Botanical Dietary Supplements Translational Research Teams (RM1 Clinical Trial Required) Technical Assistance Webinar (RFA-OD-24-014)

Purpose of the Webinar

On Tuesday, May 7, 2024, the National Institutes of Health's (NIH's) National Center for Complementary and Integrative Health (NCCIH) hosted a technical assistance webinar to answer questions about the notice of funding opportunity (NOFO) Botanical Dietary Supplements Translational Research Teams (RM1 Clinical Trial Required), a joint initiative of NCCIH and the NIH Office of Dietary Supplements (ODS) with additional support from NIH's National Institute on Drug Abuse (NIDA). This NOFO supports one component of the NIH Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) Program.

Webinar Speakers

- Patrick Still, Ph.D., Co-Director, NIH CARBON Program, Basic and Mechanistic Research Branch, NCCIH
- Barbara C. Sorkin, Ph.D., Co-Director, NIH CARBON Program, ODS
- Jia Bei Wang, M.D., Ph.D., Program Officer, Division of Therapeutics and Medical Consequences, NIDA
- 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)

D. Craig Hopp, Ph.D., Deputy Director, Division of Extramural Research, NCCIH, also participated in the question-and-answer portion of the webinar.

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. Still explained that clinical translation of research on chemically complex dietary supplements has been a gap area in NIH-supported research and continues to pose technical challenges. Nutritional approaches delivered as complex mixtures are thought to act across multiple biological systems. Classic pharmaceutical development approaches that seek to identify a single active compound that acts at a single target may not readily apply to the study of multisystem and multicomponent interactions involving nutritional and other chemically complex interventions. Thus, a deeper understanding of the systems-level interactions of natural products with human biology, including the microbiome, is needed to answer fundamental questions regarding their health effects. The CARBON program reflects NCCIH's strategic interests in whole person health. It addresses multicomponent interventions, including their molecular mechanisms and targets of

action, to support future clinical trials. The type of research projects supported through this NOFO will require transdisciplinary research teams spanning different areas of expertise.

Dr. Sorkin noted the importance to ODS's mission of understanding the effects of chemically complex dietary supplements, such as botanicals, and highlighted key features of this funding opportunity:

- The participating NIH components are ODS, NCCIH, and NIDA.
- Only new applications will be accepted; resubmissions and revisions are not allowed.
- Every application must include an NIH-defined clinical trial, but efficacy clinical trials are not allowed.
- The project must have a multiple program director/principal investigator (multi-PD/PI) leadership team of three to six members.
- Foreign organizations and non-domestic components of U.S. organizations are not eligible to apply. Foreign components are allowed, but clinical trials may not be conducted at non-U.S. sites.

The goal of this NOFO, Dr. Sorkin said, is to fill in critical gaps in the data needed for design and interpretation of a future highly informative and translatable efficacy clinical trial of a chemically complex intervention that is likely to have a significant impact on health. These interventions could be botanical dietary supplements or foods of plant origin that contain bioactive components beyond basic nutrients.

The focus should be on products for which there is substantial evidence that the product and outcome proposed in the application will benefit health. That evidence must come from at least two different scientific approaches.

Specific Requirements of the NOFO

For this NOFO, research must focus on a **chemically complex botanical or other natural product,** such as:

- Terrestrial plants, algae, macroscopic fungi, or chemically complex products derived from them
- Traditionally used herbal products that are ingested
- Foods of plant origin that contain bioactive components beyond basic nutrients

Applications must include justification for the doses/concentrations you propose to study. This could be equivalence to the doses traditionally used where they can be estimated and are compatible with safe use. Your application must show that you can obtain the product and that you have the capacity in your team to monitor the integrity of the product, its stability and bioavailability. Your application needs to include strong evidence that one or more specific, identified chemicals in the product are required for the outcome you propose to study. It must also include plans to screen for additional product components that may modulate the effects of the active chemicals as well as plans to screen for additional targets of the known bioactive constituents, unless such data have already been reported.

Types of research **not** appropriate for this award include:

- Scale-up of production of natural products
- Development of tools to synthetically modify natural products to improve bioavailability or potency
- Projects that focus on highly purified individual compounds
- Projects that focus on natural products that have been developed as drugs

Your project must include a clinical trial relevant to a future efficacy trial with resilience outcomes, as defined by the trans-NIH resilience working group. In brief, resilience is the ability to resist, adapt to, grow, or recover from a challenge or stressor.

