Frequently Asked Questions

INTRODUCTION

The Funding Opportunity Announcements (FOAs) PAR-18-324 and PAR-18-307 invites applications related to the development (R21/R33) and testing (R01) of interventions for health-enhancing physical activity. The purpose of these FOAs is to fund highly innovative and promising research aimed at

developing and testing multi-level physical activity intervention programs acting on at least two levels of the socio-ecological model and designed to increase health-enhancing physical activity: 1) in persons or groups that can benefit from such activity; and 2) that could be made scalable and sustainable for broad use across the nation. To date, several questions have been submitted from various investigators about permissible research plans under these PARs. This FAQ was developed to address these questions.

APPLICATION SUBMISSION

When are applications due?

For R01 applications:

- New applications: February 5, 2018; October 5, 2018; June 5, 2019; February 5, 2020; October 5, 2020, by 5:00 PM local time of applicant organization. Please note that this FOA uses non-standard application dates.
- Resubmission applications: March 5, 2018; November 5, 2018; July 5, 2019; March 5, 2020; November 5, 2020, by 5:00 PM local time of applicant organization.
- AIDS Applications: May 7, 2018; January 7, 2019; September 7, 2019; May 7, 2020; January 7, 2021, by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related applications allowed for this funding opportunity announcement are due on these dates.

For R21/R33 applications:

- New applications: February 16, 2018; October 16, 2018; June 16, 2019; February 16, 2020; October 16, 2020, by 5:00 PM local time of applicant organization. Please note that this FOA uses non-standard application dates.
- Resubmission applications: March 16, 2018; November 16, 2018; July 16, 2019; March 16, 2020; November 16, 2020, by 5:00 PM local time of applicant organization.
- AIDS applications: May 7, 2018; January 7, 2019; September 7, 2019; May 7, 2020; January 7, 2021, by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related applications allowed for this funding opportunity announcement are due on these dates.

How should I submit my application?

Applications must be submitted electronically. Applicants should follow the instructions in the SF424 (R&R) Application Guide, including Supplemental Grant Application Instructions except where instructed in this FOA to do otherwise.

Am I required to submit a letter of intent?

A letter of intent is not required and it does not enter into the review process. Investigators are encouraged to communicate with NIH scientific contacts listed at the bottom of the FOAs (PAR-18-324 and PAR-18-307) to discuss their research ideas and specific aims prior to submitting applications.

PAGE LIMITATIONS

Does the application have a page limit?

Yes. All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed.

RESEARCH OBJECTIVES AND SCOPE

How do I know if my application is within scope for this program announcement?

The application must meet the following criteria to be considered within scope:

For R21 and R33 PARs:

- The proposed intervention must have strong scientific rationale.
- The proposed pilot interventions have physical activity as a primary outcome but are not required to have sample sizes that are sufficient to measure statistically significant changes in physical activity or related health outcomes. In these developmental or pilot interventions, physical activity should be measured, but with the goal of assessing feasibility and acceptability of the physical activity intervention and comparator arm(s), such as recruitment rates, randomization processes, adherence and compliance, fidelity of implementation, dose, data collection response rates, or other issues. Between-group comparisons of efficacy or "preliminary efficacy" are not appropriate for this FOA.
- The proposed intervention must target a specific population or age group to study the feasibility and acceptability of intervention and evaluation protocols and materials in that group.
- The proposed intervention must include interventions targeting at least two levels in the Socio-Ecological Model (See FAQ on what qualifies as a multi-level intervention).
- The proposed intervention combines and refines evidence-based physical activity interventions and makes use of innovative partnerships within and across sectors.
- The proposed intervention should be able to be made scalable and sustainable in real world settings.
- The proposed intervention is directed to a population of interest for participating Institutes which include but are not limited to:
    - Healthy but sedentary or inactive individuals
    - Persons or groups at high risk for a particular disease or condition (e.g. substance use disorder or nicotine dependence) that can be improved by physical activity
    - Persons with an existing disease or condition (e.g., cardiovascular disease, obesity, cancer, diabetes, or Alzheimer's or related dementias) whose outcomes could be improved by physical activity
        - Where the population of interest is those with obesity or overweight, the intervention should principally aim to improve physical activity and/or reduce sedentary behavior rather than weight loss as the primary aim.
    - Persons of diverse socioeconomic, ethnic, and racial groups with low physical activity levels
    - Persons with physical, developmental, or intellectual disabilities who may need special approaches for activity promotion
    - Inactive or sedentary elderly individuals or groups

