of an additional table and explain how it was used. 3. Page 9 line5 “between de predicted”???? Please correct. 4. Table 2 – please explain the meaning of “REF”. Why are some significances presented in bold font? Please explain. 5. Page 13 line 3 – please use quotation marks for the names of predictors. 6. Page 17 line 15 – how do you know that the loss of residual hearing was always solely due to the traumatic insertion of the electrode? 7. Page 17 line 39 – “advized” should be spelled “advised”.
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REVIEWER	Michael Schlussek University of Oxford, UK
REVIEW RETURNED	04-Mar-2018

GENERAL COMMENTS	<p>This is a well conducted study on the development and internal validation of a multivariable prognostic model for tinnitus recovery after unilateral cochlear implantation. The authors performed a careful work, and the article has the potential to fulfil a gap in the literature. However, a few aspects deserve further clarification, to make the manuscript more complete and transparent.</p> <p>The main issue is related to the final model presentation. In order to allow its application, any prognostic model should have its intercept and individual predictors’ regression coefficients (i.e. the actual betas, instead of the odds ratios) reported. Otherwise, it is not possible to use the model for estimating an individual’s probability of developing the outcome of interest. This might be useful, for example, when trying to externally validate a model or when comparing the performance of two different models. In this sense, I would strongly suggest that the authors update Table 3 accordingly.</p> <p>Additional points:</p> <p>Please define CI after the first time “cochlear implantation” appears in the text and then consistently use the abbreviation throughout the text.</p> <p>Under the section “Study design and participants”, I believe the authors meant that they used a “self-reported” instead of “self-</p>
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	<p>developed" questionnaire.</p> <p>Please provide more details about the CVC test (e.g. what does a lower percentage corrected score means? worse or better hearing performance?). Consider adding a reference for the article reporting the test development and/or validation study.</p> <p>Please state the rationale for producing fifteen imputed datasets.</p> <p>The authors state that in case of multicollinearity, which was observed for two of the candidate predictors significantly associated with the outcome in the univariable models, "the variable with the best predictive value" would be selected. However, it is not clear what the authors mean by that (i.e. the variable with the higher OR, smaller p-value, higher AUC, etc.)</p> <p>Regarding the results of the univariable and multivariable regression models in Tables 2 and 3, please describe the method used for pooling the estimates from the imputed datasets.</p> <p>The number of patients included in each analysis should be presented in all tables. In Table 2, it is assumed that imputed data allowed the inclusion of all 87 patients, but this is not the case for Table 3 (which also displays the results of the sensitivity analysis using the complete cases population).</p> <p>Figure 3 is supposed to present the calibration curve, but it actually displays the frequencies of observed outcomes for tenths of predicted probability in one of the imputed datasets. There is nothing conceptually wrong with that (in this case, please update the description accordingly), but a calibration plot created by regressing the outcome on the predicted probability, using a locally weighted scatter plot smoother (lowess), and plotting the resulting smoothed line against the line of perfect prediction would be more informative.</p> <p>The calibration plot could also be supplemented with estimates of the calibration slope and intercept (for a prognostic model that perfectly predicts the outcome, 1 and zero would be the estimated values for slope and intercept, respectively). Finally, if the authors decide to present calibration plots with calibration lines, they could present these in a single figure overlaying the calibration curves from each imputed dataset.</p> <p>Finally, in the discussion and conclusion (both in the text and abstract), the authors refer to their own study as a pilot study. However, this is not how the study is characterised both in the title and methods. An actual pilot study aims to provide further information for the conduction of an already planned, larger, well powered study. The authors acknowledge the limitations and adequately discuss their implications on the findings of this study. There is no reason to declare it a pilot study, if that was not the original aim of their research. Otherwise, please adjust the title and update the methods section accordingly.</p>
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VERSION 1 – AUTHOR RESPONSE

Comments to the reviewers

Reviewer: 1

Reviewer Name: Angel Ramos-Macias

Institution and Country: Las Palmas University, SPAIN Competing Interests: none

The authors present a good hypothesis, but its development presents a series of elements that must be clarified before their final publication.

