Leveraging Data at Scale to Understand Natural Product Impacts on Whole Person Health (R01 Clinical Trial Not Allowed) Technical Assistance Webinar (RFA-AT-24-008)

Purpose of the Webinar

On Tuesday, April 30, 2024, the National Center for Complementary and Integrative Health (NCCIH) hosted a technical assistance webinar to share information about the notice of funding opportunity (NOFO) RFA-AT-24-008: Leveraging Data at Scale to Understand Natural Product Impacts on Whole Person Health (R01 Clinical Trial Not Allowed), which is supported by NCCIH and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) as part of the Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) Program.

Webinar Speakers

- Barbara C. Sorkin, Ph.D., Co-Director, NIH CARBON Program, ODS
- D. Craig Hopp, Ph.D., Deputy Director, Division of Extramural Research, NCCIH
- Shiyong Huang, Ph.D., Scientific Review Officer, Division of Extramural Activities, 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 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 webinar participants. Participants will receive the speakers' slides and a brief survey by email after the webinar ends. They will be sent a detailed written summary of the webinar within 7 or 8 days. Attendance at this webinar is optional and not a requirement for application submission.

Program Perspective

Dr. Sorkin explained that the CARBON Program is a long-standing collaboration between ODS and NCCIH. The focus of ODS is on dietary supplements, which are legally defined as products that

- Contain one or more dietary ingredients or their constituents
- Are intended to supplement the diet
- Are taken by mouth.

Examples of dietary supplements include vitamins, minerals, botanicals, and probiotics. This NOFO focuses on chemically complex dietary supplements, such as botanicals, probiotics, or natural mixtures of fatty acids. Applications that propose to examine variables that modulate the effects of these complex products are of particular interest. Dr. Sorkin noted that because of the multidisciplinary nature of the research this NOFO will support, ODS and NCCIH want to ensure that appropriate expertise from different, relevant fields (e.g., nutrition) is included in each proposal.

Dr. Hopp explained that this NOFO is part of the CARBON program, which has evolved over time and is now moving in a new direction with this focus on computational tool development. The emphasis of this NOFO is on developing novel tools to aggregate and analyze large volumes of data

relevant to natural products and whole person health. This work is relevant to one of the scientific objectives in NCCIH's current strategic plan—Advance Fundamental Science and Methods Development.

Dr. Hopp explained that data about natural products and their health effects are abundant but scattered, and the biological activities associated with natural products are often subtle and dependent on context. By examining existing data at scale, it may be possible to develop novel hypotheses about when, where, and how natural products might exert their effects.

Dr. Hopp explained that only new applications will be accepted, and that clinical trials are not allowed. Late applications will not be accepted, and **the due date is June 28, 2024.**

Focus of This Funding Opportunity

The NOFO asks investigators to primarily utilize existing large data sets and to use data appropriate for the scientific questions they want to answer or the tools they are working to develop. The focus should be on understanding how natural products improve overall health. A focus on how a particular natural product influences a specific disease indication would not be appropriate for this funding opportunity. The topic should be broader and more generalizable. The long-term goals of this initiative are to better understand

- How combinations of natural products might act together to modulate whole person health
- How natural products act across multiple biological systems to modulate whole person health
- Factors that influence when, why, and how natural products may or may not be beneficial in different contexts

Dr. Hopp explained that the primary focus of applications submitted in response to this NOFO should be on analysis of existing data, but generation of some novel data may be permitted. All applications should include a cross-cutting team of scientists, including those with expertise in computational methods and data science as well as those with an understanding of the chemistry and biology of natural products. The use of artificial intelligence (AI) and machine learning (ML) approaches is encouraged but not required.

Projects that would not be considered responsive to this NOFO include:

- Purely epidemiologic studies looking at associations between dietary patterns and health outcomes
- Drug discovery projects
- Meta-analyses of clinical trial data
- Projects limited to associations between specific natural products and individual targets or pathways
- Projects that focus on specific disease conditions rather than broader health promotion
- Projects that do not involve multiple data types or do not link chemical and biological data
- Projects that do not primarily focus on development of computational tools

Nonresponsive proposals will be administratively withdrawn without review.

