PROGRAM CONTACT:

Release Date: 10/26/2018
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Application Number: 1 R01 DC017683-01A1

Principal Investigators (Listed Alphabetically):

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Applicant Organization: VANDERBILT UNIVERSITY MEDICAL CENTER

Review Group: LCOM
Language and Communication Study Section

Meeting Date:	10/18/2018	**RFA/PA:**	PA18-334
Council:	JAN 2019	**PCC:**	HR05
Requested Start:	04/01/2019		

Project Title: Image-Guided Cochlear Implant Programming: Pediatric Speech, Language, and Literacy
SRG Action: Impact Score:10   Percentile:1
Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 2A-Only Children, scientifically acceptable

Project Year	Direct Costs Requested	Estimated Total Cost
1		
2		
3		
4		
5		
TOTAL		

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the **COMMITTEE BUDGET RECOMMENDATIONS** section.

1R01DC017683-01A1 Gifford, Rene

RESUME AND SUMMARY OF DISCUSSION: This resubmitted application proposes a project to investigate the effects of individualized, image-guided cochlear-implant programming (IGCIP) on auditory processing and language outcomes in children ages 6- to 12-years-old. This project addresses a critical need for improvement in outcomes for children with cochlear implants (CI), and if successful, this project would have both clinical and theoretical impact. The premise is well-supported by prior work. The investigative team is outstanding, with excellent expertise for the project, and the environment is also strong. The application is highly responsive to prior review. The approach is rigorous and well-designed, using a variety of close and distal outcome measures, and has a detailed and feasible timeline. The panel noted only minor weaknesses, including that the project is not highly innovative, but panel members agreed that the level of innovation is appropriate for this project. Additional concern was raised that the length of testing may pose challenges for data collection from this age group. These weaknesses do not detract from the likelihood that this outstanding project will exert a large, sustained impact in a significant and much-needed area of research.

DESCRIPTION (provided by applicant): Although the recent literature has indicated that children receiving cochlear implants (CIs) often have dramatically improved speech and language ability relative to previous generations of children with hearing loss, many pediatric CI recipients display persistent speech and language disorders despite early implantation and associated speech/language intervention. There is a striking paucity and ongoing need for studies that systematically examine the relationship between intracochlear electrode location, audiological profile, and subsequent phonological awareness, speech, language, and literacy in pediatric CI recipients. This project provides a unique opportunity to examine whether individualized, image-guided CI programming (IGCIP) significantly improves outcomes in pediatric CI patients. The proposed research activities will examine the impact of personalized IGCIP in pediatric CI recipients on measures of basic auditory function (spectral, temporal, and spectrotemporal resolution), word and non-word recognition, speech production, language, phonological awareness, and reading comprehension using a double blind, waitlist control randomized clinical trial (RCT) design. A total sample of 72 children with CIs aged six to twelve years old will be enrolled in the project: half (n = 36) will be randomized to an immediate IGCIP condition and half to a waitlist control condition. The waitlisted participants (n = 36) will undergo IGCIP after 12 months of monitoring and then followed for an additional 12 months after intervention (total time in the study for both groups: 24 months). Those immediately provided with IGCIP will also be followed for a total of 24 months. All participants will undergo extensive audiological assessment as well as tests of phonological awareness, speech, language, and literacy at baseline as well as at regular intervals: 2, 6, 12, 14, 18, and 24 months. We will use predictor analyses to determine the impact of immediate and deferred IGCIP on subsequent auditory, speech, language, and literacy outcomes.

PUBLIC HEALTH RELEVANCE: Despite significant advancements in technology and outcomes, pediatric cochlear implant (CI) recipients display persistent delay on measures of speech, language, and literacy despite early implantation and extensive speech/language intervention. Most CI recipients are programmed using a one-size-fits-all approach to setting upper and lower stimulation levels, maximum number of active electrical contacts, and selection of various signal processing parameters for electrical stimulation of the auditory system. Our interdisciplinary research team will examine the impact of a personalized, image-guided approach to CI programming and its effect on auditory processing, speech recognition, speech production, phonological processing, language, and literacy.

