



US Deprescribing Research Network

Advancing Research to Optimize Medication Use Among Older Adults

Call for Applications:

Pilot Studies That Use Complementary and Integrative Health Methods to Support Deprescribing of Benzodiazepine Receptor Agonists

Overview: The US Deprescribing Research Network (USDEN) is seeking applications for pilot studies of interventions that employ complementary and integrative health (CIH) modalities to support deprescribing of benzodiazepines and/or non-benzodiazepine, benzodiazepine receptor agonists (i.e., the “Z drugs” such as zolpidem or eszopiclone) in older adults. Proposals may request a budget of up to \$160,000 (combined direct and indirect costs), or higher with advance permission, and the resultant studies should be able to be completed over approximately one year. The goal of these studies should be to test study procedures, refine interventions, assess feasibility and acceptability, and/or other such goals, such that by the end of the one-year study period the research team will be well-positioned to apply for a large grant funding opportunity to conduct a definitive clinical trial. In addition, the goal of this initiative is not only to select and fund promising pilot studies, but to use the existing infrastructure of the US Deprescribing Research Network to provide ongoing support and guidance about research design, implementation, and engaging stakeholders so as to give pilot awardees the best chance of succeeding in their work and using it as a springboard for larger, definitive studies. This initiative is a special, one-time funding opportunity made possible by an administrative supplement award to USDEN from the National Center for Complementary and Integrative Health available [here](#).

The U.S. Deprescribing Research Network is a collaborative research network with the overall goal to support development of investigators studying deprescribing for older adults and to catalyze a range of high-quality, clinically impactful research in this area. Solutions to these challenges require attention to geriatric principles, including (but not limited to) clinical complexity and multimorbidity, transitions across multiple providers and sites of care, older adults’ values and priorities, and the shifting balance of medication benefits and harms in late life. Our overarching aim is to expand the quality, quantity, and translational impact of deprescribing research.

1) Background: Benzodiazepine receptor agonists (BZRAs), which include classic benzodiazepines as well as newer non-benzodiazepine, benzodiazepine receptor agonists such as zolpidem, are a major source of problematic prescribing for older adults. A number of interventions have demonstrated promise to support deprescribing of BZRAs in older adults. A common thread that connects many successful interventions is attention to involving patients in the deprescribing process, including through shared decision-making, promoting self-management, and otherwise empowering them to be active participants in these efforts. Many complementary and integrative health (CIH) modalities engage these psychological processes and/or are well-suited to complement them. Beyond this, evidence for a variety of complementary and integrative interventions to support deprescribing of BZRAs in older adults is limited, with studies that are mostly small and of limited methodologic quality. Cognitive-behavioral therapy (CBT) is endorsed as first-line therapy for management of chronic insomnia and thus potentially promising to support deprescribing of BZRAs. However, studies have found mixed effects on its ability to achieve this goal when added to other educational and counseling interventions

(although newer e-health variants of CBT show promise). Other psychological therapies such as relaxation therapy, stimulus control, and sleep restriction may be useful, but the evidence base for their ability to enhance sedative-hypnotic deprescribing is sparse. The same holds for substituting BZRAs with other pharmacologic agents including melatonin, trazadone, valerian, and cannabinoids. The state of the literature thus points to several promising directions related to complementary and integrative health for increasing deprescribing of BZRAs in older adults, but there is a critical need to provide a more definitive evidence base of what works and what does not. Moreover, widespread acceptance and interest in many CIH approaches among older adults creates fertile ground for broad adoption of CIH modalities that are proven to be effective. Thus, expanding research on CIH-based approaches to support deprescribing BZRAs has potential to meaningfully impact the widespread overuse of these medications in older adults.

What is ultimately needed is large, definitive clinical trials that test interventions among older adults in real-world settings. To prepare for this, investigators must develop and refine their interventions, pilot test them to test study procedures and evaluate and troubleshoot challenges to feasibility, acceptability, measurement, and where appropriate obtain preliminary evidence of efficacy. The goal of this initiative is to support pilot studies that will do this early-stage work such that by the end of the study period, investigators will be well-positioned to apply for a large-scale grant (e.g., NIH or AHRQ R01, major PCORI award, or other) to conduct a definitive test of the intervention in older adults.

To date NIH has not developed a specific follow-on funding opportunity; to our knowledge major funding agencies have not released a specific RFA that offers large-grant funding focused on trials of CIH interventions to promote benzodiazepine receptor agonist deprescribing in older adults. Thus, applicants should prepare pilot studies with the understanding that future large-grant funding opportunities may well come in the form of broad-based RFAs.

