Introductions

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NCCIH wants to support definitive multi-site clinical trials whose results will impact health care delivery and provide evidence for treatment guidelines.

In most areas of clinical inquiry, there is a need for additional preliminary data or building blocks to design these definitive clinical trials.
Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Robert M. McLean, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

**Description:** The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on noninvasive treatment of low back pain.

**Methods:** Using the ACP grading system, the committee based these recommendations on a systematic review of randomized, controlled trials and systematic reviews published through April 2015 on noninvasive pharmacologic and nonpharmacologic treatments for low back pain. Updated searches were performed through November 2016. Clinical outcomes evaluated included reduction or elimination of low back pain, improvement in back-specific and overall function, improvement in health-related quality of life, reduction in work disability and return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects.

**Target Audience and Patient Population:** The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute, subacute, or chronic low back pain.

**Recommendation 1:** Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)

**Recommendation 2:** For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation)

**Recommendation 3:** In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)

Ann Intern Med. doi:10.7326/M16-2367
For author affiliations, see end of text.
This article was published at Annals.org on 14 February 2017.
Quality of the Current Evidence

- ACP Guideline recommendations were strong **yet** the evidence they were based on was described as moderate to low quality.
“NIH must ensure that supported trials investigate a mission-relevant question that is of high priority, do not needlessly duplicate previously conducted trials (in contrast to providing needed replication), and have the highest likelihood to advance knowledge and improve health. To achieve this goal, a number of challenges in the design, efficiency, and reporting of clinical trials need to be addressed.”

“NIH has launched a multifaceted effort to improve the quality and efficiency of clinical trials.”
“Specifically, these changes are aimed at enhancing the application and award processes, increasing NIH’s ability to assess the merits and feasibility of clinical trial applications; improving over-sight and transparency; and increasing the sharing of clinical trial results.”

- Good Clinical Practice (GCP) training for investigators and NIH staff responsible for conducting or overseeing clinical trials (NOT-OD-16-148)
- All applications for clinical trials to be submitted in response to clinical trial specific Funding Opportunity Announcements (NOT-OD-16-147 & NOT-OD-17-043)
- Single IRB of record for NIH multisite studies (NOT-OD-16-094)
- Clinical trial registration and summary results information reporting (NOT-OD-16-149)
Human Subjects Research

- NCCIH: 64%
- NIH: 40%
Define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative interventions and their roles in improving health and health care.
Objectives:

NCCIH Strategic Framework

Overview
NCCIH Mission and Vision
Priority Setting

Advance Fundamental Science
Foster Health Promotion & Disease Prevention
Improve Care for Hard to Manage Symptoms

Enhance Research Workforce
Disseminate Evidence-based Information
Objective 2. Improve Care for Hard-to-Manage Symptoms

- Develop and improve complementary health approaches and integrative treatment strategies for managing symptoms such as pain, anxiety, and depression.
- Conduct studies in “real world” clinical settings to test the safety and efficacy of complementary health approaches, including their integration into healthcare.
Objective 3. Foster Health Promotion & Disease Prevention

- Investigate mechanisms of health resilience and practices that improve health and prevent disease.
- Study complementary health approaches to promote health and wellness across the lifespan in diverse populations.
- Explore research opportunities to study and assess the safety and efficacy of complementary health approaches in non-clinical settings such as community- and employer-based wellness programs.
What Does NCCIH Fund?

Mind and Body Practices
- acupuncture, massage, meditation, spinal manipulation, deep breathing exercises, hypnotherapy, 5-HTP, L-tryptophan, melatonin, etc.

Natural Products
- herbs, botanicals, dietary supplements, probiotics, etc.

- pain
- interactions & safety
- biological effects
- mechanisms
- stress, anxiety, & other symptoms
- healthy behaviors
All applications for clinical trials to be submitted in response to clinical trial-specific Funding Opportunity Announcements.

NOT-OD-16-147 & NOT-OD-17-043
Why a New Approach for Clinical Trials?

• NCCIH is participating in the NIH-wide initiative to strengthen the clinical trial research portfolio.

• Clinical trials are important to us because we study health interventions widely used by the American public – interventions often used with scarce evidence of efficacy and inadequate understanding of potential safety concerns.

• NCCIH funds research that helps people manage important health issues, especially research that focuses on nonpharmacologic approaches to pain.
Yoga, acupuncture effective for chronic pain management

Written by: Honor Whitehead
Published: Monday 5 September 2016

Yoga, tai chi, and other complementary health approaches are effective in helping to alleviate some chronic pain conditions, concludes a new study by researchers from the National Institutes of Health.