CRITIQUE 1

Significance: 1
Investigator(s): 1
Innovation: 3

Approach: 2
Environment: 1

Overall Impact: This application seeks to teach a new cochlear implant programming strategy against the current standard of care programming strategy for 6- to 12-year-old children. Children are monitored for 1 to 2 years following programming on a variety of measures of working memory, auditory processing, speech, language, and pre-literacy skills to examine differences in closely related (auditory processing) and less closely related skills (speech, language, preliteracy). The scientific design is strong with an appropriate double blind randomization design, a well-specified and likely sensitive outcome measures, and an appropriately powered and detailed statistical analysis plan. The investigators and consultants have deep expertise in all aspects of the research and the environment is well suited to the type of research and the selected patient population. Although there are very minor weaknesses in innovation and in the preliminary data, these do not detract from the likely impact of the research. The proposed research is well suited to determining whether the new programming strategy has benefits over the standard programming strategy and will provide clear direction in whether and how the development of this new programming strategy should proceed.

1. Significance:

Strengths

- There is tremendous variability in the outcomes of cochlear implantation. This application seeks to improve functioning of CIs by using a more individualized fitting strategy based on the actual location of the CI in the cochlea.

- The proposed research examines differences between programming strategies (current standard of care versus the new Image-Guided Cochlear Implant Programming - IGCIP) on auditory functioning and then subsequent differences in speech, language, and pre-literacy skills over a 1- to 2-year period. As such, the research evaluates the impact of the different programming strategies on near and distal outcomes.

- In addition to evaluating the different programming strategies, the longitudinal nature of the design combined with analysis of complex relationships among skills (e.g., mediated relationships between auditory processing and speech/language/pre-literacy skills) has strong potential to inform our understanding of how development in these areas influence each other.

- The scientific premise is strong and preliminary data demonstrates the potential promise of the new programming strategy.

Weaknesses

- No major weaknesses noted.

2. Investigator(s):

Strengths

- The local team is excellent with well-established and well-qualified scientists in all significant topic areas: CI, auditory function, speech perception (Gifford); child speech and language (Camarata), surgical/bioengineering (Labadie, Noble, Dawant), and biostatistics (Dietrich).

- The expertise of the local team is further bolstered by external consultants who add expertise in speech perception, phonological awareness, and reading (Nittrouer, Bunta)

- The local team has been collaborating on the development of the new programming strategy across several grants and publications, demonstrating the ability to work effectively together and to run large scale collaborative projects.

Weaknesses

- No major weaknesses noted.

3. Innovation:

Strengths

- The proposed research is among the first to test this new programming strategy with children

- This study is among the first to examine such a wide array of skills with sufficient power to unpack subtle relationships (e.g., mediation) among these skills.

Weaknesses

- Other aspects of the design are fairly standard (e.g., standardized tests, research protocols). This increases feasibility and confidence that the measures will be sensitive to the outcomes but somewhat limits innovation.

4. Approach:

Strengths

- The overall design (double blind randomized immediate treatment vs. waitlist control) is a strong design for addressing the aims

- The outcome measures have been carefully chosen based on past research. There is evidence that the measures will be sensitive to differences between treatment and control conditions as well as change over time.

- The statistical analysis plan is well specified including how common challenges (e.g., missing data, intention to treat, baseline differences) will be addressed.

- Sample size was determined using a power analysis and included appropriate attention to likely attrition.

- Initial outcomes are appropriately assessed 1-month post treatment to allow families to opt out of the treatment if it is detrimental. This is an ethically appropriate way to allow families to choose whether to continue in the trial or not once the treatment has been applied.

- The timeline is specified in detail and appears to be feasible.

Weaknesses

- Preliminary data suggest the potential benefits of the new mapping strategy but effects are somewhat modest and potentially variable. This is only a minor concern because the proposed clinical trial is appropriately powered to test for the effect sizes observed in the preliminary data and also appropriately powered to explore individual differences as a means of informing further development of this treatment.

