

U.S. Department of Health & Human Services • National Institutes of Health



# NCCIH Natural Products Technical Assistance Webinar: Exploratory Clinical Trials and Studies of Natural Products

October 26, 2016

Moderator: Catherine Law

**Presenters: Ashlee Tipton, PhD; Wendy Weber, ND, PhD, MPH; Martina Schmidt, PhD**



# Overview



Framework for Natural Product Clinical Trials and  
Outline of Funding Opportunity Announcements (FOAs)  
**Ashlee Tipton, PhD**



NCCIH Priorities, Required Milestones, Required  
Attachments, and Transition Award Process  
Wendy Weber, ND, PhD, MPH



Review Criteria Unique to these FOAs  
Martina Schmidt, PhD

— Questions and Answers





**National Center for  
Complementary and  
Integrative Health**

## 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.

## Vision

Scientific evidence informs decision making by the public, by health care professionals, and by health policymakers regarding use and integration of complementary and integrative health approaches.



# Funding Opportunity Announcements

- [\(PAR-16-418; R61/R33\)](#) – 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



# NIH New Definition of “Clinical Trials”

- 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.



# Definition and Examples of Natural Products

- As described in NCCIH's 2016 Strategic Plan, natural products are a group of complementary health approaches that includes a variety of products such as herbs (also known as botanicals), vitamins and minerals, and probiotics. These products are widely marketed, readily available to consumers, and often sold as dietary supplements.
- For these FOAs, the term “natural products” refers to:
  - Herbal Medicines
  - Botanicals
  - Dietary Supplements
  - Probiotics
- Excluded if it meets the FDA definition of ‘New Dietary Ingredient’



# Application Timeline

- Earliest Submission Date: November 2, 2016
- Letter of Intent Due Date: November 2, 2016 (not required)
  - The letter of intent should be sent to:  
Martina Schmidt, Ph.D.  
National Center for Complementary and Integrative Health (NCCIH)  
Telephone: 301-594-3456  
Email: [SchmidMa@mail.nih.gov](mailto:SchmidMa@mail.nih.gov)
- **Application Due Date: December 2, 2016, by 5:00pm local time of applicant organization**
  - AIDS-related Application Due Date: December 16, 2016, by 5:00pm local time of applicant organization
- Scientific Merit Review: February 2017
- Advisory Council Review: May 2017
- Earliest Start Date: July 2017