  - Minority and underserved populations at higher risk for conditions associated with inactivity
  - Comparison or contrasting of populations of interest on the desired outcome

For R01 PARS:

- The proposed intervention must have strong scientific rationale.
- The proposed intervention must include physical activity change over the 1- to 2-year intervention period as a primary outcome and be designed to test statistically and clinically significant differences in the outcome based on the intervention.
- The proposed intervention must target a specific population or age group to study how physical activity benefits them.
- The proposed intervention must encompass multiple levels and should not focus on only the individual (See FAQ on what qualifies as a multi-level intervention).
- The proposed intervention combines and refines evidence-based physical activity interventions and makes use of innovative partnerships within and across sectors.
- The proposed intervention should be able to be made scalable and sustainable in real world settings.
- The proposed intervention is directed to a population of interest for participating Institutes which include but are not limited to:
  - Healthy but sedentary or inactive individuals
  - Persons or groups at high risk for a particular disease or condition (e.g. substance use disorder or nicotine dependence) that can be improved by physical activity
  - Persons with an existing disease or condition (e.g., cardiovascular disease, obesity, cancer, diabetes, or Alzheimer's or related dementias) whose outcomes could be improved by physical activity
    - Where the population of interest is those with obesity or overweight, the intervention should principally aim to improve physical activity and/or reduce sedentary behavior rather than weight loss as the primary aim.
  - Persons of diverse socioeconomic, ethnic, and racial groups with low physical activity levels
  - Persons with physical, developmental, or intellectual disabilities who may need special approaches for activity promotion
  - Inactive or sedentary elderly individuals or groups
  - Minority and underserved populations at higher risk for conditions associated with inactivity
  - Comparison or contrasting of populations of interest on the desired outcome
- Secondary outcomes of interest include: persistent post-treatment conditions or toxicities affecting physical and cognitive function, cardiorespiratory fitness, skeletal-muscle and bone health, substance abuse, smoking cessation, cognition and memory, age-related chronic conditions/multi-morbidities, cardiovascular disease, prevention of secondary conditions (such as decrement in skeletal muscle strength and functioning, decline in bone and joint health) as they impact rehabilitation outcomes (reduced impairment, improved function, or reduced disability), inflammation, insulin resistance, sex hormones, insulin or insulin-like growth factors or their binding proteins, glucose metabolism, leptin and other adipokines, immunologic or inflammatory factors, oxidative stress and DNA damage or repair capacity, angiogenesis, or prostaglandins, dyslipidemia, dysglycemia, atherosclerosis, and obesity. Where inclusion of

obesity as secondary outcome occurs, the intervention should principally aim to improve physical activity or reduce sedentary behavior and include rationale for health benefit independent of weight loss.

Applicants are strongly encouraged to contact the NIH scientific research contacts listed in the program announcements (PAR-18-324 and PAR-18-307) for feedback regarding if the topic is within scope and of scientific priority before submitting an application. Applicants should also review the IC priority statements in the program announcements. Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by the Center for Scientific Review, in accordance with NIH peer review policy and procedures, using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

What if my population, intervention components, and/or secondary outcomes do not match well with any of the participating Institutes/Centers (ICs) research priorities?

Your application will get assigned to an IC based on the IC research priorities as stated in the FOAs. Importantly, NIH Offices (Office of Disease Prevention) participating in these FOAs do not manage grants. Therefore, the primary awarder of the grant will be one of the participating ICs. Applicants are *highly encouraged* to discuss potential research aims with contact program officials at participating ICs well in advance of the application deadline to ensure overall fit of the proposed research with programmatic priorities, as stated in the FOAs. Applications that are not well-aligned with programmatic priorities of any of the participating ICs are unlikely to get funded, even if they are accepted for review and score well. A participating IC might choose to award a grant that is not well-aligned with their priorities if the Office of Disease Prevention provides significant co-funding for the award, but this is not standard or guaranteed. Program officials can help applicants identify alternative FOAs if it is determined that the applicant's research goals are not well-aligned with any of the participating IC's research priorities.

What are examples of research designs that are appropriate for these program announcements?