1. The indication for a cochlear implant in cases of profound hearing loss should be differentiated from those patients whose priority is the treatment of tinnitus, as it is a different situation to be evaluated and to differentiate in the prognosis.

Answer:

We fully agree with the reviewer that the indications for cochlear implantation (profound hearing loss or tinnitus) are different situations with corresponding evaluation and prognosis. In the Netherlands, a cochlear implant is only reimbursed for the indication profound hearing loss. In all patients from our study, the indication for cochlear implantation was profound hearing loss. The presence or severity of tinnitus were not indications for cochlear implantation. We clarified this in the revised version of our manuscript.

“All patients received a CI because of severe to profound hearing loss and the presence or severity of tinnitus were not part of the indication criteria.” (page 10)

2. The duration of tinnitus was missing in 45% and severity of tinnitus was missing in 28% , it is not clear if the authors exclude these patients in the final evaluation

Answer:

We used multiple imputation for all predictor variables with missing data, including duration and severity of tinnitus. In the final model we show the pooled results of the 15 imputed datasets, and also a sensitivity analysis of the results in the original dataset with missing data.

As stated in the method ‘missing data’ section:

“The Little’s missing Therefore, multiple imputation was performed for all of above mentioned predictor variables with missing data.....are also reported.” (page 8)

3. Not data related to programming method, adjustment and strategy used in patients or rehabilitation data are presented. All these factors have been considered as important factors related to prognosis.

I recommend to include these comments before publication.

Answer:

We thank the reviewer for these suggestions. We added this to the limitation section of the discussion.

“Although we investigated a long list of potential predictors, it is likely that some potentially relevant factors were missed or not available in the current study, data related to coding strategies and rehabilitation for example.” (page 16)

Reviewer: 2

Reviewer Name: Elisabeth Wallhausser-Franke Institution and Country: Senior Researcher, Medical Faculty Mannheim, Heidelberg University, Otorhinolaryngology, Phoniatrics and Audiology, Germany
Competing Interests: None

Moderate Revision

In a retrospective study, the authors aim to identify predictors for future complete tinnitus remission (= recovery) following unilateral CI implantation in a sample of 87 with severe to profound hearing impairment in both ears.

Lower preoperative CVC score, unilateral localization of tinnitus (ipsi- or contralateral to CI-ear?) and larger deterioration of residual hearing at 250Hz (CI-ear pre- vs post-surgery?) were significant predictors of recovery.

This is an interesting and timely approach but validity of the model should have been checked in a second independent sample.

Answer:

We agree with the reviewer that external validation is an important part in the development of a clinically useful prediction model. In the current study however, we were not able to perform an external validation in a second independent dataset with similar data. We think that external validation is indeed important in future studies, and therefore we recommend this in the discussion section:

“In order to increase the performance of the current prediction model, we would recommend to conduct a larger prospective study to develop and internally and externally validate a prediction model for tinnitus recovery following unilateral cochlear implantation.” (page 18)

Furthermore, significance of own findings for counselling of prospective CI patients with tinnitus should be discussed in more detail.

Answer:

We thank the reviewer for this suggestion. However, because this is the first study to develop a prediction model regarding tinnitus recovery following cochlear implantation, and the AUC is lower than 0.75, we think the performance of this model is too low for direct clinical implementation of this model. Therefore we rather not give recommendation for counseling of future CI patients according to this study only.

According to Table 3, 2 predictors reach statistical significance ($p < 0.05$), but their ORs are close to 1, while a third predictor (bilaterality of tinnitus) does not reach statistical significance, but has an OR which implies a potentially clinical significant effect (OR 0.412). Please explain the relevance of this finding for the clinician / patient.

Answer:

This difference is due to the measurement scale of the predictors. For a dichotomous predictor (such as bilaterality of tinnitus), the OR of 0.412 means a 0.412 times higher odds (i.e. lower risk) for a patient with bilateral tinnitus compared to a patient with unilateral tinnitus, i.e. comparing two groups. For a continuous variable the OR can be interpreted as the ‘ratio per unit’. For example, the OR of ‘difference in audiometry on 250 Hz’ is 1.024. This means that a patient with an increase of 1 dB on ‘difference in hearing threshold after surgery’ has a 1.024 times higher ‘odds’ on recovery compared to a patient with 0 dB difference. But when the difference is way more than 1 dB, for example 20 dB this difference in odds becomes much larger and thus also more relevant.