Dr. Sorkin cautioned that routes of exposure other than ingestion are acceptable only if you have evidence that the mechanisms of action are similar to those for ingestion of the product.

The RM1 funding mechanism is for **research that requires multiple laboratories working together as equal contributors** on a single overarching set of integrated specific aims. Each PD/PI must be willing to devote a major part of their research effort to the team project. Each biological question (sub-aim) should require multiple members of the team.

Required application components include:

- A data management and sharing plan
- **Both** a multi-PD/PI leadership plan and a team management plan
- A mechanistic or early-phase NIH-defined clinical trial

NIDA-Specific Areas of Interest

Dr. Wang explained that NIDA's mission is to advance science on drug use and addiction and apply that knowledge to improve individual and public health. NIDA's specific interests within this NOFO are

- Chemically complex botanicals or natural products with strong evidence of clinical safety and effects on resilience to drug addiction
- Chemically complex botanicals or natural products with strong evidence of harm reduction for substance use

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, "The applicant **must** explain how achieving the proposed Specific Aims will significantly and critically enhance design of a future, highly informative clinical trial of the product…"

The NOFO outlines specific examples of why an application would be considered nonresponsive. Dr. Huang encouraged applicants to review this list.

Compliance

Compliance factors specific to this NOFO include the following:

- Budget
    - Application budgets are limited to **up to $1.5 million** in **Total Costs per year,** including consortium facilities and administrative (F&A) costs, but need to 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.
    - Inclusion of a scientific project manager or coordinator as a Senior/Key Person with adequate authority is recommended.
- Project period
    - The scope of the proposed project should determine the project period.
    - The maximum project period is **5 years.**
- Eligibility
    - Non-U.S. entities (foreign institutions) and non-U.S. components of U.S. organizations **are not** eligible to apply. Foreign components **are** allowed. Clinical trials **cannot** be performed at a foreign site.
- Page limitations
    - In the Research Strategy, the Research Program section is limited to **30 pages** and the team management plan is limited to **3 pages.**
- Post-submission materials
    - Post-submission materials are allowed and are due 30 calendar days before the peer review meeting date.
    - See NOT-OD-19-083 for details about allowable post-submission materials.
    - Information accidentally left out of the application cannot be submitted as post-submission material.

Completeness

The application **must** be submitted as a **multi-PD/PI application,** with **three to six PDs/PIs,** and a multi-PD/PI leadership plan **must** be included.

The Research Strategy **must** include a Research Program and team management plan.

Two tables are required and must be included within the page limit for the Research Program:

- A table, organized by specific aims, that identifies the **contributions expected from each PD/PI toward accomplishing each aim**
- A table that identifies **critical milestones and performance criteria, a timeline for completion,** and whether critical milestones depend on the completion of antecedent milestones

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. The webinar slides include an example of a match.
- 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 preparing 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 **June 7, 2024.**
- Applications are due **July 8, 2024,** by 5 p.m. local time of the applicant organization, and late applications will not be accepted.
- The review meeting will be held in **November 2024.**
- The earliest start date is **July 2025.**

Letters of intent should be sent to Barbara C. Sorkin, Ph.D., Co-Director, NIH CARBON Program, at sorkinb@mail.nih.gov and should include the following:

- Descriptive title of proposed activity
- Name, address, and telephone number of each PD/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.

In conclusion, Dr. Huang emphasized that **key specific features of this NOFO** include the requirement for team research and the inclusion of a mechanistic or early-phase clinical trial relevant to a chemically complex natural product for resilience.

Who Can Answer Your Questions?

Ms. McRae-Williams advised applicants to direct their questions as follows:

Before submitting your application, send questions to:

- Barbara Sorkin at ODS or Craig Hopp at NCCIH
- Jia Bei Wang at NIDA for NIDA-relevant applications
- Jessica McKlveen at NCCIH for review-related questions

After submitting your application, send questions to Dr. McKlveen.

After your application is reviewed, send questions to your assigned NIH program official.

Questions and Answers

Q: Could you please expand on the need for evidence from two different types of sources? Can you give examples?

A: Dr. Sorkin explained that funding should go to product/outcome pairs for which there is strong evidence of an effect from sources of evidence based on different scientific principles, such as evidence from animal model or in vitro studies plus epidemiologic, ethnobotanical, or early-phase clinical evidence. If there have been definitive phase 3 clinical trials for your product/outcome pair, it may not be appropriate for this funding opportunity. Dr. Sorkin advised getting in touch offline for additional information.

Q: What about supplements that may have negative impacts as well as positive impacts, such as plant sterols or seaweeds?