Dr. Hopp explained that questions regarding the scientific content of an application that arise before application submission should be directed to him, and those related to application review should be directed to Dr. Jessica McKlveen, director of the NCCIH Office of Scientific Review. Questions that arise after application submission but before review should be directed to Dr. McKlveen. Questions that arise after review should be directed to Dr. Hopp.

Review Perspective

Dr. Huang provided details on factors that impact the review of applications under this NOFO. He cautioned that applications that are incomplete, noncompliant, or nonresponsive to the NOFO may not be accepted for review.

Responsiveness

Dr. Huang explained that applications must be responsive to the scope and responsiveness criteria in the NOFO. Responsiveness will be determined by program staff in collaboration with review staff. Dr. Huang advised applicants to look for the words "must," "need," and "required" when reading through the NOFO. For example, the NOFO says, "Projects **must** leverage and merge multiple compatible or interoperable sources and/or types of data."

Projects that do not meet the responsiveness criteria (for example, purely epidemiologic projects or meta-analyses of clinical trial data for a particular natural product) will be administratively withdrawn and will not be reviewed.

Compliance

Compliance factors specific to this NOFO include the following:

- Budget
    - Application budgets are limited to less than **$500K** in direct costs **for each year** of the project.
    - Budgets must reflect the actual needs of the proposed project.
    - Applications must allocate part of the budget toward attending virtual and in-person meetings associated with CARBON Program activities, including yearly annual meetings of the full consortium.
- Project period
    - The scope of the proposed project should determine the project period.
    - The maximum project period is **5 years.**
- Post-submission materials are allowed and are due 30 calendar days before the peer review meeting date.
    - See NOT-OD-19-083 and NOT-OD-23-106 for details about allowable post-submission materials.
    - Information accidentally left out of the application cannot be submitted as post-submission material.

Completeness

The NOFO has specific instructions on elements that must be included in the **Approach, Innovation,** and **Investigators** portions of the **Research Strategy** section of the application. For example:

- For **Approach,** there are multiple requirements, including:
  - Evidence that the applicant has permission to access the data if the underlying resource is not completely open access
  - A plan to identify and account for data problems
  - A strategy to conduct preliminary tests of the validity of any hypotheses generated using the data
  - Evidence that the proposed source data sets are fit for purpose
  - Rigorous controls to demonstrate that initial models have acceptable levels of sensitivity and specificity in their outputs
  - Specific identification of multiple large data sets relevant to natural products and health outcomes associated with their consumption and evidence the data sets proposed are available and appropriate
  - A plan to account for missing and implausible data and for the many synonyms associated with natural products
- For **Innovation,** applications must specify how the proposed tools are novel and will lead to new hypotheses.
- For **Investigators,** applications must include evidence of appropriate expertise as it relates to the type of data to be used, the outcomes to be assessed, and the computational tools proposed.

Review Criteria

- Applications will be scored according to the five standard review criteria: significance, investigator(s), innovation, approach, and environment. Additional review criteria will be taken into account in determining the overall impact score.
- Aspects that reviewers are asked to address match what applicants are asked to address in the application.
- NOFO-specific language has been added to the five standard review criteria.

Dr. Huang advised applicants to make sure to read and consider the review criteria when planning their applications.

Review Panel

Applications submitted in response to this NOFO will be reviewed in a special emphasis panel at NCCIH.

Reviewers will be selected based on:

- Specific area of expertise in the target areas of the NOFO
- Clinical disciplines and scientific areas proposed in the applications

Reviewers will be oriented to use the additional review criteria and the additional review language added to the standard criteria in their assessment.

Dr. Huang reminded applicants to address how their applications would be impactful, considering the goals of the NOFO.

Key Dates

- Letters of intent (requested but not required) are due **May 28, 2024.**
- Applications are due **June 28, 2024,** and late applications will not be accepted.
- The review meeting will be held in **November 2024.**
- The award decision will be made in **April 2025.**

Letters of intent should be sent to Jessica McKlveen, Ph.D., NCCIH Office of Scientific Review, at jessica.mcklveen@nih.gov and should include the following:

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

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

Questions and Answers

Q: Will the rescheduling of cannabis as Schedule III take cannabinoids completely off the table?

