National Center for Complementary and Integrative Health (NCCIH)

Natural Products Technical Assistance Webinar: Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics

Background

About the Webinar

On Wednesday, October 26, 2016, the National Institutes of Health (NIH) NCCIH hosted a webinar to provide information on PAR-16-418 and PAR-16-419, two funding opportunities that support "Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics." The webinar speakers described the NCCIH mission and conceptual framework, listed relevant NCCIH high-priority interest topics, defined key terms, explained the nature of the clinical studies each funding opportunity announcement (FOA) is designed to support, enumerated review criteria and submission deadlines, and answered questions submitted by e-mail by webinar participants. The webinar was moderated by Catherine Law, MTSC, (Office of Communications, NCCIH) and presented by Ashlee Tipton, Ph.D. (Division of Extramural Research [DER], NCCIH); Wendy Weber, N.D., Ph.D., M.P.H. (Branch Chief, DER, NCCIH); and Martina Schmidt, Ph.D. (Chief, Office of Scientific Review, NCCIH). This report summarizes in bullet point format the information provided to potential applicants during the webinar.

NCCIH Mission and Conceptual Framework

MISSION: to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care (NCCIH was formerly known as the National Center for Complementary and Alternative Medicine, or NCCAM).

CONCEPTUAL FRAMEWORK: conduct exploratory or pilot studies on interventions using natural products; identify and characterize mechanisms, optimize protocols, evaluate feasibility and efficacy of interventions; disseminate results of basic research and clinical studies; facilitate translation of basic research.

Relevant FOAs

- PAR-16-418; R61/R33 – Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics
- PAR-16-419; R33 – Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics

Purpose of the FOAs

These FOAs are meant to be used by investigators who are gathering preliminary data on the effects of a natural product in humans, with the goal of proceeding toward efficacy studies in the future. Thus, these FOAs support early stage clinical testing of natural products in human subjects. More specifically, these FOAs support research designed to

- Demonstrate and/or reproduce effect in humans of a natural product on a well-defined, biological signature or mechanism of action.

- Demonstrate bioavailability, characterize pharmacokinetics, and evaluate toxicity of a natural product in humans.
- R33 phase (or independent R33) is specifically for studies to replicate and/or extend the observations of a completed study; for example, determine dose/response curve on the biological signature or mechanism of action.
- R61 phase is specifically for natural products whose effects in humans are less well characterized.

Excluded from Support by PAR-16-418 and PAR-16-419

- Clinical trials solely to estimate intervention effect size for power calculations of future efficacy trials.
- Preclinical studies conducted in “other than human” species.
- Clinical trials to determine efficacy or effectiveness in humans.
- Clinical studies of cancer therapeutic or preventive properties of a natural product (investigators should contact the National Cancer Institute [NCI] for appropriate FOAs).

Excluded from Support by PAR-16-419

- Applications lacking preliminary data demonstrating that the specific natural product under study impacts the proposed biological signature in humans.
- Applications lacking preliminary data demonstrating that the natural product is bioavailable in humans.

NCCIH Priorities for Natural Product Clinical Trials

Symptom management, especially for

- sleep disturbance
- pain
- mental health conditions treated in primary care, such as mild-to-moderate depression, anxiety, and post-traumatic stress.

Products, such as probiotics, that modulate the influence of the gut microbiome

- probiotics or other natural products that interact with the brain and/or immune system to modulate biological signatures linked to depression, anxiety, or chronic pain.

Definitions

Clinical Trial (per Notice Number: NOT-OD-15-015; Effective: January 25, 2015)

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Natural Product (as relevant to PAR-16-418/419)

Compounds such as herbs (also known as botanicals), vitamins, minerals, and probiotics. These compounds are generally readily available to consumers and can also be referred to as dietary supplements. However, compounds classified by the FDA as “New Dietary Ingredient(s)” are not appropriate for this funding opportunity.

Budget, Duration, and Page Limit

- **R61**: duration up to 2 years
  Not to exceed $400K in direct cost over 2 years
- **R33**: duration up to 3 years
  Not to exceed $750K in direct cost over 3 years
- PAR-16-418: 12-page limit, including both R61 and R33 components
- PAR-16-419: 12-page limit

Required Application Documents

- SF424 (R&R)
- PHS 398 Research Plan
- Clinical Protocol Synopsis (12 pages)
- Clinical Trial Experience Table (3 pages)
- Regulatory Communication Plan (3 pages)

Applications lacking any of these elements will not be reviewed

Milestones (R61 to R33)

- Briefly, milestones should include:
  - Operational definition and objective measure(s) of the biological signature(s)
  - Definition of clinically significant change in the biological signature
  - Satisfactory recruitment and retention of study participants
  - Demonstration of human bioavailability of the natural product
- Additional milestones that can be included in the R61
  - Short-term human pharmacokinetic (PK) data
  - Feasibility and appropriateness of dosing regimen
- Elements that must be completed prior to transition to R33 phase
  - NCCIH-approved protocol and data and safety monitoring plan for the R33 trial
  - Regulatory approvals as required (institutional review board [IRB], FDA investigational new drug [IND]) for the R33 trial

See funding opportunity for full details.