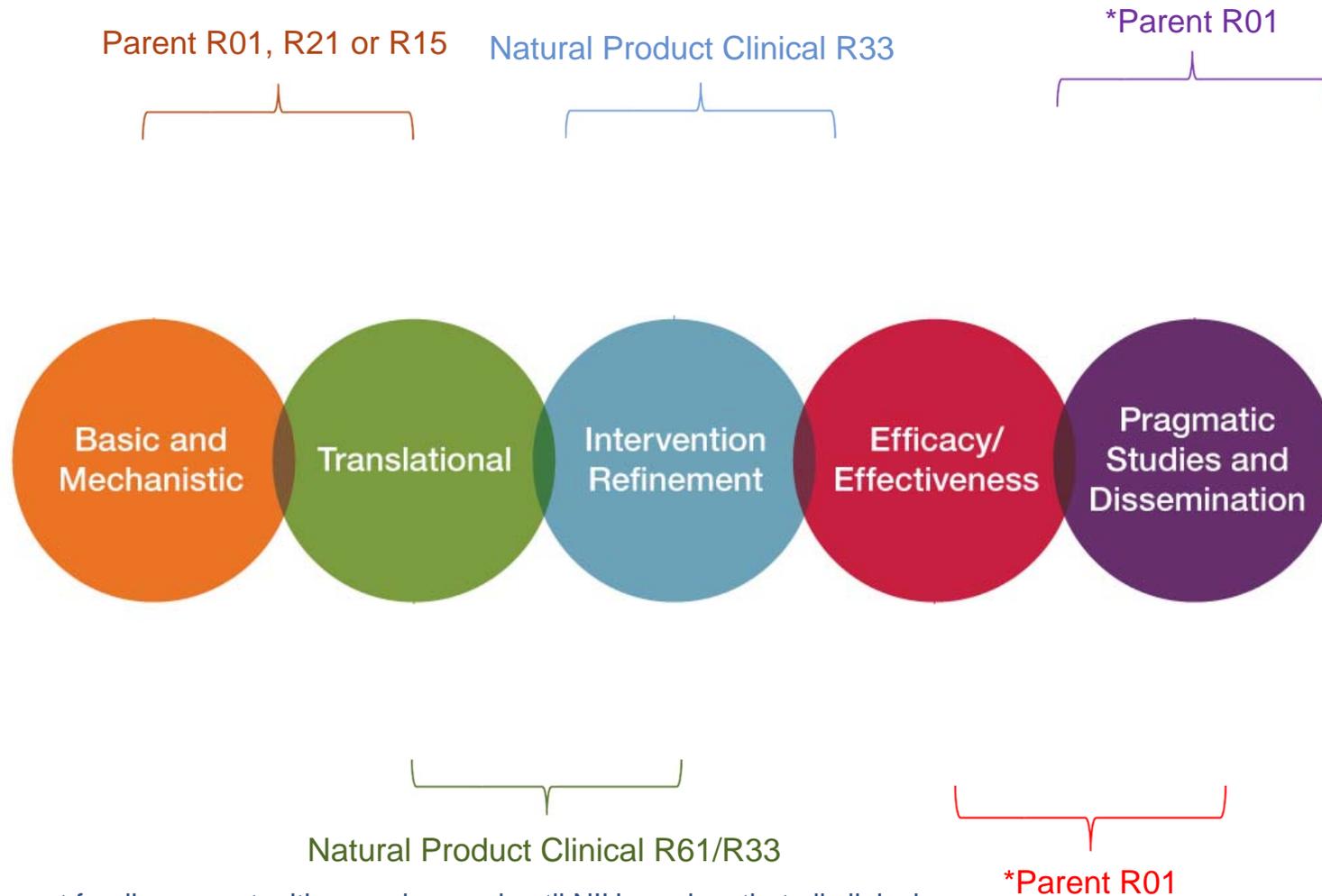


# Importance of Well-Designed Clinical Trials

- NCCIH has a broad interest in studying the biological activities of natural products, including the potential effects of these products on a variety of clinical conditions, and their potential to promote wellness or resilience.
- Clinical trials of natural products are maximally informative if they incorporate well-formulated biological hypotheses, are built on a sound foundation of basic mechanistic and pharmacologic understanding, and incorporate assessment of defined signatures of biological effects.
- The design of maximally informative clinical efficacy trials of natural products requires mechanistic insight as a first step.



# Framework for Natural Products Clinical Studies



\* Parent funding opportunities can be used until NIH requires that all clinical trials must be submitted via a clinical trial specific FOA (NOT-OD-16-147)

# Preliminary Data Needed Before an Efficacy Trial of a Natural Product

- Demonstration that the natural product can produce a clinically meaningful change in a measurable biological signature (e.g. mechanism of action) in the human population of interest.
  - Evidence that the change in biological signature has been replicated in a separate human study with the same natural product.
- Dosing data to justify the selection of the dose(s) of the product proposed
  - Data should demonstrate that the selected doses are likely to have the greatest impact on the biological signature and minimize the risk of adverse events.
- Evaluate the pilot study data for strength of correlation between the impact on the biological signature and changes in the clinical outcomes that will be studied in the proposed clinical trial.
- Pharmacokinetic data on the specific natural product and formulation to be used in the proposed trial to justify the dosing frequency in the proposed trial and demonstrate initial safety of the product.
- Demonstration that the natural product does not produce frequent or severe adverse events in human pilot trials.



# Purpose of the Two FOAs

- Support phased early staged clinical testing of the natural product.
- First phase of the R61/R33 is designed to demonstrate the effect of the natural product's impact on a well-defined, hypothesized biological signature, or mechanism of action, when used by humans.
  - Human bioavailability, pharmacokinetics and toxicity testing
- Second phase of the R61/R33 or the independent R33 is designed to replicate the biological effect in a second study. Investigators can also evaluate what dose of the natural product maximizes the impact on the biological signature with minimal adverse effects.
- **NOTE: Both phases should be adequately powered for the effects on the proposed biological signature.**
- Neither FOA will support randomized clinical trials with primary objectives to determine efficacy or effectiveness of clinical outcomes.
- R61 grants will be administratively reviewed to determine if the negotiated milestones have been met. If milestones are met and funds are available, R61 awards will transition to the R33 phase.



