Technical Assistance Webinar for "Feasibility Trials of the NIH Music-based Interventions Toolkit for Brain Disorders of Aging" (R34 Clinical Trial Required) (PAR-23-256)

Purpose of the Webinar

On Tuesday, December 19, 2023, the National Center for Complementary and Integrative Health (NCCIH) and National Institute on Aging (NIA) hosted a technical assistance webinar to share information about the notice of funding opportunity (NOFO) PAR-23-256: Feasibility Trials of the NIH Music-based Interventions Toolkit for Brain Disorders of Aging (R34 Clinical Trial Required).

Update: This funding opportunity will be revised and reissued. The NOFO for PAR-23-256 was expired on December 21, 2023, in NOT-AT-24-026. **No further applications will be accepted for consideration under PAR-23-256.** The revised NOFO is expected to be published in March 2024, with an expected application due date in June 2024.

Webinar Speakers

- Coryse St. Hillaire-Clarke, Ph.D., Program Director, Division of Neuroscience, NIA
- Sekai Chideya, M.D., M.P.H., Program Director, Clinical Research Branch, NCCIH
- Lisa Onken, Ph.D., Director, Behavior Change and Intervention Program, NIA
- Baila Hall, Ph.D., Scientific Review Officer, Office of Scientific Review, NCCIH
- Anita McRae-Williams, M.A., Outreach Communications Program Manager, Division of Extramural Research, NCCIH (webinar moderator)

Ms. McRae-Williams welcomed the webinar participants. She explained that there has been much interest in music and health research, sparked by the Sound Health initiative, over the past 6 years. Sound Health, a partnership between the National Institutes of Health (NIH) and the John F. Kennedy Center for the Performing Arts, in association with the National Endowment for the Arts, has increased public awareness of music and health and created opportunities for research. The workshop Music as Medicine: The Science and Clinical Practice, held on December 14 and 15, 2023, highlighted recent studies in this field and aimed to develop a blueprint for future research.

Ms. McRae-Williams explained that the webinar would be an hour long, with the first half devoted to presentations by program and review staff and the second half devoted to answering questions from the webinar participants. Participants who have additional questions after the webinar may send them to NCCIHWebinarQ@nih.gov. Participants will receive the speakers' slides and a brief survey after the webinar ends. They will be sent a detailed written summary of the webinar within 7 or 8 days.

Background: The Music-Based Intervention Toolkit

Dr. St. Hillaire-Clarke explained that Sound Health was established following a 2017 workshop on music and the brain. NIH has taken action on all the recommendations made at that workshop. The NOFO discussed here focuses on the recommendation for development of methods and outcomes assessments to support rigorous research.

In 2021, NIH, in collaboration with the Foundation for the NIH and the Renée Fleming Foundation, held three workshops to address the recommendations on methods and outcomes from the 2017 workshop.

Input was gathered from experts in different fields. The workshops led to the development of the NIH Music-Based Intervention (MBI) Toolkit, published in May 2023. The toolkit is a set of guidelines and recommendations on components that need to be included in MBI studies to ensure rigor and replicability. Brain disorders of aging were used as a model because evidence of the benefits of MBIs for these disorders is especially compelling.

Essential components of MBI studies include a conceptual model or framework to guide the design of the intervention, a clear research question and provision of supporting data to test the hypothesis, and a core set of common data elements or building blocks. The toolkit includes examples of potential measurable outcomes and biomarkers specific to MBIs for brain disorders of aging.

The R34 Grant Mechanism and the Current Funding Opportunity

Dr. Chideya explained that the current NOFO, jointly administered by NCCIH and NIA, uses the R34 grant mechanism and is intended to fund **early-stage (i.e., pilot) single-site music clinical trials.** It will support the exploration of factors essential to a later fully powered trial, but the budget at this stage is too small to support an appropriately powered efficacy trial.

Dr. Chideya showed NCCIH's framework for mind and body clinical trials, which requires that an intervention be established as feasible, acceptable, and capable of being delivered with fidelity before its efficacy or effectiveness is assessed. Dr. Onken described the NIH Stage Model for Intervention Development, which is used by NIA. This model is designed to facilitate the scientific development of potent and implementable interventions. It is intended to help create interventions defined by their principles or mechanisms of behavior change. Consideration of the ease and fidelity of implementation is encouraged throughout the intervention development process.

Dr. Chideya gave examples of feasibility and acceptability questions that an application submitted in response to this NOFO might address, including:

- Can I recruit my target population? Can I randomize them?
- Can I keep participants in my study? Will they do what they are asked to do?
- Can the treatment be delivered, per protocol?
- Are the assessments too burdensome?
- Are the treatment conditions acceptable to participants? Are they credible?