Lead author Richard L. Nahin, Ph. D., of the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH), and colleagues publish their findings in the journal Mayo Clinic Proceedings.

In any given year, around 100 million adults in the United States experience chronic pain—a pain that persists for at least 12 weeks—of whom around 40 million have severe chronic pain.

While there are medications available to help ease chronic pain—such as nonsteroidal anti-inflammatory drugs (NSAIDs)—they are not always effective.

This new review suggests yoga, acupuncture, and...
A Randomized Trial of Tai Chi for Fibromyalgia

Chenchen Wang, M.D., M.P.H., Christopher H. Schmid, Ph.D., Ramel Rones, B.S., Robert Kalish, M.D., Janeth Yinh, M.D., Don L. Goldenberg, M.D., Yoojin Lee, M.S., and Timothy McAlindon, M.D., M.P.H.

Original Investigation
Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial

Daniel C. Charlin, PhD; Karen J. Sherman, PhD; Benjamin H. Baldwin, PhD; Andrea J. Cook, PhD; Melissa A. Anderson, MS; Rane J. Hawkes, BS; Kelly E. Hansen, BS; Judith A. Turner, PhD

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Daniel O. Clegg, M.D., Domenic J. Reda, Ph.D., Crystal L. Harris, Pharm.D., Marguerite A. Klein, M.S., James R. O’Dell, M.D., Michele M. Hooper, M.D., John D. Bradley, M.D., Clifton O. Bingham III, M.D., Michael H. Weisman, M.D., Christopher G. Jackson, M.D., Nancy E. Lane, M.D., John J. Cush, M.D., Larry W. Moreland, M.D., H. Ralph Schumacher, Jr., M.D., Chester V. Oddis, M.D., Frederick Wolfe, M.D., Jerry A. Molitor, M.D., David E. Yocum, M.D., Thomas J. Schnitzer, M.D., Daniel E. Furst, M.D., Allen D. Sawitzke, M.D., Helen Shi, M.S., Kenneth D. Brandt, M.D., Roland W. Moskowitz, M.D., and H. James Williams, M.D.
Common Limitations of Trials

- Single site studies reduce generalizability and it is unclear if the intervention can be delivered in other places with fidelity

- When the study fails to demonstrate the hypothesized benefit…
  - Was the intervention delivered correctly?
  - Did the participants get enough of the treatment?
  - Was it the right duration or frequency of the intervention?
  - Was the right population selected or were they too progressed in condition or symptoms?
  - For natural product studies, was the right product selected?

Often lack key **building blocks** for designing the efficacy trial
Building Blocks of Natural Product Clinical Trials

- Historical Use and Fundamental Pre-Clinical Knowledge
- Product Development and Testing
- Optimization of Dose and Trial Methods
- Multi-Site Efficacy Trials
Building Blocks of Mind and Body Clinical Trials

- Historical Use and Fundamental Knowledge
- Intervention Refinement and Feasibility Testing
- Optimization of Intervention and Trial Methods
- Multi-Site Efficacy Studies
- Pragmatic Trials
New FOAs provide investigators with funding options to establish the building blocks along the research continuum.
Framework for Human Subjects Research

- Basic and Mechanistic
  - How does it work?
  - Can the mechanistic impact be reliably measured in humans?

- Translational
  - Can the intervention be modified to enhance impact or adherence?

- Intervention Refinement and Optimization
  - Does it work in comparison to an appropriate control?

- Efficacy/Effectiveness
  - Is it still effective when implemented in “real world” conditions?
Research Continuum

- The new FOAs provide pathways to support the developmental steps for relevant clinical trials on complementary and integrative health approaches.
  - Each FOA is targeted for studies at different stages of the research continuum:
    - early phase trials
    - intermediate trials
    - full-scale multi-site efficacy, effectiveness or pragmatic trials
Research Continuum

- NCCIH will support investigators working to establish “building blocks” that bridge the gap from basic research to high-impact clinical trials.

- In the past, it was often difficult for investigators to find research funding to establish these building blocks.