A: Dr. Hopp explained that NCCIH is interested in research on cannabis, particularly the minor cannabinoids and terpenes found in the cannabis plant. The proposed rescheduling won't change either NCCIH's or ODS' research interests. NCCIH already funds cannabis-related research. Cannabis remains generally out of scope for ODS.

Q: Is cannabis considered a botanical dietary supplement?

A: Dr. Sorkin explained that cannabis is not considered a dietary supplement because certain constituents from cannabis are approved as drugs. Dr. Hopp added that dietary supplements cannot contain drugs approved by the U.S. Food and Drug Administration (FDA).

Q: Will this request for applications (RFA) be renewed, or is June 28, 2024, the last deadline?

A: Dr. Hopp said that June 28, 2024, is the only deadline date. There are currently no plans to reissue this RFA.

Q: Would you please clarify the amount of funding? The NOFO states $500K direct costs and $800K total costs. Is that per year or over the full time period of the project?

A: Dr. Hopp explained that direct costs must be less than $500K **per year,** which would be approximately $800K in total costs per year.

Q: Because this NOFO is part of the CARBON Program, is there an expectation that the projects would leverage data generated by the CARBON Program's Botanical Dietary Supplements Research Centers?

A: Dr. Hopp explained that this is not an expectation or requirement. However, there is a large library of literature from the current and former Botanical Dietary Supplements Research Centers that may be valuable. Dr. Sorkin said that applications will be prioritized based on how exciting and strong the science is and how much they could add to the understanding of the biological activities of natural products.

Q: How large does the data set need to be?

A: Dr. Hopp explained that there is no required quantity of data, and there is no required number of data sets. The amount of data needs to be large enough to answer the questions or create the tool proposed in the application. It's important to note that this NOFO is for research "at scale," so the data sets need to be large. Exactly how large they need to be depends on what the applicant intends to do with the data. Dr. Sorkin added that a large enough data set is one that can rigorously answer the question that you're setting out to address, with a reasonable probability of limiting false positives and false negatives. It would be helpful to make this clear for reviewers in your application.

Q: Can I submit post-submission materials?

A: Dr. Huang explained that post-submission materials are allowed by this NOFO. They must be submitted no later than 30 calendar days prior to the peer review meeting. Concurrence of the authorized organization representative is required. More details about post-submission materials are given in the NOFO and in NOT-OD-19-083 and NOT-OD-23-106.

Q: An attendee raised additional points regarding FDA approval of synthetic cannabinoids and isolates from the cannabis plant.

A: Dr. Hopp explained that this specific regulatory issue doesn't impact the details of the NOFO discussed here. Ms. McRae-Williams asked the attendee to contact NCCIH or ODS if additional information is needed.

Q: What does success look like for this NOFO? Is it freely available software for people to upload and analyze their database? Could it be a database? Does the software tool created as a final product need to be freely available?

A: Dr. Hopp explained that although projects would involve aggregating large amounts of data, the end product is not a database. The end product should be a computational tool that has generated a hypothesis about how natural products might be beneficial in different contexts related to whole person health. Language in the NOFO explicitly states the expectation that any tools developed will be made open-source and freely available, as follows:

Any interoperable databases, standards, or software produced must be made open-source and freely available to the research community while adhering to privacy and ethics concerns.

Q: Could you elaborate more about nonresponsive research, such as "purely epidemiological projects looking at associations between dietary patterns and components and specific health outcomes"? Would linking dietary patterns with whole person health be responsive?

A: Dr. Hopp said that if the proposal is just about dietary patterns, it would not be responsive. The project needs to go deeper. It needs to focus on specific chemical components of diets that might be correlated with effects on whole person health. Dr. Sorkin added that the funding opportunity requires the linking of at least two orthogonal data sets for chemistry and biology. If you are using a data set that links dietary patterns to health outcomes, you would need to link another data set to it, for example, a data set on the composition of specific foods or on environmental variables. A single dietary survey associated with health outcomes would not be sufficient.