Appropriateness of statistical procedures should be checked by a statistician.

Answer:

One of the authors (Martijn W. Heymans) is statistician. He advised on statistical procedures, checked procedures and critically revised the manuscript.

It would be helpful to the reader to explain the consequences of the TRIPOD statement and Akaike’s information criterion and why this criterion was used instead of others.

Answer:

As stated in the method section, the TRIPOD stands for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis. This is just a guideline for authors on how to transparently report and conduct a prediction model study. Akaike’s information criterion is the same as using a p-value of 0.157 for variable selection. This p-values is recommended according to the TRIPOD statement to prevent unwanted selection of predictors in models and to develop models with a better clinical performance.

Esp. choice of predictors for final model based on p-values and not on OR or a combination of both. Is this the best choice? OR are close to 1 for two (preoperative CVC, Difference 250Hz threshold; Table2) of the 3 final predictors, while other ORs deviate much more from 1 indicating higher potential relevance although p values are higher.

Answer:

As advised by the TRIPOD statement, we chose a predictor selection strategy on forehand. We chose to select predictors, based on the Akaike's criterion ($p < 0.157$). As mentioned before, the difference in size of OR is because of the difference in measurement scale between dichotomous and continuous variables and not due to the difference in predictive ability.

Specify tinnitus recovery: Does recovery mean absence of the tinnitus while the CI is switched on (which appears to be more common) or also when CI is not in use?

Answer:

We thank the reviewer for this question and clarified this in the text:

"Tinnitus recovery was defined as the presence of tinnitus preoperatively and complete absence of tinnitus postoperatively at the moment of completing the questionnaire. Complete absence was defined as absence of tinnitus in all situations: when the CI was switched 'on' and 'off'." (page 6)

More information on the self-developed questionnaire would be helpful, esp. which potential predictors were interviewed, which information was dropped and why it was dropped.

Answer:

We thank the reviewer for this suggestion. We translated our questionnaire and provided the questionnaire as an appendix in the revised version of our paper.

Table 2/3: It should be stated in the legend that ORs >1 are in favor of tinnitus recovery.

Answer:

We thank the reviewer for this suggestion and added this information in the legends of Table 2 and 3.

It should be stated more clearly at the beginning that deterioration at 250Hz means deterioration of residual hearing in the CI-ear after surgery.

Answer:

We clarified this in the method section:

"Deterioration of hearing was defined as difference in hearing threshold after surgery per frequency in the operated ear (pure tone threshold after surgery minus threshold before surgery)." (page 7)

How does deterioration of residual hearing relate to the interval between surgery and conducting of the survey?

Answer:

We thank the reviewer for this question. We used the hearing thresholds, measured shortly after surgery. So this was not related to the moment of completing the survey (follow up duration). We added the information that this was measured shortly after surgery:

"Deterioration of hearing was defined as difference in hearing threshold after surgery per frequency in the operated ear (pure tone threshold shortly after surgery minus threshold shortly before surgery)." (page 7)

In recent years surgery became less invasive, therefore it can be expected that more recent CI-implantation leads to more residual low-frequency hearing. In line, the time between surgery and the survey is longer (median 5 years) for the group with recovery as opposed to the group without recovery (median 3 years), although follow-up duration in itself does not reach statistical significance. Together, these factors could suggest that it takes time until the tinnitus vanishes which is in line with the unpublished assumptions of some clinicians and patients.

Report percentage of those with worsening of the tinnitus and percentage of those who developed tinnitus after surgery. It would be helpful to know if you found predictors for this group.

Answer:

This article focuses on the 87 patients with preoperative tinnitus. We added the information of the percentage of patients whose tinnitus worsened after surgery. As this is a small group, we were not able to develop a prediction model for worsening of tinnitus. The patients without preoperative tinnitus

are not in the scope of the current article. We will discuss induction percentages (and other findings) in another article (we refer to in the method section).