- Our new funding opportunities provide for these foundational components.
New Clinical Trial Funding Opportunities

- NCCIH has developed a new series of FOAs specifically for investigator-initiated clinical trials that are focused on:
  - Mind and body intervention studies
  - Natural product studies
## Investigator-Initiated Mind and Body Clinical Trial FOAs

<table>
<thead>
<tr>
<th>Title</th>
<th>FOA Number</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Exploratory Clinical Trials of Mind and Body Interventions for NCCAM High Priority Research Topics (R34)</td>
<td>PAR-14-182</td>
<td>Early phase intervention refinement; assessment of fidelity and adherence; selection of appropriate patient population and outcome measures.</td>
</tr>
<tr>
<td>Phased Innovation Award for Mechanistic Studies to Optimize Mind and Body Interventions in NCCIH High Priority Research Topics (R61/R33)</td>
<td>PAR-17-149</td>
<td>Establish the impact of the intervention on a biological mechanism/psychological process. In the next phase, optimize the impact on the mechanism/process by modifying delivery of the intervention, combining it with other known interventions, or selecting for a more mechanism-relevant population, and assess the association with relevant clinical outcomes.</td>
</tr>
<tr>
<td>Innovation Award for Mechanistic Studies to Optimize Mind and Body Interventions in NCCIH High Priority Research Topics (R33)</td>
<td>PAR-17-162</td>
<td>Optimize the impact on the mechanism or process by modifying delivery of the intervention, combining it with other known interventions, or selecting for a more mechanism-relevant population, and assess the association with relevant clinical outcomes.</td>
</tr>
<tr>
<td>NCCIH Mind and Body Clinical Trial Cooperative Agreement (U01)</td>
<td>PAR-17-215</td>
<td>Mid stage intervention testing to refine recruitment and retention methods, improve fidelity of intervention delivery, and improve data collection quality across multiple sites. Alternatively, evaluate which components of an intervention are necessary, or identify the best algorithm for delivery of care.</td>
</tr>
<tr>
<td>Clinical Coordinating Center for NCCIH Multi-Site Investigator-Initiated Clinical Trials of Mind and Body Interventions (Collaborative UG3/UH3)</td>
<td>PAR-17-175</td>
<td>Clinical Coordination of a multi-site efficacy, effectiveness, or pragmatic trial. Trial should be fully powered to measure clinical outcomes and use multiple sites to enhance generalizability of study outcomes.</td>
</tr>
<tr>
<td>Mind and Body Intervention Multi-Site Clinical Trial Data Coordinating Center (U24)</td>
<td>PAR-17-173</td>
<td>Companion Data Coordinating Center for multi-site clinical trials to ensure independence and objectivity of data collection and analysis.</td>
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# Investigator-Initiated Natural Product Clinical Trial FOAs

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<tr>
<td>Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics (R61/R33)</td>
<td>PAR-16-418</td>
<td>Early stage testing to establish the impact of the natural product on a biological signature. In the second phase, replicate the impact on the biological signature and assess correlation between change in biological signature and clinical outcomes. Additionally, can assess pharmacokinetics and impact of varying doses on the biological signature.</td>
</tr>
<tr>
<td>Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics (R33)</td>
<td>PAR-16-419</td>
<td>Replicate the impact of a natural product on the biological signature and assess correlation between change in biological signature and clinical outcomes. Additionally, can assess pharmacokinetics and impact of varying doses on the biological signature.</td>
</tr>
<tr>
<td>NCCIH Natural Product Phase II Clinical Trial Cooperative Agreement (U01)</td>
<td>PAR-17-216</td>
<td>Midstage intervention testing to refine recruitment and retention methods, improve fidelity of intervention delivery, and improve data collection quality across multiple sites. Additionally, can assess which dose has greatest impact on biological signature with low risk of adverse events.</td>
</tr>
<tr>
<td>Clinical Coordinating Center for NCCIH Multi-Site Investigator-Initiated Clinical Trials of Natural Products (Collaborative UG3/UH3)</td>
<td>PAR-17-174</td>
<td>Clinical Coordination of a multi-site efficacy, effectiveness, or pragmatic trial. Trial should be fully powered to measure clinical outcomes and use multiple sites to enhance generalizability of study outcomes.</td>
</tr>
<tr>
<td>Natural Product Multi-Site Clinical Trial Data Coordinating Center (Collaborative U24)</td>
<td>PAR-17-172</td>
<td>Companion Data Coordinating Center for multi-site clinical trials to ensure independence and objectivity of data collection and analysis.</td>
</tr>
</tbody>
</table>
Framework for Human Subjects Research

How does it work?
— Parent R01, R21 or R15
— Other active FOAs

Can the intervention be modified to enhance impact or adherence?
— Natural Product R33 or U01
— Mind Body R33, R34, or U01