- 2) Research objectives:** This funding opportunity is intended to support pilot studies of complementary and integrative health (CIH) interventions to support deprescribing of benzodiazepine receptor agonists in older adults. The intention is that by the end of the funding period, investigators will be well-positioned to apply for large-grant funding to conduct a definitive clinical trial of the intervention(s) that was tested in the pilot study.
- 3) Intervention targets and study population:** Interventions must aim to discontinue, reduce dose of, or otherwise lessen the burden of BZRA use in older adults. Other related medications may also be evaluated, but benzodiazepine receptor agonists should be an important focus. Older adults are typically defined as people age 65 years and older, and the US Deprescribing Research Network has a particular (although not exclusive) interest in older adults with heightened vulnerabilities such as frailty, multiple chronic conditions, dementia, etc. Studies may include some subjects younger than age 65 years, but the predominant focus must be on older adults.

Interventions may include a range of cognitive/behavioral interventions, other non-pharmacological interventions, or pharmacological ones that fall under the rubric of CIH; questions about whether a given intervention is within-scope as a CIH modality should be directed to the US Deprescribing Research Network at admin@deprescribingresearch.org. While all CIH modalities will be considered, strong justification for pharmacologic substitutes will be required, given potential for adverse effects in older adults and their contribution to excessive polypharmacy. Interventions which, if proven effective, have potential for future widespread dissemination will be especially encouraged. In addition, proposals that employ pragmatic clinical trial approaches are

especially encouraged, although these methodologies are not required (for more information on pragmatic clinical trials, see <https://rethinkingclinicaltrials.org/>)

We will strongly encourage inclusion of diverse populations. All applications will be required to have a stakeholder engagement plan as described in section 9 below.

- 4) Appropriate outcomes:** Pilot studies funded under this mechanism should focus on developing and refining interventions, testing study procedures, and evaluating intervention feasibility and acceptability, ability to successfully measure outcomes, and other such metrics. Examples of appropriate pilot study outcomes are listed in the table below. Other essential elements will in most cases include preliminary plans for the future large clinical trial that will emerge from this work (e.g., proposed study design, funding type, timeline). Studies are not required to obtain preliminary evidence of intervention efficacy, although in certain cases it is reasonable to do so. However, studies that aim to definitively determine intervention effectiveness or efficacy will not be considered appropriate for this mechanism.

Examples of appropriate pilot study outcomes

- Assessment of intervention acceptability and feasibility
- Assessment of adherence to intervention (e.g., including intervention dose, frequency, duration).
- Intervention refinement to optimize approach to BZRA deprescribing, assessment and iterative improvement of subject recruitment and retention, randomization, intervention adherence and fidelity, outcome selection and operationalization, and data collection processes

- 5) Investigators:** This mechanism is most appropriate for established investigators, namely people who at the conclusion of the 1-year award period will be well-equipped to be competitive applicants for a large grant (e.g. R01, major PCORI award) that supports a definitive clinical trial of the proposed intervention(s). Investigators very early in their research careers are welcome to participate as co-investigators, but except in unusual cases are not suitable to be PIs given the goal of proceeding immediately from the pilot award to a large-scale grant submission.
- 6) Non-financial support for funded applications:** An essential part of this mechanism is to provide support for funding investigators throughout the course of their awards, with a goal of enhancing the quality, efficiency, and impact of their research and helping them prepare for a future large-grant submission based on their pilot study results. As such, funded investigators will meet with leaders of the USDeN Pilot Core and Stakeholder Engagement Core over the course of the project period to support and identify opportunities to leverage resources to assist their work, and will attend the annual meeting of the US Deprescribing Research Network. In addition, at the 9-month mark of each project, we will ask investigators to produce a draft specific aims page and application plans for the large-grant proposal that will emerge from their pilot study. We will provide constructive feedback on that aims page and associated plans, including directing investigators to appropriate resources and funding opportunities that will help them advance to that next stage.
- 7) Consultation:** We welcome prospective applicants to request consultations through the infrastructure of our USDeN Consultation service program, whereby investigators can obtain a free, 1-hour one-on-one consultation with an expert to help with specific questions. Examples of consultations may include advice on how to identify and engage stakeholders in the proposed research or on choice of outcome measures. To request a consultation, please visit the following [link](#), and indicate that your request pertains to this RFA.