Milestones (R33 Phase)

- Milestones that must be included in the R33 phase:
  - Replicate clinically significant change in biological signature(s) (as observed in R61 or equivalent)
  - Demonstrate correlation between change in biological signature and functional/clinical outcomes
  - Detailed assessment of feasibility, safety, and acceptability
  - Assessment of risk of adverse events
  - Satisfactory recruitment and retention of study participants, adherence to sample collection and other study protocols, appropriate reporting of adverse events

- Additional milestones that can be included in the R33
  - Assessment of dose-response curve on the biological signature
  - Detailed PKs at variable doses

Scored Review Criteria

- Significance
- Innovation
- Investigator
- Approach
- Environment

Additional Review Criteria

- Milestones and Timeline
- Protections of Human Subjects
- Inclusion of Women, Minorities, and Children
- Vertebrate Animals
- Biohazards

Additional Review Considerations

- Select Agent Research
- Resource Sharing Plans
- Budget and Period of Support
- Authentication of Key Biological and/or Chemical Resources

Other Requirements

Product Quality/Integrity Evaluation is also required; if it is part of the research strategy and included in the Research Plan it will be considered during scientific review. Additionally, if an application is being considered for funding, NCCIH will require more detailed product quality information after scientific review is complete.

Application Timeline

Earliest Submission Date: November 2, 2016

Letter of Intent (LOI) Due Date: November 2, 2016 (not required)

Application Due Date: December 2, 2016, 5:00 PM (applicant's local time)

AIDS-related Application Due Date: December 16, 2016, 5:00 PM (applicant's local time)

Scientific Merit Review: February 2017

Advisory Council Review: May 2017

Earliest Start Date: July 2017

Key Contacts

Scientific questions prior to submission or after review
Dr. Wendy Weber at weberwj@mail.nih.gov

Questions about the scientific review process
Dr. Martina Schmidt at schmidma@mail.nih.gov

Questions and Answers

Post-Webinar Most Frequently Asked Questions (added 11-21-16)

Q. During the webinar and on slide 29, it mentions that a draft informed consent form must be included in the Appendix. However, I could not find any reference to this in the FOA. Could you confirm whether this is a requirement in the application, and, if so, where this should be included?

A. Thank you for bringing this to our attention. The funding opportunity is a re-issue of a previous FOA, so it is possible some of the slides had information from the previous FOA.

The FOA states the following must be provided as other attachments (See Section IV.2):

1. Clinical Protocol Synopsis of up to 12 pages
2. FDA or Other Applicable Regulatory Agency Strategy and Communication(s)
    a. Note that if you have a waiver from the FDA for the specific studies that will be performed under the R61 and/or R33, you can include this letter as part of this attachment.
3. Clinical Trial Experience Table

There is no need to include a full study protocol or a draft informed consent document, as referenced on slide 29; slide 29 has been edited to reflect this.

Q. Are we allowed to randomize and blind participants to the study product?

A. We encourage both randomization and blinding as long as the primary outcomes are assessing the impact on the biological signature and not focused on clinical efficacy.

Questions During the Webinar

1. Please define the term "biological signature."

An objective measure of the postulated mechanism of action by which the natural product might ultimately modify the clinical condition or symptom(s) of interest. Biological signatures may be molecular/cellular, tissue/organ, or somatic measures that are consistent with the natural product and specific aims of the study.

2. Is a detailed budget for the R33 phase required at the time of the initial submission or only if the grant later progresses to that phase? We ask because the design in sample size for the R33 phase is dependent upon the findings from the R61 phase.

Yes. A budget for both phases is required at time of submission. Because the study design specifics and possibly the budget of the R33 phase might be dependent on outcomes of the R61 phase, it is appropriate to suggest alternative or contingency plans that take this into account in your application.

3. If a co-investigator on this grant submission holds an IND for a specific natural product and the principal investigator (PI) of this submission would like to amend the existing IND for his product, is a pre-IND meeting or FDA communication required?