A: Dr. Still explained that the answer depends on the positive aspects that you want to investigate and how the evidence of negative aspects affects the project as a whole. He recommended considering whether the project is a good one to pursue despite the potentially negative effects of the natural product. Dr. Hopp said that this NOFO is not intended for toxicology studies. The focus is on benefits of the natural products. However, if products include both beneficial and potentially harmful constituents, studies that differentiate between these constituents would be appropriate. Dr. Sorkin said that for products that have narrow therapeutic windows or cost-benefit issues, it is important to understand how they can be used for benefit. If there is evidence of adverse effects as well as strong evidence of benefit, it is important to understand for whom, when, and how they have adverse effects. Learning about this will help people use the products as safely as possible.

Q: To justify a product, do you need to know what individual compounds are active or is it enough to show evidence for broad chemical groups?

A: Dr. Sorkin said that you need evidence that you understand the chemistry of what's exerting the effect well enough so you can provide a product with reproducible effects. For example, if you have something that has the same effects with or without a glycan added to it, you might include both in your product. Dr. Hopp added that projects that focus on highly purified individual compounds are not responsive to this NOFO. Dr. Sorkin said that multiple compounds in a natural product may

contribute to benefits in different ways; there is a need to fill the gaps in this challenging research area.

Q: Please define "major part of research effort"?

A: Dr. Sorkin said that in general, anything less than 15 percent effort would not be considered a major research effort for multi-PDs/PIs.

Q: Will NIDA funding be extra to ODS funding?

A: Dr. Wang said that NIDA will support applications appropriate to NIDA's interests both scientifically and financially. NIDA will provide funds to support these projects in addition to those provided by ODS and NCCIH.

Q: If we have PIs from different institutions, how will budgets be handled? Will there be separate awards or separate indirect costs?

A: Dr. Hopp explained that the award will go to the parent institution, that is, the one where the contact PD/PI is located. There could then be subawards from the parent institution to other collaborating institutions. He suggested contacting him offline to discuss indirect costs.

Q: Can you please clarify whether a U.S. firm can apply and work with a foreign laboratory? Also, can a trial be in a foreign hospital?

A: Dr. Huang said that a U.S. firm could apply; for-profit organizations are allowed. As foreign components are allowed in this NOFO, applicants could work with a foreign laboratory. However, a clinical trial cannot be conducted at a foreign site.

Q: Will a recording of this webinar be available online?

A: Ms. McRae-Williams explained that speaker slides would be sent to all registrants immediately after the webinar, and a detailed written summary would be provided 7 to 8 days after the webinar.

Q: Regarding the team management plan, a scientific project manager or coordinator is recommended. What defines a project manager or coordinator as having adequate authority?

A: Dr. Sorkin explained that adequate authority is the authority to mediate between PDs/PIs and ensure that all team members have adequate resources. Dr. Hopp explained that this role is usually administrative. For example, people in this role may help ensure that administrative tasks are completed on time, coordinate communication with NIH, and coordinate submission of research performance progress reports. Responsibilities may vary for different projects.

Q: Regarding the required Table 2, can you give an example of performance criteria? Is it obvious that completing the clinical trial is one of them?

A: Dr. Sorkin agreed that completing the trial would be one of the criteria. She also explained that a clinical trial, even one that is not an efficacy trial, might take more than a single year to complete. The performance criteria might include kicking off the trial on time and completing recruitment on time.

Q: Can we propose to study more than one botanical product?

A: Dr. Sorkin said that you can, but you have only 5 years and a limited amount of funds from the award, and your project must have a single overarching specific aim. Studying more than one product could be challenging. You should have strong evidence that at least one of your products is worth pursuing at the level of commitment this NOFO requires.

Q: Please clarify page numbers. Is it correct that the Research Strategy is 33 pages, Research Program is 30 pages, Team Management Plan is 3 pages, and Specific Aim is 1 page and is separate from the Research Strategy?

A: Dr. Huang said that this is correct.

Q: Does the request for applications (RFA) call for a format similar to that used in other NIH applications, with specific aims, preliminary data, and strategies, given the 30 pages? Is primary data relevant?

A: Dr. Hopp said that the format is the normal NIH application format.

Q: Can you provide the email address for the person who can answer questions?

A: Ms. McRae-Williams explained that the names and contact information are given in the NOFO.

Q: If you know that a complex extract is active, do you have to know one or more individual compounds in it that are active, or can you use this grant to find out what the active components are?