8) Funds available: Maximum period of performance is one year. The total award (direct + indirect costs) for this grant opportunity is a maximum of \$160,000. The budgeted costs may not include an indirect cost rate exceeding each organization's negotiated rate. The possibility of total funding exceeding \$160,000 or a period greater than one year may be considered with special permission; initiate such a request as early as possible through an email to admin@deprescribingresearch.org. Within these guidelines, please request the amount needed to perform the proposed pilot study. More than one application is permitted from the same institution but not from the same individual(s).

9) Application and Submission Information:

- a) **Letters of Intent (LOIs):** An LOI is required.
 - i) Formatting: 1 page in length, ½" margins, 11-point Arial font
 - ii) Include members of the proposed research team (including who will serve as PI) and a brief synopsis of your research aims and approach. It is fine if these elements change between the LOI and the final proposal.
 - iii) Include a description of planned stakeholder engagement. This may include descriptions of the stakeholders, methods of engagement and ways in which stakeholder feedback will inform research. Please see the proposal section below for online resources related to stakeholder engagement.
 - iv) Requests for funding above the standard budget cap should be listed here and also separately communicated via email to admin@deprescribingresearch.org
 - v) If you require specific guidance from USDeN core members about the appropriateness of your project for this funding mechanism, how to engage stakeholders, or other topics, please contact us at admin@deprescribingresearch.org and also state any outstanding queries within your LOI.
 - vi) LOI due date is **14 November 2022 11:59 PM (PST)**. Please submit through a web-based portal on the pilot awards section of the network website [here](#).
- b) **Proposals:**
 - i) Formatting: A maximum of six pages (including the cover page) in length, ½" margins, 11-point Arial font
 - (1) Please note that a reference list does not count toward the six-page application limit.
 - ii) Cover page (one page)
 - (1) Project title
 - (2) Principal investigator(s)' Name(s) and Title(s)
 - (3) Organization/Institution Name
 - (4) Institution Address (including zip +4), phone and email
 - (5) DUNS number
 - (6) Congressional district
 - (7) Total Requested amount (directs + indirects)
 - (8) Names, titles, and institutions of mentor(s), collaborator(s)/co-investigator(s), and/or consultant(s) on the project
 - iii) Must include the following sections in this order:
 - (1) Study aims: Detail the study aims, significance, and approach, and explain how the pilot study will directly lead to a large-grant proposal for a definitive clinical trial.
 - (2) Significance: Describe the importance of the problem to be addressed, relevance to deprescribing in older adults, and description of the population and/or community to be served.
 - (3) Stakeholder Engagement: Participation from at least one stakeholder, either in an advisory capacity or as a full member of the research team, is required. Stakeholders may include patients, caregivers, front-line clinical providers, health systems administrators and leaders, or others depending on the focus of the project. (For

additional information on stakeholder engagement please see our [Frequently Asked Questions Page](#), [our webinar recording focused on stakeholder engagement](#), [PCORI's Engagement Plan Template](#), and [PCORI's website on how stakeholders can be defined](#)). Questions about stakeholder engagement will be addressed during the webinar for this RFA (see [USDeN's webinars webpage](#) for how to attend the webinar and to access an archived recording once it has occurred). Please contact us with additional questions at admin@deprescribingresearch.org. Please also visit our website at <https://deprescribingresearch.org>.

- (a) Include a detailed description of your stakeholder(s) including how they relate to the study topic in terms of their organizational affiliation (if applicable), background and relevant experience, motivation for participating, and projected activities.
 - (b) Describe how you will incorporate meaningful engagement with one or more stakeholders or stakeholder groups that informs some aspect of the grant planning process—including development of study design, creation of research materials and establishment of the research team.
 - (c) Detail how selected stakeholders and engagement goals intersect with study aims and objectives. Detail how stakeholders were/will be recruited and selected.
 - (d) Include a budget compensation plan that outlines how stakeholders will be compensated for their time and efforts.
 - (e) Include a timeline of stakeholders' expected study-related activities along with information about planned compensation for their involvement, which should be further specified in the budget plan/justification pages.
- (4) Innovation: Explain how the application addresses important gaps in knowledge or challenges and/or seeks to shift current shortcomings in deprescribing as an essential component of safe and effective health care for older adults including any novel concepts, approaches, methodologies, or intervention(s) to be developed. Note whether the application addresses the priority areas outlined above (see Section (4) "Research topics and methodologies"). Innovative approaches for community/stakeholder engagement should also be highlighted in this section if applicable, with more specific details provided in the stakeholder engagement section.
 - (5) Approach: Describe the overall strategy, methodology, outcomes to be assessed, and planned analyses, keeping in mind requirements of this RFA as listed above.
 - (6) Future plans: Describe plans for how to take the findings of the pilot project and convert them into a large-grant application for a definitive clinical trial. Where possible, be specific about specific funding mechanisms, outlines of how a future definitive clinical trial will be structured, and proposed timelines.
- iv) Required Supplemental Documents (Does not count toward the 5-page limit):
 - (1) Include a half-page description of the proposed grant planning activities and the envisioned study that will lead to using lay terminology geared toward non-researchers and the general public and its relevance to stakeholders.
 - (2) Submit NIH-style biosketches (using the current NIH format) for the PI, primary mentor (if the PI is at a junior level) and any additional investigators being paid by the grant. Please ensure that each biosketch includes position/title, education/training, personal statement, positions/honors, and contributions to science.
 - v) Fellows and post-docs are not eligible to apply for this award. Faculty status at beginning of award period: Any fellows and post-docs who are a PI on the proposal should describe plans for being appointed as a faculty member by the time this award begins, which is likely to occur in August 2022. Any possibility of moving between institutions should also be described. This description should include the support that will be available for the proposed research at the new institution. Note that since this