These questions are particularly important for the unique population targeted by this NOFO.

The specific objectives of the funding opportunity are to support **proof-of-concept feasibility trials guided by the Toolkit** and to generate evidence supporting the validity, practicality, and acceptability of the Toolkit's guiding principles. Other objectives include facilitating generation of pilot data to support the design of future large-scale trials and addressing gaps in scientific knowledge.

Essential elements of the application include:

- Stating the conceptual framework guiding the proposed research, as described in the Toolkit
- Addressing all MBI building blocks as outlined by the Toolkit
- Identifying relevant clinical outcomes and/or biomarkers for brain disorders of aging
- Proposing a multidisciplinary research team

Dr. Chideya explained that the current non-responsiveness language in the NOFO may be confusing, as it only mentions trials with the "sole purpose" of estimating an effect size and "Phase III trials of efficacy or effectiveness." **The NOFO will be revised and reissued to clarify that efficacy and effectiveness outcomes are not allowed, even in early-stage trials and/or as secondary and "exploratory" outcomes.** Clinical outcomes can and should be measured but not compared between arms. Also, the budget does not support sample sizes needed to power efficacy outcomes.

This NOFO will **not** support trials that:

- Attempt to assess safety/tolerability of a treatment
- Repeat a feasibility or acceptability trial previously conducted in the same or similar populations, with the same or a similar intervention, and with the same primary objectives
- Propose to solely develop a protocol, manual of operations, or infrastructure for a trial

Examples of aims that would be considered responsive include:

- Assessment of acceptability and adherence to dose, frequency, and/or duration of the MBI for testing in a future trial
- MBI refinement to tailor it to a new patient population
- Iterative intervention refinement to address challenges with fidelity, adherence, retention, etc.
- Development and feasibility testing of an appropriate control/comparison intervention for a future larger study
- Assessment of acceptability or feasibility of randomization or other aspects of trial design

Review Perspective

Dr. Hall discussed review considerations for this NOFO. Applications that are incomplete, noncompliant, or nonresponsive may not be accepted for review.

Responsiveness:

Applications that are not responsive to the Scope and Responsiveness Criteria will not move forward to review. Dr. Hall recommended looking for "must" and "need" when reading through these criteria and making sure you are responding to these requirements.

Responsive applications should have the potential to increase understanding of the science of music and health and to inform MBIs using brain disorders of aging as a model system. **Applications that do not use the guiding principles of the Toolkit will be deemed nonresponsive and not reviewed.** Applications must support planning activities and analyses of existing data needed to design a trial or clinical research project and develop a protocol.

Compliance:

- **Budget:** limited to direct costs requests of up to $450,000 over the entire project period, with no more than $225,000 in direct costs in any one year.
- **Project period:** up to 3 years.
- **Eligibility:** Nondomestic entities and nondomestic components of U.S. organizations are not eligible to apply. Foreign components, as defined in the NIH Grants Policy Statement, are allowed.

- **Page limitations:** Specific Aims: 1 page; Research Strategy: 12 pages.
- **Clinical trial:** Required.
- **Allowable appendix materials:** These include blank informed consent/assent forms, blank surveys or questionnaires, blank data collection forms, and simple lists of interview questions. As explained in NOT-OD-17-098, applications will not be reviewed if they include appendix materials not specifically allowed by this notice or the NOFO.
- **Post-submission materials:** In addition to the allowable post-submission materials specified in NOT-OD-19-083, a clinical trial experience table is also allowed. The due date is 30 calendar days before the peer review meeting date. **Information accidentally left out of the application cannot be provided as post-submission material.**

Completeness:

To be complete, applications must include:

- A study timeline
- A clinical trial experience table demonstrating key personnel trial experience in the last 5 years
- A Resource Sharing Plan (following the instructions in the SF424 (R&R) Application Guide)
- A Data Management and Sharing Plan (attached in the Other Plan(s) attachment in FORMS-H application forms packages)

Review Criteria

Dr. Hall explained that applications will receive separate scores for each of the five scored review criteria (significance, investigator(s), innovation, approach, and environment), and that additional review criteria will also be factored into the overall impact score. **NOFO-specific language has been added to the standard review criteria,** and the aspects of the application that reviewers are asked to assess correspond to those that applicants are asked to address in their applications. Dr. Hall provided an example of a match between submission information requested and review criteria, taken from the NOFO. She also highlighted an example of NOFO-specific language that has been added to the announcement.