“Worsening of tinnitus in the years after surgery was reported by 9 (10%) patient”. (page 10)

“The 10-year results concerning prevalence rates of tinnitus in our center are previously reported using the same database as the current study¹⁴.” (page 5)

Reviewer: 3

Reviewer Name: Agnieszka J. Szczepiek

Institution and Country: Department of ORL, Head and Neck Surgery, Charite University Hospital,

Berlin, Germany Competing Interests: None declared

The authors of „The development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation” posed an important and timely question and offered a method to address it. Creation and validation of a prediction model could prove to be a very important tool in dealing with CI candidates who are also affected by tinnitus. The paper is written very clearly and reads well.

There are; however, few minor points that should be addressed to make this paper even better.

1. In the very first sentence of the Introduction, the authors cite a recent systematic review of McCormack and colleagues to support their statement about tinnitus prevalence. However, that particular review examined what and how was reported world-wide in terms of tinnitus prevalence. The prevalence range the authors refer to (5 – 49%) is not a real tinnitus prevalence but rather, it reflects the inclusion and exclusion criteria used by individual authors of publications included in the review. Please revise.

Answer:

We thank the reviewer for this suggestion and revised the text.

“Tinnitus is a common problem, but uncertainty exist about its true prevalence. Estimates range between 5% and 43%.¹” (page 4)

2. The mysterious “self-developed questionnaire”. You refer to it eight times in the text but you do not show what it actually is. Please provide the questionnaire in form of an additional table and explain how it was used.

Answer:

We thank the reviewer for this suggestion. We agree that this was not transparently done in the previous version of our manuscript. We translated our questionnaire and provided this questionnaire as an appendix in the revised version of our paper.

3. Page 9 line5 “between de predicted”???? Please correct.

Answer:

Changed accordingly to “the”.

4. Table 2 – please explain the meaning of “REF”. Why are some significances presented in bold font? Please explain.

Answer:

In the revised version, we explained both features in the legend of Table 2.

5. Page 13 line 3 – please use quotation marks for the names of predictors.

Answer:

Changed accordingly.

6. Page 17 line 15 – how do you know that the loss of residual hearing was always solely due to the traumatic insertion of the electrode?

Answer:

We thank the reviewer for this question and realized that we do not know this for sure. Therefore, we revised this sentence:

“Our study showed that deterioration of residual hearing at 250 Hz, most probably due to the traumatic insertion of the electrode into the cochlea, is positive for tinnitus recovery after surgery.” (page 17)

7. Page 17 line 39 – “advized” should be spelled “advised”.

Answer:

Changed accordingly.

Reviewer: 4

Reviewer Name: Michael Schluskel

Institution and Country: University of Oxford, UK Competing Interests: None declared

This is a well conducted study on the development and internal validation of a multivariable prognostic model for tinnitus recovery after unilateral cochlear implantation. The authors performed a careful work, and the article has the potential to fulfil a gap in the literature. However, a few aspects deserve further clarification, to make the manuscript more complete and transparent.

The main issue is related to the final model presentation. In order to allow its application, any prognostic model should have its intercept and individual predictors' regression coefficients (i.e. the actual betas, instead of the odds ratios) reported. Otherwise, it is not possible to use the model for estimating an individual's probability of developing the outcome of interest. This might be useful, for example, when trying to externally validate a model or when comparing the performance of two different models. In this sense, I would strongly suggest that the authors update Table 3 accordingly.

Answer:

We thank the reviewer for this suggestion. We added the linear predictor rule in the legend of the table. We chose to report this prediction rule with the beta's and intercept instead of extra columns in the table, for the readability of the table.

“Prediction rule of the pooled dataset after internal validation: linear predictor = 0,247- (0,017*preoperative CVC score)-(0,691*bilateral tinnitus)+(0,019*difference in hearing threshold at 250 Hz)” (Table 3)

Additional points:

Please define CI after the first time “cochlear implantation” appears in the text and then consistently use the abbreviation throughout the text.