Multiple research designs are appropriate for these program announcements, and the choice will depend on the stage of development of the research, the research question, and whether randomization is possible. Investigators should describe the strongest study design that can evaluate the effects of the intervention program with high internal validity, taking into account external validity and generalizability. In general, this would be a randomized controlled trial (RCT). Most studies proposed for this announcement may require randomization at the group level (Group Randomized

Trial, or GRT) to match the level of intervention and to minimize or prevent contamination of the comparison group. For more guidance, please visit these resources developed by NIH on GRTs and pragmatic clinical trials. For R01 applications, the methods proposed for data analysis and the methods used for sample size calculation should reflect both the extra variation expected in the data and the degrees of freedom available to estimate that extra variation. R21/R33 applications do not need to be powered to assess differences in physical activity since the goal of this FOA is on developing the multi-level intervention, and not on testing efficacy. If proposing a GRT in R21/R33 applications, applications should be testing the feasibility of group randomization.

In some cases, a randomized design may not be possible or feasible, or would raise ethical concerns that are difficult to address. In such instances, investigators could propose and justify alternative, high-quality study designs. Such designs include, but are not limited to, quasi-experimental designs such as multiple baseline or interrupted time series, regression discontinuity, pre-to-post intervention with external comparison, natural experiments, or others.

Interventions for the R21/R33 applications are anticipated to be pilot tests and prototype studies while interventions for R01 applications are expected to be full tests of efficacy or effectiveness.

What qualifies as a multilevel intervention?

Applicants are encouraged to use the Socio-Ecological Model as a framework for conceptualizing ways to develop a multilevel intervention (i.e. incorporating intervention targets at the intrapersonal, interpersonal, organizational, community, and/or public policy levels). For example, an intervention might include pedometer-based challenges at the interpersonal level, as well as the initiation/strengthening of joint-use agreements for community members to use school recreation facilities at the public policy level. A different intervention might focus on methods for enhancing motivation at the intrapersonal level and creating online social support groups for physical activity at the interpersonal level. Policy or built environmental intervention across worksites at an organizational level may be paired with individually targeted intervention components to promote physical activity. There are many ways for an intervention to qualify as multilevel.

Is a research proposal in which the outcomes do not include physical activity considered within scope?

No. Physical activity must be one of the outcome measures for an application to be within scope for these program announcements. For R01 proposals, the proposed intervention must include physical activity change as a primary outcome and be designed to test statistically and clinically significant differences in the outcome based on the intervention over the 1- to 2-year intervention period. While R21/R33 applications must address physical activity change, they are not required to have sample sizes sufficient to measure statistically significant changes in physical activity or related health outcomes. In these developmental or pilot interventions, physical activity should be measured, but with the goal of assessing feasibility and acceptability of the physical activity intervention, such as recruitment rate, randomization processes, adherence and compliance, fidelity of implementation, dose, data collection response rates, or other issues.

For all applications, the intervention and any comparison/control group should use appropriate and well-justified physical activity measures to enable proper comparisons that are also feasible in real world settings. Measurement of intervention processes and impacts is also encouraged to enable assessment of intervention fidelity and whether hypothesized mediators were affected. For R21/R33 applications, tests of the effects of the intervention on behavioral mediators and/or intermediate outcomes of physical activity change can be used to enable the identification of components of the intervention that appear most promising to investigate in an efficacy study, provided the study is appropriately powered to analyze these indicator variables. Measurement of secondary outcomes may also be included. The Research Objectives section of PAR-18-324 provides a list of secondary outcomes of interest to participating Institutes and Centers.

In my proposal, what type of information is helpful to include about the interventions proposed?

Specific interventions incorporated into the application should be justified by the population group of interest and the suitability and tailoring of the intervention, physical activity goals, and measures for the target population. Investigators should pay close attention to the quality of measurement of physical activity and/or factors influencing physical activity at the individual and other levels, ensuring that the measures are reliable and sensitive to change. Using intervention components with previously developed tools is encouraged.

Investigators are encouraged to address how specific intervention(s) selected at each level will reinforce each other to potentiate a larger effect for the overall intervention(s). To clarify how interventions are related, investigators are encouraged to develop a graphic representation of the overall logic model for the proposed study. To facilitate more complete understanding of the logistics of the intervention(s), investigators are also encouraged to develop a graphic representation of the timeline for the intervention and associated measurements.

Settings for the interventions can include but are not limited to healthcare settings, worksites, households, schools, green space, parks and recreation centers, other community organizations and settings, or entire communities.

Is a research proposal that includes cost-effectiveness aims considered within scope?

Complete cost-effectiveness analyses are beyond the scope of this announcement. However, an assessment of resources spent on intervention development and maintenance and data on costs of implementing and sustaining the intervention are encouraged. Costs can include actual costs for intervention development, implementation and, to a lesser degree, maintenance.