Review Panel

Applications will be reviewed in a Special Emphasis Panel at NCCIH. Reviewers will be selected based on specific areas of expertise in the target areas of the NOFO as well as clinical disciplines and scientific areas proposed in the applications. Reviewers will be oriented to use the additional review criteria and additional language for the standard criteria in their assessment.

Applicants should keep in mind to address how their applications would be impactful considering the goals of the funding opportunity.

Timeline: The timeline for this funding opportunity will change when the NOFO is revised and reissued. However, the original NOFO discussed at the webinar included the following dates:

- **Letter of intent (optional):** Due 30 days prior to the application due date
- **Application receipt dates:** ~~February 20, 2024; June 20, 2024~~
- **Review meetings:** ~~July 2024; November 2024~~

- **Expected award dates:** ~~December 2024; April 2025~~

Letters of intent should include the following information:

- Descriptive title of proposed activity
- Name, address, and telephone number of the program director(s) (PD[s])/principal investigator(s) (PI[s])
- Names of other key personnel
- Participating institutions
- Number and title of the funding opportunity

The letter should be sent to Jessica McKlveen, Ph.D., NCCIH Office of Scientific Review, at jessica.mcklveen@nih.gov when the application is submitted.

To expedite review, applicants are asked to notify the NCCIH Referral Office by email at jessica.mcklveen@nih.gov when the application is submitted. Please include the NOFO number and title, PD/PI name, and title of the application.

Questions and Answers

Q: Can audio or video be included in the application?

A: Dr. Hall said that video or hyperlinks cannot be included in the application. However, videos may be submitted as post-submission materials, as outlined in the post-submission policy and further delineated in NOT-OD-20-061.

Q: Will the due dates be replaced or will new due dates be added?

A: Dr. Chideya explained that the dates will probably change. It depends on how long the formal NIH approval process for the reissued funding opportunity takes.

Q: Can you clarify why fully powered remotely delivered trials are considered nonresponsive?

A: Dr. Chideya explained that many NIH Institutes and Centers have specific NOFOs for fully remote, fully powered efficacy and effectiveness studies. Applicants should submit proposals for such studies in response to those NOFOs rather than this funding opportunity. This NOFO **will** support fully remote **feasibility and acceptability** trials, but it will not support fully remote efficacy and effectiveness trials.

Q: Is modular budget a requirement?

A: Dr. Hall recommended touching base with the internal grants management offices and office of sponsored research regarding modular budgets. Generally, you must use the Public Health Service (PHS) PHS Modular Budget Form if you are submitting a research grant application from a domestic organization, and you are applying for $250,000 or less per budget period in direct costs. Refer to your NOFO and to instructions in SF424 (R&R) for guidance on which budget form to use.

Q: Are efficacy data required? Do you welcome pilots for Stage II trials?

A: Dr. Onken said that this is an announcement to obtain feasibility and acceptability data, not efficacy data. The data obtained in your study could be used to determine whether a Stage II trial is appropriate, but a Stage II trial is an efficacy trial, and this NOFO won't support it.

Q: Is a comparative condition required?

A: Dr. Chideya said that there should be a control or comparator group, but it would not necessarily consist of people who have a different medical condition. The participants in the control or comparator group may have and probably should have the same medical condition as those in the group receiving the intervention that is being evaluated. Additionally, this NOFO does **not** support proposing a waitlist comparative condition, due to lack of rigor and potential expectancy effects. Utilizing a waitlist control is included in the nonresponsiveness criteria.

Q: Would a study in which the MBIs would be delivered virtually via Zoom with in-person visits for assessment be eligible?

A: Dr. Chideya said that a proposal of this type would be eligible. Fully remote means that everything is done remotely, including recruitment, the intervention, and assessment. A study in which an MBI is delivered virtually via Zoom but has in-person visits for assessment would not qualify as a fully remote project, and it would be appropriate for this NOFO.

Q: Can members of the interdisciplinary team include people from other sites as long as participants come through one site?

A: Dr. Hall explained that members of the interdisciplinary team can be from different institutions. Dr. St. Hillaire-Clarke said that trials should be conducted at a single site, but it is fine for investigators located at different sites to be part of the team. She explained that the limited budget is one of the reasons for the single-site requirement. Conducting a study at multiple sites increases costs.

Q: Are those trials that apply to those experiencing subjective cognitive impairment also considered an important part of brain health? Previously, this announcement was an R33/R61. Is there an R61 component to this mechanism? Can this be extended if successful?

A: Dr. Chideya said that the announcement that used the R33/R61 mechanism was a different one that was more basic and mechanistic in focus. The current funding opportunity is complementary but different, focusing on feasibility and acceptability clinical trials.

Q: Are there consultants experienced with MBIs available to help applicants who are new to this topic?