award is designed to directly lead to a large clinical trial with R01-type or an equivalent level of funding, in most cases investigators at the very beginning of their research careers would not be competitive applicants.

vi) Interdisciplinary research teams are encouraged.

vii) Budget Forms

(1) Special note: The total budget must comprise both direct and indirect (“F&A”) funds. Indirect costs should be charged by the recipient’s institution at that institution’s federally negotiated rate. Foreign organizations may charge an F&A rate of no more than 8% of modified total direct costs. Please work with your local grants management office early in the process of preparing your grant budget to clarify budgeting of direct and indirect dollars, keeping in mind that the total budget may not exceed \$160,000.

(2) Scope of work (i.e., brief paragraph outlining what work will be done under the proposed project and who will do it)

(3) Detailed budget summary, including any expenses allocated to stakeholder involvement.

(4) Budget justification

(5) Other required documents

(a) Subrecipient commitment form (if applicable)

(b) F&A rate agreement letter

c) Please submit all materials as one PDF document through a web-based portal on the grant planning awards section of the network website [here](#). If you encounter any issues with the submission process, please email admin@deprescribingresearch.org

d) Proposals will be reviewed and scored based on consistency with the goals of this mechanism, innovation, scientific rigor, feasibility, investigators, stakeholder engagement, relevance to aging, and potential to lead to a future large-scale clinical trial of the intervention(s).

e) These funds come from the National Institute on Complementary and Integrative Health as an administrative supplement to a National Institute on Aging-funded parent grant, and are administered by NCIRE. Please provide the information below to your grants specialist, if needed.

i) Type of Institution: NCIRE is a public, nonprofit institution exempt under Section 501(c)(3) of the IRS code. Institutional Name and Address: Northern California Institute for Research and Education 4150 Clement Street, Mail Code: 151 NC, San Francisco, CA 94121-1545. County: San Francisco County. Congressional District: CA-012. Main Telephone Number: (415) 750-6954. Fax Number: (415) 750-9358.

10) Eligibility Criteria:

a) Institutions

- i. Eligible institutions include colleges, universities, medical or nursing schools, or other fiscally responsible organizations.
- ii. Proposals may be submitted by non-US institutions, but such proposals must articulate how the proposed research applies to settings outside of the applicant’s home country, including to the US.
- iii. Prior to submitting an application, applicant organizations must be registered with System for Award Management ([SAM](#)) and have a Dun and Bradstreet Universal Numbering Systems (DUNS) number (<http://fedgov.dnb.com/webform>).

b) Principal Investigator

- i. Applicants must hold a doctorate degree (MD, PhD, PharmD or equivalent)
- ii. Applicants must hold a faculty, research scientist, or equivalent position at an eligible institution by the start date of the award.

- iii. Applicants from under-represented racial and ethnic groups as well as individuals with disabilities are strongly encouraged to apply for funding

11) Key Dates:

Application FAQ session, an informational webinar about this mechanism. (Visit https://deprescribingresearch.org to register and to see an archived version after the session has occurred)	October 11, 2022, 1 – 2 PM CST (11 – 12 PST)
Letters of intent (required)	November 14, 2022
Full application due	December 16, 2022
Awards announced	February 2023
Beginning of funding for selected awards	Estimated April/May 2023