A: Dr. Sorkin explained that you need preliminary data to show that at least one compound in the product is required for the activity you are planning to study. This NOFO is not appropriate for determining what you need to standardize in your product. You should already have that information and have solid, convergent evidence that you know what the active agent(s) is/are. Dr. Hopp added that you are required to describe how you will assess your proposed product for the presence of additional active ingredients that might affect the outcome.

Q: An attendee who is from a foreign country and is interested in collaborating with a U.S.-based institution asked whether NIH could offer assistance.

A: Dr. Hopp said that this question would be better addressed offline. He asked the questioner to email one of the program officials who participated in the webinar.

Q: Is outsourcing the clinical work to a well-established contract research organization (CRO) allowed, or must the co-PIs conduct the clinical research themselves?

A: Dr. Hopp said that a CRO could be part of the team, but you would need to indicate how you are maintaining control and oversight of the CRO's work. Nothing in the NOFO precludes using a CRO to conduct the trial, as long as the trial is not performed outside the United States. Dr. Sorkin pointed out that this is an RM1 for translational research teams. She asked applicants to consider whether the CRO would be able to work with them in an interactive, dynamic fashion.

Q: Can one of the PIs also be the project coordinator?

A: Dr. Hopp said yes. Dr. Sorkin added that in this instance, it would be important for the team management plan and multi-PD/PI leadership plan to show that there would be evenhanded sharing and distribution of resources throughout the project.

Q: Is investigating a botanical combination product, for example, one consisting of three botanicals, responsive?

A: Dr. Hopp said yes. Dr. Sorkin said that you need to know what the active components are and be able to characterize the product.

Q: Can we study one supplement for two disease types?

A: Dr. Sorkin explained that this funding opportunity is not for studies of diseases. It is for studies about increasing resilience and promoting health, and the studies can include more than one outcome. She encouraged applicants to look at whole person effects of the products they plan to study, as this is a research priority for both NCCIH and ODS.

Q: How complex must a product be? Would a fractionated extract with two or three components or a combination of several purified substances be responsive?

A: Dr. Sorkin asked the questioner to follow up offline with specific details.

Q: Is the use of a proprietary commercial product responsive, particularly if it has unique content?

A: Dr. Hopp said it could be responsive, but the composition of the product cannot be kept secret. An application that does not give the composition of the product would likely not do well in review because without sufficient product information, reviewers may not be able to fully evaluate the significance, feasibility, and scientific strength of the project. The NCCIH Natural Product Integrity Policy may be a helpful resource.

Q: Is there any specific guidance for numbers of patients or healthy controls for clinical trials?

A: Dr. Sorkin explained that appropriate numbers would depend on the question you are asking and the data you already have. She recommended including a biostatistician in the planning of the project.

Q: The RFA mentions that product formulation is allowed. Are there types of formulation research that would not be acceptable, such as adding pharmaceuticals or nanoparticles?

A: Dr. Hopp said that the mention of product formulation referred to different preparations of a product. Adding pharmaceuticals probably would not be acceptable. Adding nanoparticles probably would be. Dr. Hopp asked the questioner to contact him offline.

Q: Is there a preference between potential new uses of established products versus novel products?

A: Dr. Sorkin said that novelty is desirable, but it must have strong science behind it. Because of the level of commitment involved in this initiative, a high level of supporting data is required. She recommended talking to one of the program officials before submitting an application.

Q: Must every PI be involved in every aim?

A: Dr. Hopp said that this is not required, but you should be able to show across your aims that you have a true collaboration. Having separate PIs for each aim would not fulfill the goals of this NOFO. There should be cross-pollination across the aims. Dr. Sorkin added that applicants must submit a table of specific aims that explains which investigators will contribute to each aim. Reviewers will be looking at whether the project really requires the team approach.

Q: How many projects are anticipated to be funded?

A: Dr. Sorkin said that NIH hopes to fund two meritorious but different applications. However, funding depends on the merit of the applications and the budget.

Q: Can a foreign collaborator collaborate with a U.S.-based PI?

A: Dr. Sorkin said that this can be done, but clinical research cannot be done at a foreign site.

Final Comments

Dr. Sorkin said that the questions indicate that there are exciting ideas out there. She encouraged all potential applicants to read the NOFO carefully, including the review section and the section on submitting your application. Make sure your application addresses the specific questions for review. She advised all applicants to contact her or one of the other program officials to ask questions about their applications. Applicants should include their specific aims in the initial email to a program official.

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, Wang, or McKlveen as needed. She then closed the webinar.