The required Regulatory Communication Plan associated with the application should describe the status of the IND being considered by/submitted to the FDA. In addition, the co-investigator who holds the IND on the product should determine if he/she can add a new protocol to the existing IND. The co-investigator that holds the IND will also need to consider if he/she is able and willing to sponsor the applicant's proposed trial (by modifying the existing IND). Another option would be that the holder of the IND establishes a drug master file with the FDA for the product and then the PI for the application can submit a new IND relevant to use of that product in the proposed study. The new IND can reference the drug master file for the natural product that already is being studied under the previous IND. Ultimately, the applicant would need to negotiate with the FDA in order to identify an acceptable way to meet the regulatory requirements for the proposed study. There can be multiple ways to satisfy the FDA requirements. A summary of the plans for how the applicant will meet the regulatory requirements for the trial needs to be provided in the Regulatory Communication Plan attachment that is required in the application.

4. What is the difference between the PK milestones in the R61 part versus the R33 part?

For R61 phase: the only required PK milestone is to demonstrate bioavailability of the product (i.e., clearance time does not need to be evaluated). For probiotics, standard bioavailability parameters are not relevant because the probiotic is not absorbed.

For R33 phase: bioavailability of the product must already be established; PK milestones permitted include evaluating the bioavailability of different formulations of the product, dosing studies to determine frequency of dosing need to establish a steady state dose, or other pharmacokinetic studies that will help to determine the appropriate dose for the future efficacy study.

5. Are randomized controlled trials acceptable under the R33 part of the FOA?

Randomized, placebo-controlled trials are acceptable under both these FOAs and in both the R61 and the R33 phase. It may be just as important to demonstrate that giving a placebo does not change the biological signature as demonstrating that the natural product has an impact. However, trials supported by these FOAs may not evaluate efficacy of a natural product for a clinical outcome.

6. Is an IND application required to test botanicals for topical applications?

FDA must be contacted to determine whether an IND is needed for the specific study. If a compound is used topically to treat, mitigate, or prevent a clinical sign/symptom of disease, it is likely that an IND will be needed. Only the FDA can make the determination as to whether an IND is needed for the proposed clinical trial that will be conducted under the R61 or R33 phases. If the FDA grants a waiver, written documentation from the FDA indicating that an IND is not needed should be included in the application or prior to funding.

7. Does the described PAR funding mechanism include proposals aimed at the study of a bioactive ingredient derived from a natural product (for example, resveratrol)? If yes, can the bioactive ingredient be a synthetic agent (for example, chemically synthesized resveratrol)?

Products like resveratrol could potentially be studied. However, if the specific product is classified by the FDA as a "New Dietary Ingredient," it cannot be studied under these FOAs. Synthetic versions of natural products are acceptable if other criteria specified by the FOAs are met.

8. For those of us with difficulty meeting the December deadline, is this (or a similar) request for applications likely to be renewed any time in the next 12 months?

At this time, there are no published FOAs on this topic with a deadline later than December 2017. NCCIH has offered a similar FOA once in the past (i.e., this is the second round). NCCIH is committed to supporting early clinical studies of natural products. NCCIH will continue to have FOAs for this type of research in the future.

9. If a previous application to this PAR was done under the R21/R33 mechanism, would a revision of that application submitted to the R61/R33 mechanism be considered a resubmission (with a 1-page introduction) or a new submission?

CORRECTION: All applications to these FOAs will be considered new applications. No resubmissions are allowed. If you applied to the previous RFAs on this topic (RFA-AT-16-001 or RFA-AT-16-002), you can submit an application to the new FOAs on the same topic as your previous application, however it must be submitted as a **new application**. NCCIH expects that applicants will nevertheless take advantage of previous reviewers' comments to strengthen the new application. In this case, the new application cannot refer to the previous review and cannot include any response to reviewers' previous concerns, so you will not be able to include an introduction page as would be allowed for resubmission applications.

10. Will slides be available after webinar?

Yes.

11. What about the "product integrity profile"? Is it necessary for the R61?

Yes. Sufficient data on product quality must be included in the application for reviewers to be able to evaluate the quality of product being studied. For applications that are being considered for funding, more detailed information on product integrity will be requested by NCCIH after review is complete and prior to funding.

12. Can we do a comparison of doses in the R61 phase rather than the R33?

Yes, either the R61 or R33 phase can use multiple doses. However, the applicant can consider the feasibility of studying more than one dose of a product within the 2-year time frame of the R61. If multiple doses or formulations are used in the R61 phase, a decision rule would need to be included for determining which dose or doses would be studied during the R33 phase of the project.

13. What are the opportunities for resubmission of this application if not funded in the first round?

See answers to question 8 and 9.