Answer:

In this manuscript we used the abbreviation CI for cochlear implant instead of cochlear implantation.

Under the section “Study design and participants”, I believe the authors meant that they used a “self-reported” instead of “self-developed” questionnaire.

Answer:

We mean self-developed. We translated our questionnaire and provided this questionnaire as an appendix in the revised version of our paper.

Please provide more details about the CVC test (e.g. what does a lower percentage corrected score means? worse or better hearing performance?). Consider adding a reference for the article reporting the test development and/or validation study.

Answer:

We thank the reviewer for this suggestion and added this information:

“the Consonant-Vowel-Consonant (CVC) test, which results in a percentage correct score (a higher score reflects a better hearing performance)” (page 7)

Please state the rationale for producing fifteen imputed datasets.

Answer:

We thank the reviewer for this suggestion. As a general rule of thumb you can use the total percentage of missing observations for the numbers of imputed dataset. The total percentage of missing observations was about 15% and therefore, we used 15 imputed dataset.

“Fifteen multiple imputed datasets were created, as the total percentage of missing observations was about 15%.”(page 8)

The authors state that in case of multicollinearity, which was observed for two of the candidate predictors significantly associated with the outcome in the univariable models, “the variable with the best predictive value” would be selected. However, it is not clear what the authors mean by that (i.e. the variable with the higher OR, smaller p-value, higher AUC, etc.)

Answer:

With the best predictive value, we mean the smallest p-value in combination with the type of predictor variable. (for example we think a dichotomous variable with a significant p-value has a better predictive value than a variable with multiple categories with only 1 significant p-value).

“In case there was multicollinearity between variables, the variable with the best predictive value (i.e. combination of p-value and type of predictor variable) was selected.” (page 9)

Regarding the results of the univariable and multivariable regression models in Tables 2 and 3, please describe the method used for pooling the estimates from the imputed datasets.

Answer:

Rubin’s rules were used to pool the estimates.

“Rubin’s rules were used to pool the regression coefficient estimates from the imputed datasets.” (page 8)

The number of patients included in each analysis should be presented in all tables. In Table 2, it is assumed that imputed data allowed the inclusion of all 87 patients, but this is not the case for Table 3 (which also displays the results of the sensitivity analysis using the complete cases population).

Answer:

We thank the reviewer for this suggestion and added the number of patients in the Tables.

Figure 3 is supposed to present the calibration curve, but it actually displays the frequencies of observed outcomes for tenths of predicted probability in one of the imputed datasets. There is nothing conceptually wrong with that (in this case, please update the description accordingly), but a calibration plot created by regressing the outcome on the predicted probability, using a locally weighted scatter plot smoother (lowess), and plotting the resulting smoothed line against the line of perfect prediction would be more informative. The calibration plot could also be supplemented with estimates of the calibration slope and intercept (for a prognostic model that perfectly predicts the outcome, 1 and zero would be the estimated values for slope and intercept, respectively). Finally, if the authors decide to present calibration plots with calibration lines, they could present these in a single figure overlaying the calibration curves from each imputed dataset.

Answer:

We thank the reviewer for this suggestion and revised the description of Figure 3.

Finally, in the discussion and conclusion (both in the text and abstract), the authors refer to their own study as a pilot study. However, this is not how the study is characterised both in the title and methods. An actual pilot study aims to provide further information for the conduction of an already planned, larger, well powered study. The authors acknowledge the limitations and adequately discuss their implications on the findings of this study. There is no reason to declare it a pilot study, if that was

not the original aim of their research. Otherwise, please adjust the title and update the methods section accordingly.

Answer:

In retrospect, we think 'pilot study' was not a correct name for our study. Therefore, we deleted the terms 'pilot' throughout the manuscript.