Is it still effective when implemented in “real world” conditions?
— Natural Product Clinical UG3/UH3 & U24
— Mind Body Clinical UG3/UH3 & U24

Basic and Mechanistic

Translational

Intervention Refinement and Optimization

Efficacy/Effectiveness

Pragmatic Studies and Dissemination

Can the mechanistic impact be reliably measured in humans?
— Natural Product Clinical R61/R33
— Mind Body Mechanistic R61/R33

Does it work in comparison to an appropriate control?
— Natural Product Clinical UG3/UH3 & U24
— Mind Body Clinical UG3/UH3 & U24
What has changed?
Changes in How to Submit Clinical Trial Applications to NCCIH

- NCCIH is no longer accepting most clinical trial applications through the Parent R01 FOA (NOT-AT-17-006).
  - We have developed more specific funding opportunities that will allow researchers to incorporate a higher degree of relevant information in their grant applications.
  - Use the new FOAs for all stages of clinical outcome trials.

- What human subjects applications will NCCIH accept via the Parent R01 FOA?
  - Observational human studies – cohort, case control, survey
  - Secondary data analysis – datasets or biorepositories
  - Mechanistic focused human studies (no aims to examine clinical outcomes)
What is a U Mechanism?

- U mechanisms – U01, UG3/UH3, and U24 – are cooperative agreement awards
  - Used for Investigator-Initiated applications
  - Used by the federal government when the funding agency anticipates federal staff will have involvement in the activities of the award
  - At the time of funding, NCCIH will assign two staff members to work with investigators:
    1. Program Director who is responsible for the administration of the award, review of progress reports, etc.
    2. Project Scientist who works directly with the investigators as part of the team and participates in trial planning and oversight
Why Multi-Site Efficacy Trials?

- To meet evidence guidelines for rigor and reduce bias, efficacy trials are most informative if they:

  1. Are conducted as multi-site trials
     - Increases likelihood of generalizability of the results
     - Increases diversity of the population to meet NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research
     - Demonstrates intervention can be delivered with fidelity at more than one location

  2. Have independent data coordination (companion U24)
     - Provides methods for consistent data collection from sites
     - Assures independent data quality confirmation and analysis
Review Process

- Applications submitted to our new clinical trial FOAs will be reviewed by special review panels familiar with NCCIH’s research priorities and the goals of the new FOAs.
- Applications must include special attachments (described in the FOA) that will allow applicants to provide study details in a standardized way.
  - Review panels will be able to use this additional information for their assessment of important aspects such as rigor, feasibility, and potential impact of the trial.
Upcoming Webinars

- NCCIH Funding Opportunities for Mind and Body Clinical Trials
  - **Date:** April 24, 2017  **Time:** 2:00 p.m. ET

- NCCIH Funding Opportunities for Natural Product Clinical Trials
  - **Date:** May 09, 2017  **Time:** 2:00 p.m. ET

- [https://nccih.nih.gov/ClinicalTrialFOAWebinars](https://nccih.nih.gov/ClinicalTrialFOAWebinars)
Resources

- NCCIH new website for information about clinical trial FOAs:
  - [https://nccih.nih.gov/clinicaltrials-funding](https://nccih.nih.gov/clinicaltrials-funding)
  - FOA description, link, and Program Director contact information

- NCCIH Clinical Trial FOA Frequently Asked Questions
  - [https://nccih.nih.gov/grants/funding/clinicaltrials/faq](https://nccih.nih.gov/grants/funding/clinicaltrials/faq)

- General questions about which FOA to use:
  - nccihderinquiries@mail.nih.gov
NCCIH wants to support definitive multi-site clinical trials whose results will impact health care delivery and provide evidence for treatment guidelines.

In most areas of clinical inquiry, there is a need for additional preliminary data or building blocks to design these definitive clinical trials.

Use the New NCCIH Clinical Trial FOAs!!

Contact a Program Director if you have questions! nccihderinquaries@mail.nih.gov
Range of Research Questions

- **Basic and Mechanistic**: How does it work?
- **Translational**: Can the mechanistic impact be reliably measured in humans?
- **Intervention Refinement and Optimization**: Can the intervention be modified to enhance impact or adherence?
- **Efficacy/Effectiveness**: Does it work in comparison to an appropriate control?
- **Pragmatic Studies and Dissemination**: Is it still effective when implemented in “real world” conditions?
Questions?

Send questions now: NCCIHWebinarQ@mail.nih.gov

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