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# NCCIH Priorities for Natural Products Clinical Trials

- Symptom management, particularly the use of natural products for:
  - sleep disturbance
  - management of pain conditions
  - mental health conditions such as those commonly managed in primary care (e.g., mild to moderate depression, anxiety, and post-traumatic stress)
- Studies to examine the effects of probiotics and other natural products on gut microbiome interactions with the brain or the immune system
  - Of particular interest are biological signatures that may be impacted by probiotics and be linked to symptoms such as depression, anxiety, or chronic pain.



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# Clinical Trials *Not* Supported by these FOAs

- **Both FOAs will not support:**
  - Clinical trials solely to estimate intervention effect size or power calculations for a future trial.
  - Applications that do not propose to give the natural product to human participants and measure the impact on a biological signature(s) or mechanisms of action.
  - **Clinical trials proposing to test efficacy or effectiveness.**
  - Applications that propose to test natural products for the treatment or prevention of cancer (investigators interested in cancer treatment or prevention should contact the National Cancer Institute).
- R33 FOA will not support:
  - Applications lacking preliminary data demonstrating that the specific natural product under study impacts the proposed biological signature when used by humans.
  - Applications lacking preliminary data demonstrating that the natural product is bioavailable in humans.



# Which FOA is right for you?

- Both FOAs are for support of preliminary clinical trials to build the evidence base and improve design of a future efficacy study
- R61 is appropriate when:
  - There is pilot data in animals or humans that the product is likely to have an impact on the proposed biological signature in the proposed patient population
  - There is a strong scientific premise and rationale as to why the specific natural product proposed is likely to benefit the clinical condition or indication
- R33 is appropriate when there is pilot data demonstrating:
  - The specific natural product has a measurable and clinically meaningful impact on a biological signature when used by humans
  - The specific natural product is bioavailable



# R61/R33 FOA PAR-16-418

## Budget, Duration, and Page Limit

- Phase 1: R61 mechanism – up to 2 years

Not to exceed \$400K in Direct Cost over 2 years

- Phase 2: R33 mechanism – up to 3 years

Not to exceed \$750K in Direct Cost over 3 years

- Total page limit: 12 pages including both R61 and R33 components



# R33 FOA PAR-16-419

## Budget, Duration, and Page Limit

- R33 mechanism – up to 3 years

Not to exceed \$750K in Direct Costs over 3 years

- Total page limit: 12 pages



# Additional Important Sections in the FOAs

Part 2. Full Text of Announcement  
Section I. Funding Opportunity Description

Section IV. Application and Submission Information  
2. Content and Form of Application Submission

**SF424(R&R) Other Project Information  
Other Attachments**

**PHS 398 Research Plan**

Section V. Application Review Information  
1. Criteria

**Carefully read these sections!**



# Required Other Attachments

- Clinical Protocol Synopsis up to 12 pages
- Clinical Trial Experience Table up to 3 pages
- Regulatory Communication Plan up to 3 pages

**Without these attachments, applications will not be reviewed!**



# Required Other Attachments

- Clinical Protocol Synopsis up to 12 pages
  - The synopsis will provide a concise snapshot of the overall trial to be completed during the first phase of funding
    - R61 trial for R61/R33 applications
    - R33 trial for R33 applications
- Clinical Trial Experience Table up to 3 pages
  - Describe the trials the study team has conducted in the last five years including: title, role, planned and actual enrollment, number of sites, and references for trial results



# Required Other Attachments

- Regulatory Communication Plan up to 3 pages
  - Describe the process for attaining all FDA or other regulatory approvals necessary for the trial(s). Provide summary of communications with FDA about whether an IND is needed for the proposed trial(s).
  - For trials using an FDA regulated product that require an IND application, the grant application must include evidence regarding the outcome of a pre-IND meeting, or other evidence of communication with FDA
  - If the protocol is exempt from an IND, a copy of the exemption letter from the FDA should be provided

When communicating with the FDA, applicants should describe the series of phased human studies that would be conducted if all milestones are met and the eventual future efficacy trial is pursued. Applicants are encouraged to ask the FDA at what point in the series of human studies would an IND be needed and if the proposed designs of each study will provide sufficient data to the FDA, such that they would allow the subsequent proposed study to be conducted under the IND.



# R61 Milestones for Transition to R33 phase

- ❖ Operational definition and objective measure(s) of the biological signature(s) that will be measured in humans (i.e., the hypothesized mechanism of action) and definition of a clinically meaningful change for each measure.
- ❖ Demonstration of adequate impact on the biological signature to provide a basis for future subsequent studies in humans.
- ❖ Demonstration of the ability of the investigative team to recruit and retain participants in the R61 trial.
  - Demonstration of human bioavailability of the natural, and short term human pharmacokinetic data.
  - Feasibility data to indicate that an adequate dose of the natural product (defined by biological signature) can be applied in the select human population.
- ✓ NCCIH approved protocol, and data and safety monitoring plan for the planned R33 phase project.
- ✓ Completion of necessary regulatory approvals for proposed R33 clinical studies (e.g., IRB, FDA IND).