5. Environment:

Strengths

- Infrastructure for clinical research and recruitment of participants is excellent. Environment is highly conducive to accomplishing the aims in the planned timeline.

Weaknesses

- No major weaknesses noted.

Study Timeline:

Strengths

- Timeline contains ample detail. Timeline is feasible.

Weaknesses

- No major weaknesses noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Risks are minimal with appropriate safeguards and consent procedures

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- The local IRB has indicated that a data safety monitoring board is not needed given the low risk of the research.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically

- Race/Ethnicity: Distribution justified scientifically

- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable

- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically

- Demographics of the participants are expected to match the Vanderbilt CI patient characteristics.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- Investigators were highly responsive to prior critiques.

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 3
Environment: 1

Overall Impact: This proposal aims to evaluate the impact of a personalized, image-guided approach to CI programming and its effect on the development of speech and language measures as well as on phonological processing and reading skills. Using a double-blinded randomized waitlist control trial with a longitudinal monitoring component, the efficacy of an innovative image-guided CI mapping method will be evaluated. Overall, the study has the potential to change the current standard of care for children with CIs by providing customized CI mapping to improve speech and language outcomes. It will also provide a rich data matrix that will inform theoretical models of speech language development in CI users. The approach is well designed and all outcome variables are justified and the environment at Vanderbilt Medical Center is excellent for conducting this study. The team is outstanding and the proposed timeline is justified and feasible. However, a few critique points remain, mostly related to the approach. The proposed age range is not adequately justified. The youngest participants will be 6 years which means that it is likely that they already received 1-2 years of formal reading instruction with suboptimal CI programming which may already resulted in poor pre-literacy and reading outcomes as well as a negative attitude towards reading which may be prevented with a younger start age. Furthermore, environmental variables that have been shown to influence reading outcome in typical developing children are not considered and reading fluency has been ignored as a potential construct but it could play an important role in the relationship between phonological processing, oral listening comprehension and reading comprehension.

1. Significance:

Strengths

- Children with CI show profound deficits in language processing even if the CI was implanted early. Examining lower level auditory function and speech recognition skills and their relationship to the development of speech, language, phonological awareness and reading skills is of high significance.

- The current clinical 'one-fits-all' approach to CI programming is often suboptimal and the proposed study testes the efficacy of the novel ICGP approach which employs a personalized, customized approach to mapping

- The proposed study will have strong implications for clinical care and will add to theoretical foundations

Weaknesses

- The construct of reading fluency is absent in the theoretical foundation of this proposal but may explain variance in reading comprehension.

2. Investigator(s):

Strengths

- The investigative team and consultants are very well suited to address the project's aims. The team members have a history of collaborations in adults with CI.

- The team has the expertise to manage a project of this scope and has experience with clinical trials.

Weaknesses

- No major weaknesses noted.

3. Innovation:

Strengths

- The development of 'expected' longitudinal growth trajectories for speech and language development in pediatric CI users is highly innovative and has the potential to impact clinical care and assessments.

- The application of image-guided CI mapping in children in order to develop personalized CI mapping is innovative and has the potential to replace current clinical care models.

- The investigation of auditory function and speech perception as well as phonological awareness measures and reading skills and their interactions will provide a rich data matrix.

Weaknesses

- No major weaknesses noted

4. Approach:

Strengths

- The study is well designed and all aspects of the analysis plan are well specified. The use of waitlist control and a longitudinal timeline is important for examining the aims of this proposal.

- The preliminary studies show promising results in pediatric populations but this RCT is needed to further characterize effects, especially on reading skills.

- All outcome variables are well designed and justified.

Weaknesses

- Although the age range has been justified, the argumentation is weak. Standardized tests for phonological awareness and early reading are normed for children younger than 6 years. The proposal aims to investigate phonological awareness and its relationship to reading skills but the youngest children will be examined after the onset of formal reading instruction which may be too late to close the gap between CI users and controls.

- Environmental variables that could potentially influence outcome measures, especially reading skills are not examined. This includes quality and type of instruction, quality of reading in the home, etc.