A: Dr. Chideya and Dr. St. Hillaire-Clarke explained that no such consultants are available. Program staff can discuss a proposal's specific aims with a prospective applicant, but they are not MBI experts.

Q: Can you clarify further about the requirement for a clinical trial and the guidance against primary outcomes? How can analysis of outcomes be described?

A: Dr. Chideya explained that clinical trials can have many different kinds of outcomes. Clinical outcomes can be measured but not compared. There can be outcomes that are not clinical, such as those related to feasibility, acceptability, fidelity, retention, and recruitment. Having data on these outcomes is essential before proceeding to trials to evaluate efficacy and effectiveness. The trials supported by this

funding opportunity will not have sufficient power to analyze data and obtain accurate results for efficacy and effect size, and data should not be analyzed in a way that could be misleading.

Q: With regard to fully remote studies, does that mean that an intervention delivered via Zoom is nonresponsive, or does fully remote refer to the research team activities as well?

A: Dr. Chideya said that fully remote means that there is never any in-person contact with the participant. She stated that an intervention delivered remotely may be appropriate for this NOFO if there are in-person components to the study. However, to clarify, the restriction against fully remote trials applies only to studies evaluating efficacy and effectiveness. This NOFO **will** support fully remote **feasibility and acceptability** trials, but it will not support fully remote efficacy and effectiveness trials. The revised NOFO will make this clearer. We apologize for the confusion.

Q: If the subjects are breast cancer survivors, most of whom are older, can I limit them to a certain age group? Would that fit the aging requirement?

A: Dr. St. Hillaire-Clarke said that the age group could be limited. However, the NIH MBI Toolkit was modeled for brain disorders of aging, so the proposed study should incorporate one of those conditions. Dr. Onken added that breast cancer is not a brain disorder of aging.

Q: Can a proposed intervention include mind and body practices such as yoga or guided imagery as well as music?

A: Dr. Chideya said that the answer is yes, but the non-music intervention must have strong evidence of effectiveness from previous research, and the rationale for including the non-music intervention must be explained.

Q: If a person had feedback from previous submissions to Sound Health funding opportunities, would this be a resubmission, and would it be appropriate to respond to the feedback from previous reviewers?

A: Dr. St. Hillaire-Clarke explained that all applications in response to this NOFO should be new applications. If you have received feedback on previous applications, you could incorporate it into your current study design and application, but your application should not refer to previous applications.

Q: Would a study with multiple principal investigators from two institutions with one community partner be ineligible?

Dr. St. Hillaire-Clarke said that more information would be needed to address this question and asked the questioner to follow up by email. Later in the Q&A session, the questioner clarified that recruitment would take place at one community partner site. Dr. Chideya said that if this is the case, the proposal would be considered single site.

Q: Can the trial focus on the sensitivity of a process measure, such as measuring the level of musical engagement?

A: Dr. Chideya said that more clarification would be needed to answer this question. She asked the questioner to contact one of the program staff.

Q: Do you provide guidance on benchmarking, setting go/no go criteria for feasibility and acceptability outcomes? What are appropriate Ns [numbers of participants] for these types of outcomes?

A: The webinar speakers recommended consulting this guidance on feasibility studies mentioned in the NOFO and pointed out that the number of participants needed for feasibility and acceptability studies is much smaller than the number needed to assess efficacy or effectiveness. This paper and this blog post by NCCIH Program Director Dr. Lanay Mudd may be helpful. You can reach out to the webinar speakers for additional information.

Q: Can you elaborate on the preliminary data needed? Should the study use an intervention that has previously been tested in some way?

A: Dr. Chideya said that there should be some plausible justification for why the applicant thinks the proposed intervention would work. That may mean that there are preliminary data or mechanistic data that are ready to be translated. Even for feasibility and acceptability trials, having preliminary data strengthens an application. However, they are not always necessary.

Q: What about cognitive impairment acquired post-acute illness? Would that be appropriate for this NOFO?

A: Dr. St. Hillaire-Clarke said that this might be acceptable if it is focused on delirium. Dr. Chideya added that it depends on the illness. For example, if the acute illness is stroke, it would certainly be acceptable. But if it's an illness that is not a brain disorder of aging, such as COVID-19 or head trauma, it would not be acceptable. The questioner followed up, saying that it could potentially be delirium but it could be something else. Dr. St. Hillaire-Clarke recommended contacting program staff.

In conclusion, Ms. McRae-Williams reminded attendees that they will soon receive the webinar slides and a survey. A summary of the webinar will be sent to registrants by email in 7 to 8 calendar days. She urged applicants who have further questions to follow up with NCCIH or NIA program staff. She then closed the webinar.