# What Makes for Good Milestones?

- Specificity of what biological signature(s) will be primary outcome and how much and what direction of change is clinically meaningful
  - Preliminary data to guide this definition
  - Power trial based on change in biological signature(s)
- Multiple Potential Biological Signatures
  - Limit to 1-5 biological signature(s) for primary outcome
  - If more than one, create a decision rule about what defines success for transition to R33 phase. For example:
    - Proceed to R33 if 2 of 5 markers move in the hypothesized direction and amount defined a priori, and the other 3 markers move in directions consistent with hypothesis
    - Do not proceed to R33 if 1 of 5 markers move in hypothesized direction but other 4 markers move in direction opposite of hypothesis
- Additional biological signature data can be collected as secondary or exploratory outcomes
  - Cannot use this data to meet criteria for transition to R33 phase
  - Data can be used for a new R33 application submitted for peer review



# R33 Milestones to Prepare for Future Efficacy Study

- ❖ Replicate the impact on the objective measure(s) of the biological signature(s) that will be measured in humans (i.e., the hypothesized mechanism of action) and at the a priori defined level that is a clinically meaningful change for each measure.
- ❖ Evaluate the strength of correlation between the degree of impact on the biological signature and functional or clinical outcomes in the population of interest.
  - Further assessment of the natural product's feasibility, safety, and acceptability.
  - Determine the optimal dose for a subsequent trial by assessing dose-response impact on the biological signature in response to multiple doses of the natural product.
  - Collect data to evaluate which dose(s) are likely to have the greatest impact on the biological signature and minimize the risk of adverse events.
  - Determine the pharmacokinetics of the dose and formulation of the natural product to be used in future trials to justify the frequency of dosing.
  - Demonstrate ability to recruit, randomize, retain, collect all assessments and samples, adhere to the protocol, and report adverse events.



# Phased Award Transition Process R61 to R33

- Funding of the R61 does **not** guarantee funding of the R33 phase
- Transition request must be submitted by investigator
  - Data demonstrating milestones of the R61 phase have been met
    - Achieve a priori defined change in biological signature
    - Demonstrate bioavailability
    - NCCIH approval of proposed R33 protocol and DSMP
    - Regulatory approvals in place for R33 phase trial
- NCCIH conducts an administrative review to determine if milestones have been met and funds are available for next phase (2-3 months)



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# Once your application arrives at NIH:

1. Administrative Review
2. Assembling the Review Panel
3. Reviewers evaluate/discuss the applications
4. Scores and Summary Statements are released



# Administrative Review I:

- **Completed at CSR and NCCIH**
  - Assesses if all FOIA required elements included in the application?
  - PAR-16-418 specific requirements:
    - Research Strategy section is limited to 12 pages
      - Specific Aims page states the specific objective of both phases (R61 and R33)
      - Future Clinical Trial
      - Preliminary Data justifying the NP
      - Description of the NP
      - Description of the Study design and R61/R33 methodology
      - Description of outcome measures
      - Data management and quality control
      - Milestones and Timeline
      - IND, FDA-submitted application, or plan for an IND submission



# Administrative Review II:

- A DSMP must be proposed and must be included in the study protocol.
- Other Attachments:
  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
- => **Watch out for words like “must” and “required”**
- => **Keep in mind, information “accidentally” left out of the application cannot be accepted as post-submission material except as stated in NOT-OD-13-030**



# Review Criteria

## Scored Criteria

- Significance
- Investigators
- Innovation
- Approach
- Environment

## Additional Review Criteria influencing the Overall Impact score:

- **Milestones and Timeline** (R61 and R33)
- Protection of HS
- Inclusion of Women, Minorities and Children
- Vertebrate Animals
- Biohazards

⇒ **All these aspects are considered by reviewers and influence the “Overall Impact” score of an application.**



# Significance

Does the project address an important problem or a critical barrier to progress in the field? **Is there a strong scientific premise for the project?** If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Is there a sufficient body of preclinical or clinical research of high **scientific rigor** to support the **study rationale**? Is this clinical trial necessary to generate preliminary data to plan for testing the safety, efficacy, or effectiveness of an intervention that could lead to a change in clinic practice, community behaviors or health care policy? **Does the applicant provide justification as to why it is important to perform the future larger clinical study in the context of the present knowledge on clinical research in natural products?** Is it clear why the proposed exploratory trial is essential to inform the design and implementation of subsequent steps in the evaluation of the natural product? Is the proposed project likely to yield clear answers needed to proceed to the next step of research as proposed in this application? Will the proposed study **advance knowledge of intervention or disease mechanisms**, whether the results are positive or negative?