Q: Is there a specific preference for a particular type of data for use with AI, such as imaging, text, or omics?

A: Dr. Hopp said there is no preference. All those types of data are great examples, and there are others. The type or types of data to be used depends on the question you're trying to answer.

Q: What are the appropriate existing repositories?

A: Dr. Hopp explained that there are no required or forbidden data sets. There are existing NIH-supported data repositories, but you are not required to use them. If you have access to a private repository and want to use it, that's fine. The data are more important than their location; the data sets need to be of sufficient size and complexity to allow for robust training and testing of the computational tools you create.

Q: Could you clarify what qualifies as chemical data sets and biological data sets?

A: Dr. Hopp said that chemical data are about the composition of natural products. Biological data are about the activities associated with the substances. Chemical and biological data might be present in the same repository. You may need to combine chemical and biological data to address the question of how the chemistry of the natural product is affecting the biology.

Q: Will reviewers be selected based on the types of applications received? For example, if we have an imaging AI-specific proposal, will reviewers with computer vision expertise be recruited?

A: Dr. Huang said that yes, reviewers will be selected based on the types of applications received and the types of expertise needed to review them. For imaging AI-specific applications, reviewers with expertise in imaging AI will be recruited. Broadly, reviewers with expertise in computer vision may be recruited.

Q: Are foreign organizations eligible to apply?

A: Dr. Huang said that foreign organizations and nondomestic components of U.S. organizations are eligible to apply. Foreign components such as foreign collaborators are also allowed.

Q: Can you clarify the budget allowed in this NOFO?

A: Dr. Huang said that the budget must be less than $500K per year in direct costs and needs to reflect the actual needs of the proposed project. If the budget for any year is $500K or more, the application would be noncompliant. In addition, the application needs to allocate part of the budget toward attending the annual meeting of the CARBON consortium.

Q: What types of new data generation will be allowed?

A: Dr. Hopp said that new data generation should be only a small minority of the overall project. For example, you might generate some data to help you develop a tool or to validate or test your hypothesis. In the late stages of the project, you might do some experimentation to test any hypotheses generated by the computational tools.

Q: What are the desired qualifications of the PIs or data scientists?

A: Dr. Hopp said that the individuals need to be qualified to perform the planned research. There is no minimum seniority level. Early-stage scientists are encouraged to apply, but the research team must include the requisite expertise to do the work that is proposed. One reason for using the R01 funding mechanism was to make this opportunity available to a wide range of investigators. Dr. Sorkin explained that this NOFO calls for a transdisciplinary team that includes people with data science and computational expertise along with those with biological and chemical expertise. The PI could have any of these types of expertise, but the team as a whole needs appropriate expertise to understand and interpret the data in biologically meaningful ways.

Q: Is it required that all data used be publicly available? Or can you have a mix of public and private data?

A: Dr. Hopp said that privately held data sets are allowed. Investigators would not be expected to make a private data set public, but the tools developed during the project must be public. Dr. Hopp recommended contacting him offline to discuss this question further. Dr. Sorkin added that it is important in your application to show that you have access to the data sets you propose to use and have the expertise to appropriately use and interpret the data.

Closing Remarks

In final comments at the end of the webinar, Dr. Hopp urged potential applicants to contact him before submitting a proposal. He does not want applicants to have to withdraw an application because it is not responsive. Dr. Sorkin said that ODS and NCCIH are very excited about this initiative, which will take the CARBON program in a new and innovative direction. Dr. Huang urged applicants to read the NOFO carefully to make sure their applications are complete, compliant, and responsive, and to submit applications as early as possible. He recommended reaching out to NCCIH or ODS with any questions.

Ms. McRae-Williams reminded attendees that they would receive slides and a summary shortly after the conclusion of the webinar and a written summary in about a week. She urged applicants to follow up with Drs. Hopp, Sorkin, or McKlveen as needed. She then closed the webinar.