What is the Phased Innovation (R21/R33) grant mechanism?

The R21/R33 Phased Innovation Award consists of two phases:

1. The **Exploratory/Developmental Research Grant Award (R21)** phase supports investigation of novel scientific ideas or new model systems, tools, or technologies that have the potential for

significant impact on biomedical or biobehavioral research. The R21 phase provides up to two years of funding for innovative projects, supported by limited or no preliminary data, to allow investigators to demonstrate feasibility of the proposed approach. Reviewers will emphasize the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. The applicant is required to include well-defined, quantifiable milestones that can be used to judge the success of the R21 project. These milestones are evaluated during peer review and negotiated prior to the award of the R21 phase. If the applicant achieves the proposed milestones, the award of the R33 phase will be considered.

2. The **Exploratory/Developmental Grant Phase II Award (R33)** provides the second phase of support for the research initiated under the R21 phase for a period of up to three additional years. Transition to the R33 phase is not guaranteed, but rather will be based upon program priorities, the availability of funds, and the successful completion of negotiated milestones for the R21 phase, as determined by NIH administrative review.

For the R21/R33 grant, the Specific Aims must fully describe both the R21 and R33 phases and should be combined on one page in the application. The Research Plan should also describe both phases.

What are examples of research proposed within the Phased Innovation (R21/R33) grant mechanism?

Due to the phased nature of this R21/R33 award, applications should propose to conduct formative assessments and feasibility studies in the R21 phase with possible transition to expanded research support in the R33 phase in order to optimize the multi-level intervention and/or conduct larger-scale feasibility studies in preparation for a powered efficacy study.

Examples of research projects that may be appropriate for the R21 phase include but are not limited to the following:

- Qualitative or mixed-methods approaches to determine acceptability and refine intervention components
- Assessment of adherence to dose, frequency and/or duration of intervention components
- Feasibility study of a single-level intervention with measurement of contextual factors operating at another level of the socioecological model to inform the design of a multi-level intervention in the R33 phase
- Separate feasibility studies for each level or component of the proposed multi-level intervention
- Single site feasibility study for the combined multi-level intervention

Examples of research projects that may be appropriate for the R33 phase include but are not limited to the following:

- Larger scale feasibility study of the combined multi-level intervention
- Multi-site feasibility study of the multi-level intervention to assess fidelity of implementation
- Assessment of the effect of the multi-level intervention on hypothesized mediators of physical activity change
- Optimization of the multi-level intervention

How are milestones for the R21 phase of the Phased Innovation R21/R33 grant mechanism determined?

The Transition Milestone section must propose milestones for completion of the R21 part of the project, a discussion of the suitability of the proposed milestones for assessing success in the R21 phase, and a discussion of the implications of successful completion of these milestones for the proposed R33 study. Transition Milestones should be well-defined, specific, quantifiable and scientifically justified; they should not be simply a restatement of the R21 specific aims. Milestones may be provided for the R33 phase at the discretion of the applicant. Transition Milestones should be sufficiently rigorous scientifically to be valid for assessing progress in the R21 phase. Any available preliminary data that will support or justify the proposed hypothesis, rationale or development plan may be included. However, preliminary data are not required for an R21/R33 application.

What are the funding levels for these R21 and R33 program announcements?

The R21 phase may not exceed $275,000 in direct costs for the 2-year project period, with no more than $200,000 in direct costs in any single year of the R21 phase. The R33 phase may not exceed $750,000 in direct costs for the 3-year project period, with no more than $250,000 in direct costs in any single year of the R33 phase.

AWARD SELECTION

On what basis are applications selected for funding?

Applications will be selected for funding based on scientific merit, current NIH program research priorities, and availability of funds. Applicants are highly encouraged to discuss potential research aims with contact program officials at participating NIH Institutes/Centers (ICs) to determine fit with programmatic research priorities. Applications which do not align with research priorities at any of the participating ICs are unlikely to be funded may be rejected without review.

POST AWARD MANAGEMENT & REPORTING

Which NIH Institute/Center (IC) will manage my award?

IC assignment is dependent on the nature and scope of the research projects proposed. Applicants may request assignment to a particular Institute in their cover letter, but NIH will make the final determination regarding Institute management and oversight. NIH Offices (Office of Disease Prevention) participating in these FOAs do not manage grants. Therefore, the primary awarder of the

grant will be one of the institutes or centers that are participating on these FOAs. The offices can provide co-funding on selected grants.