5. Environment:

Strengths

- Vanderbilt University Medical Center is one of the largest CI programs in the US and the environment is well suited for this study.

Weaknesses

- No major weaknesses noted.

Study Timeline:

Strengths

- The timeline is well designed and described in great detail

Weaknesses

- No major weaknesses noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically

- Race/Ethnicity: Distribution justified scientifically

- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable

- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The team has been very responsive to the previous critique and has addressed most challenges and barriers.

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Significance: 1

Investigator(s): 1
Innovation: 3
Approach: 2
Environment: 2

Overall Impact: This is a highly significant, and well-specified proposal from a top team of researchers, with very few weaknesses. It was already a strong proposal on the previous review, and the changes made have enhanced the proposal.

1. Significance:

Strengths

- Addressing the underlying causes for variability in CI outcomes is highly significant.

- Many individuals do not appear to make the gains from their CI as might be expected; this proposal represents a potential way of addressing this.

- Image-guided cochlear implant programming (IGCIP) has been shown to be beneficial in adult CI users, and thus testing it in pediatric users is a logical next step.

- Understanding how spectral resolution relates to auditory skills, phonological skills, speech skills, and reading skills, allows for the development of better models of the process of skill development in this population.

Weaknesses

- Given that Nittrouer has shown that children place less weight on spectral cues than adults, why would a strategy that aids in spectral/spatial selectivity be advantageous?

2. Investigator(s):

Strengths

- The team has a history of productive collaboration

- PIs both have a strong publication and grant record.

- Other members of the team have complementary strengths (speech perception, otology, imaging, biostatistics, phonological development, etc.), and generally have strong records.

- The team are experts in image-guided cochlear implant programming (IGCIP).

Weaknesses

- No major weaknesses noted.

3. Innovation:

Strengths

- Attempting to develop individualized programming techniques for pediatric CI users is innovative.

Weaknesses

- The tasks used are fairly standard, although this does help in interpreting them and relating them to the prior literature.

4. Approach:

Strengths

- Approach includes a wide array of assessments.

- Participant size is based on a power analyses

- Detailed statistical plans are in place, as well as plans for addressing missing data, and plans for addressing a decrement in performance.

- Timeline is reasonable and well-specified.

Weaknesses

- Given the large number of assessments, might attentional skills be a relevant factor in these children?

- Children will have already been implanted for some time; given that, one concern is that families who opt to participate in this study will specifically be those who were not gaining as great of a benefit from their CI as was expected/desired; this could artificially inflate the overall benefits of IGCIP.

- The data management plan stops midsentence on page 125; it is not clear how an aberrant change in performance in a child whose programming was not changed would be addressed.

5. Environment:

Strengths

- Physical environment is adequate.

- Access to software platforms that aid in collaboration and data management.

- Vanderbilt's CI surgical facilities and Hearing & Speech Sciences department are co-located, as are the labs, making collaboration easier.

- VU Medical Center has a large number of CI implantees as patients; as PI is the director of the CI program, there is presumably no question about recruiting from there.

Weaknesses

- No discussion of intellectual environment.

Study Timeline:

Strengths

- Well specified, with consideration of family/school schedules as well as timelines for completion.

Weaknesses

- No major weaknesses noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Minimal risk study, with the potential for clinical gains.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically

- Race/Ethnicity: Distribution justified scientifically

- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable

- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically

- They note that the ethnic/racial distribution of CI users is unknown and may not reflect the broader community.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The previous version of this proposal was seen as highly significant, and the inclusion of both near and distal outcome measures were a strength - these aspects remain.

- The approach had been seen as generally strong, but with a few particular weaknesses: the timeline was not clear, the experimenters were not blinded, there was no assessment of working memory, and the age range was not justified. All of these concerns have been addressed in the new submission.

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE
It was noted during the meeting that the Data and Safety Monitoring Plan appears incomplete.

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION OF CHILDREN PLAN: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R01 DC017683-01A1; PI Name: Gifford, Rene H

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Language and Communication Study Section
Biobehavioral and Behavioral Processes Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
LCOM
10/18/2018 - 10/19/2018

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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