14. Is contact with the FDA around the IND process required prior to submission even for a compound already listed as generally "safe" (i.e., is prior approval required)?

FDA must be contacted to determine whether an IND will be needed for the natural product's use in the clinical trial proposed for the R61 and/or R33 phases, independent of how a product is classified (dietary supplement, food ingredient, or on the list of generally recognized as safe as a component of food). If the FDA requires an IND, a plan for obtaining the IND must be included in the application and described in the Regulatory Communication Plan. If required, the IND does not need to be in place at the time the application is submitted.

15. Please state the funding priorities again.

The two high-priority areas are: (1) Symptom management, as relevant to sleep disturbance, pain management, or management of mental health conditions treated by primary care medical care professionals (i.e., mild-to-moderate depression, anxiety, post-traumatic stress); (2) Effects of probiotics or other products on the interaction(s) between the gut microbiome and the brain or the immune system.

Applications that do not address high-priority topics can be submitted and will be reviewed for scientific merit, independent of the topic being studied. However, if two applications have the same score, but one is in one of the specified high-priority areas while the other is not, the application that fits into one of the specified high-priority areas has a better chance of being funded. Note that any application submitted to study the impact of a natural product on cancer prevention or treatment will not be funded, regardless of score.

16. How many subjects are needed for the R33 to qualify?

A power calculation must be carried out to determine the sample size that is adequate to detect clinically significant change in the biological signature of interest. Data from previous research or published literature on the biological signature can be used to determine the minimum number of subjects for adequate power to reach statistical significance for a change in the biological signature.

17. How many grants are you planning to fund with these two FOAs?

The number of applications to be funded will depend on the number of applications received and their scientific merit (i.e., review score). Note that all early clinical studies on natural products are now being funded through these FOAs (no other mechanism is available).

18. Could a "whole food/medical food" such as a cooked bean powder or heat-stabilized rice bran qualify as a dietary supplement? And if so would the metabolite profile of the cooked bean powder or rice bran be acceptable as the measure of product standard/quality/formulation?

This is a project-specific question. The questioner is asked to follow up with Dr. Weber directly. Note that product quality would generally be evaluated before the product is metabolized and evidence of absorption is not evidence that a product generates an impact on a biological signature.

19. Are applications that investigate the impact of a natural product on gastro-esophageal reflux disease, or GERD, permitted? GERD is strongly linked to development of

esophageal premalignancy, but would a focus on reflux be permitted if cancer was not included.

Reflux is a clinical condition, so it could not be used as a biological signature of treatment with a natural product. Possible biological signatures relevant to GERD might be pH in the esophagus or mucus production in the stomach. Severity of reflux in GERD patients is a "clinical outcome." The questioner may want to follow up by submitting the proposed specific aims for this project to Dr. Weber.

20. Would you mind talking more about the LOI? The presentation said that it isn't required, but is there a template somewhere we should be using if we choose to submit it (and will it hurt our application not to submit an LOI)?

An LOI is not required. It is more a courtesy to the Office of Scientific Review to plan and prepare for the review. There is no template; one should include a list of investigators, topic (title), and institutions involved (to identify conflicts of interest). Applicants will not be penalized if they do not submit an LOI.

21. Would applications involving prebiotics be considered in general and in particular when used as a food ingredient?

Studies on prebiotics are allowed. The applicant would still need to contact the FDA to determine if an IND would be required for the proposed studies.

22. If you can, briefly highlight the distinct requirements of the two mechanisms: one is only R33 and the other is a combined R61 and R33.

R33: project duration is 3 years, and up to $750K in direct costs are allowed. Applicants must have prior evidence linking the impact on a biological signature to a specific product (not a class of natural products) and must have prior evidence that the product is bioavailable. The proposed R33 study should replicate and extend prior results and must examine the impact of the product under study on a measurable and relevant biological signature. The R33 must also examine the strength of correlation between the impact on the biological signature and the clinical outcome of interest for the future efficacy study.

R61: project duration is 2 years, and up to $400K in direct costs are allowed. In the context of the R61/R33 mechanism, the R61 phase must establish: (1) bioavailability of the product; and (2) demonstrate a measurable change in a relevant biological signature.

23. What is the page limit?

12 pages for both mechanisms.

24. Are cancer treatment/prevention protocols acceptable?

Studies proposing to examine the impact of a natural product on cancer treatment or prevention will not be considered for funding for this FOA. The applicant should contact NCI to identify appropriate funding opportunities/mechanisms. Any application submitted to study the impact of a natural product on cancer prevention or treatment will not be funded, regardless of score.