**=> Why should this study be done, is it supported by preliminary evidence, is potential risk managed, and will it lead to clear answers?**



# Investigators

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Does the application provide strong evidence of necessary experience and **expertise with the natural product, the study population, and the research methods to be employed**? Does the investigative team have a track record of publishing the results of clinical trials previously completed? With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have **clinical trial-specific expertise and experience**; the ability to organize, manage and implement the proposed clinical trial and meet study milestones and timelines? Do they have appropriate capacity in study coordination, data management and statistics? Has the investigative team successfully conducted clinical trials under an Investigational New Drug (IND) application?

**=> Experience of investigators with NP, study population, and clinical trial management.**



# Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

**Does the proposed exploratory trial have the potential to advance the field (e.g., by breaking ground for future trials in this area) even if (a) the proposed study design, methods, and intervention are not innovative, and/or (b) the results of the trial indicate that further clinical development of the intervention is unwarranted?**

⇒ **Will the study be ground breaking—independent of positive results—warranting further clinical testing?**



# Approach I

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a **robust and unbiased approach**, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? **Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?**

If the project involves **human subjects and/or NIH-defined clinical research**, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, **justified in terms of the scientific goals and research strategy proposed?**



# Approach II

Does the proposed study ensure that the underlying hypothesized biological signature is appropriate and relevant, and will be rigorously tested by giving the product to humans and assessing the impact on the biological signature? **Is the need for the R61 phase well justified?**

Does the **R33 phase** include sound methodology for (a) **replicating and extending the initial impact** of giving the natural product to humans on the hypothesized biological signature from the R61 phase, and (b) evaluating **associations between biological signature and subsequent clinical or functional outcomes**?

Does the applicant describe how the proposed study relates to a larger strategy for research of this natural product and will it provide pilot and feasibility data needed to advance that strategy? Does the application demonstrate the feasibility of methods for developing tools for data management and study oversight, finalizing protocol documents and manuals, as well as addressing appropriate regulatory requirements (FDA, IRB)? Are the outcome measures, dose/duration of study, appropriateness of inclusion/exclusion criteria, and sample size clearly justified and explained in the application? Is the proposed design feasible/adequate to provide interpretable results? Are the plans for recruitment outreach appropriate and are there follow-up procedures to ensure collection of data at stated intervals? Are the retention plans and practices described?

**=> Assesses information applicants are asked to provide in the study design section; is the study feasible?**



# Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Does the information provided in the application give reasonable assurance that the **target sample size can be enrolled in the timeframe proposed**? Does the application document the availability of the requisite **eligible subject pool** in proposed clinical center(s)? Is there documentation of the commitment of any subcontractors and consultants, as well as service agreements for personnel and facilities?

**=> Does the environment available to the investigators raise confidence that the proposed study is feasible?**



# Milestones and Timeline I (Additional Review Criterion)

**R61 Milestones:** Are quantitative criteria pre-specified and rigorously defined to assess milestone achievement and operational feasibility relevant to advancing from the R61 to the R33 phase? Are success criteria defined in terms of outcomes achieved rather than as tasks completed? Are R61 milestones feasible, well developed and quantifiable with regard to the specific aims of each stage? Is the timeline feasible? Specifically, will the investigators and NCCIH Program Officials be able to determine if the project succeeded in (a) demonstrating that when used by humans the natural product alters the biological signature or mechanism (thus providing an initial proof of principle), (b) demonstrating human bioavailability of the natural product and/or its active metabolites, and (c) providing preliminary evidence that the intervention can be applied in a clinical population with adequate acceptability and tolerability to patients? Do the interim milestones include a go no/go decision rule for continuing to the R33 phase if a measure of biological signature is not sufficiently robust? Does the application specify conditions under which they would not proceed to the R33 phase? Are likely problems anticipated?