VERSION 2 – REVIEW

REVIEWER	Michael Schlussek Centre for Statistics in Medicine NDORMS, University of Oxford Oxford, United Kingdom
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	In the new version submitted, the authors have satisfactorily addressed all issues raised in my previous review of their study. Therefore, I am happy for the manuscript to be published in its current format.
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REVIEWER	Agnieszka J. Szczepek Charité Universitätskrankenhaus Berlin, Germany
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	All the points I have made were addressed by the authors, thank you. However, I am still unhappy with the way the authors offer explanation of the post-implantation hearing loss (my old Point 6). "....most probably due to the traumatic insertion of the electrode into the cochlea....". The mechanism of residual hearing loss was not a subject of your study so either you leave it or present all possible explanations (see Ann Otol Rhinol Laryngol. 2013 Jan;122(1):33-9. Molecular and cellular mechanisms of loss of residual hearing after cochlear implantation. Jia H1, Wang J, François F, Uziel A, Puel JL, Venail F.)
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REVIEWER	Elisabeth Wallhausser-Franke Heidelberg University Medical Faculty Mannheim Phoniatrics and Audiology germany
REVIEW RETURNED	03-Apr-2018

GENERAL COMMENTS	The manuscript has improved and is acceptable for publication, but some minor mistakes should to be corrected: One severe drawback is that a quantitative measure of pre-CI tinnitus severity is missing. The authors have discussed this in detail but this should also be stated in 'Strengths and Limitations' of the study on P3. 1. Some numbers in Table 1 are incorrect: - Tinnitus severity in group without recovery adds to 51, should be 52. - Surgical approach in group without recovery adds to 51, should be 52. - Insertion depth in group without recovery adds to 57, should be 52. - 'Localization tinnitus' and 'Localization CI' in group without recovery
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	<p>is identical, is this correct?</p> <p>- Spelling or sense: P4 L6: ..., but uncertainty exists... P4 L35:and which patients will P17 L48: '...', indicating the difficulties in tinnitus mechanisms' doesn't make sense</p>
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VERSION 2 – AUTHOR RESPONSE

Comments to the reviewers

Reviewer: 2

Reviewer Name: Elisabeth Wallhausser-Franke

Institution and Country: Heidelberg University, Medical Faculty Mannheim, Phoniatics and Audiology, Germany

Competing Interests: none

The manuscript has improved and is acceptable for publication, but some minor mistakes should to be corrected:

One severe drawback is that a quantitative measure of pre-CI tinnitus severity is missing. The authors have discussed this in detail but this should also be stated in 'Strengths and Limitations' of the study on P3.

Answer:

We agree with the reviewer that this is an important drawback of our study. We added this information to the 'Strengths and Limitations' section on page 3:

'Also, a quantitative measure of preoperative tinnitus severity is lacking.'

1. Some numbers in Table 1 are incorrect:

- Tinnitus severity in group without recovery adds to 51, should be 52.
- Surgical approach in group without recovery adds to 51, should be 52.
- Insertion depth in group without recovery adds to 57, should be 52.
- 'Localization tinnitus' and 'Localization CI' in group without recovery is identical, is this correct?

Answer:

We thank the reviewer very much for these comments. We checked all the numbers in Table 1 and corrected the mistakes. (see Table 1)

The numbers for 'localization tinnitus' and 'localization CI' are correct.

- Spelling or sense:

P4 L6: ..., but uncertainty exists...

P4 L35:and which patients will

P17 L48: '...', indicating the difficulties in tinnitus mechanisms' doesn't make sense

Answer:

Changed accordingly.

Reviewer: 3

Reviewer Name: Agnieszka J. Szczepiek

Institution and Country: Charité Universitätskrankenhaus Berlin, Germany

Competing Interests: none declared

All the points I have made were addressed by the authors, thank you.

However, I am still unhappy with the way the authors offer explanation of the post-implantation hearing loss (my old Point 6). "....most probably due to the traumatic insertion of the electrode into the cochlea....". The mechanism of residual hearing loss was not a subject of your study so either you leave it or present all possible explanations (see Ann Otol Rhinol Laryngol. 2013 Jan;122(1):33-9. Molecular and cellular mechanisms of loss of residual hearing after cochlear implantation. Jia H1, Wang J, François F, Uziel A, Puel JL, Venail F.)

Answer:

We thank the reviewer for this comment and decided to remove this part in the revised version of our manuscript.