**R33 Milestones:** Are appropriate, evaluative milestones clearly defined for the aims associated with the R33 phase? Are R33 milestones feasible, well developed, and quantifiable with regard to the specific aims? Is the timeline feasible? Are the plans for sample size and timely recruitment of subjects feasible? Is there a clear strategy for tracking recruitment and facilitating retention? **Will sufficient and appropriate data be collected in the R33 phase to inform a decision whether further clinical testing is warranted?**



# Milestones and Timeline (Additional Review Criterion)

- ⇒ **Will be factored into your “Overall Impact score”!**
- ⇒ **This is a phased award. By design the R33 phase depends on successful completion of the R61 phase:**
  - ⇒ **Carefully designed R61 milestones mitigate the potential risk of prematurely moving from the R61 to the R33 phase**
  - ⇒ **Carefully designed R33 milestones will ensure that a definitive answer to the study question asked will be achieved.**

## Why is this important?

⇒ **Keep in mind: Reviewers will assign ONE “Overall Impact” score for both phases balancing the strengths and weaknesses of both the R61 and the R33) phase.**



# Review Criteria (overall)

- Potential to significantly advance knowledge

- Strength of the conceptual framework

- Level of innovation



# Additional Review Considerations

- Are considered by reviewers
- Do not receive criterion scores
- Are not factored into the score
  - Select Agent Research
  - Resource Sharing Plans
  - Budget and Period of Support
  - **Authentication of Key Biological and/or Chemical Resources:**
    - For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.
    - Any reviewer questions associated with key biological and/or chemical resource authentication will need to be addressed prior to award.



# NCCIH Policy: Natural Product Integrity

<https://nccih.nih.gov/research/policies/naturalproduct.htm>

## Research Strategy Section:

- Product name (brand name, chemical or taxonomic nomenclature)
- Active/inactive product ingredients
- Justification/rationale for :
  - product and supplier
  - form of the product (refined, complex, ...)
  - parts to be used (root, stem, leaf)
  - vehicle/route of administration (iv, ip, ...)
- Methods for product characterization/standardization
- Rationale for selection of marker compounds
- **For Human Subjects Studies:**
  - Justification for the proposed doses/concentrations/dosing schedule
  - Safety issues regarding the chosen product/dose
  - Pharmacokinetics/pharmacodynamics of known components
  - Biological/chemical markers of activity (if applicable)
  - Description of placebo or vehicle control



# NCCIH Policy: Natural Product Integrity

At the review meeting:

⇒ Evaluated by the scientific review group

## Scientific Merit

- Sufficient product quality information needs to be provided in the application to evaluate:
  - Significance
  - Feasibility
  - Scientific strength

**Investigative team needs to have appropriate product and analytical expertise**

After the review meeting:

⇒ Evaluated by NCCIH staff in Consultation with outside experts

## Product Quality

- Sufficient and more detailed product quality information has to be provided to NCCIH
- Handled as just-in-time information

**Important:**

**If product quality information will be acquired as part of the proposed Research Strategy: -> evaluated by scientific review group!**



# Key Contacts

- A brief **Letter of Intent** (including a descriptive title of the proposal; names, and phone numbers of the PIs; names of other key personnel; participating institution; and the name and title of the FOA to be cited) is due on November 2, 2016, to Dr. Martina Schmidt, [schmidma@mail.nih.gov](mailto:schmidma@mail.nih.gov). It is meant to help estimate the potential review workload and plan the review.
- For all **scientific questions** related to these two FOAs—prior to the submission and post-review—investigators should contact Dr. Wendy Weber at [weberwj@mail.nih.gov](mailto:weberwj@mail.nih.gov).
- Scientific Review Contact is Dr. Martina Schmidt at [schmidma@mail.nih.gov](mailto:schmidma@mail.nih.gov).



# We would like to hear from you!

**LIVE** Question and Answer Session.

Please email questions to:

[NCCIHWebinarQ@mail.nih.gov](mailto:NCCIHWebinarQ@mail.nih.gov)

Note: A written summary of this webinar will be available and automatically sent to all participants in 2 weeks.





# Footnotes for Clinical Trial Definition

- <sup>1</sup>See Common Rule definition of *research* at 45 CFR 46.102(d).
- <sup>2</sup>See Common Rule definition of *human subject* at 45 CFR 46.102(f).
- <sup>3</sup>The term “*prospectively assigned*” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
- <sup>4</sup>An *intervention* is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.



# Footnotes for Clinical Trial Definition

- <sup>5</sup>*Health-related biomedical or behavioral outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html#sthash.8CLyUMmd.dpuf>

