

**Request for Applications (RFA): Exercise and Nutrition Interventions to Improve Cancer Treatment-Related Outcomes (ENICTO) in Cancer Survivors Consortium**

**[RFA-CA-21-031](#) and [RFA-CA-21-032](#)**

**Frequently Asked Questions (FAQ)**

Pre-application Webinar held May 26, 2021

Slides of the Webinar are available at:

<https://cancercontrol.cancer.gov/brp/events/exercise-nutrition-interventions>

## **General Questions**

### **Q1: What elements are required? Do all elements have to be met?**

A1: Yes, all applications must include the following five aspects to be considered for review:

1. Use an exercise, medical nutrition, or a combined intervention approach, specify the knowledge gap addressed, and justify the cancer survivor population under study (e.g., age-group and cancer site) and biological plausibility of the intervention to affect the treatment-related outcome(s);
2. Employ an appropriately powered NIH clinical trial design with a treatment-related outcome as the identified primary endpoint and include a patient-reported outcome as a secondary outcome;
3. Enroll research participants in the trial shortly before or during treatment;
4. Collect robust treatment data including planned and delivered dose and type for all cancer treatment modalities (e.g., surgery, chemotherapy, radiation therapy, hormonal or immunotherapy), and where appropriate, supportive care measures (e.g., anti-emetics);
5. Use validated measures of body composition (e.g., creatine D3, computerized tomography (CT) scans, dual x-ray absorptiometry (DXA)), diet (e.g., standardized and comprehensive 24-hour recall methods), and general physical activity.

*Additionally, applications incorporating an exercise component in the intervention approach are required to:*

- Specify details of exercise prescriptions (e.g., Frequency, Intensity, Time, and Type (FITT) criteria) that are in addition to a general measure of physical activity;
- Include validated measures of prescribed exercise, exercise adherence, and exercise-related biomarkers (e.g., cardiorespiratory fitness (CRF), strength, functional status) relevant to treatment outcomes.

## **Cancer Treatment and Patient Population Questions**

### **Q2: What constitutes acceptable cancer treatments for this Request for Applications (RFA)?**

A2: For the purpose of this RFA, all cancer treatments delivered with curative or life-extending intent are considered relevant. Palliative and/or end-of-life care is not within the scope of this RFA.

### **Q3: Who is considered a cancer survivor for this RFA?**

A3: We will use the current NCI [definition](#) for this RFA - “An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. There are

many types of survivors, including those living with cancer and those free of cancer. This term is meant to capture a population of those with a history of cancer rather than to provide a label that may or may not resonate with individuals.”

**Q4: Is it acceptable to propose studies on patients with metastatic disease?**

A4: Yes, projects including patients with metastatic disease are permitted.

**Q5: Do studies of patients with poor prognosis (e.g., pancreatic cancer) qualify for this RFA?**

A5: Yes, projects proposing patient populations with aggressive cancers or disease sites with poor prognosis are permitted as long as they are receiving cancer treatment with curative or life-extending intent.

**Q6: Can applications include children and/or adults, or are they restricted to adults?**

A6: Projects are not restricted to adult populations and may include children, adults, or both children and adults receiving cancer treatment with curative or life-extending intent.

**Cancer Treatment-related Endpoint Questions**

**Q7: Are there cancer treatment-related endpoints beyond those listed examples be used?**

A7: The primary endpoint must be among the *categories* specified in the RFA (treatment completion, healthcare utilization, severe adverse event). Secondary endpoints may be included that expand beyond those categories. For example, a biomarker for chemotherapy-induced peripheral neuropathy (CIPN) may not be the primary endpoint, but could be included in a study that also measures severe adverse events such as the Common Terminology Criteria for Adverse Events (CTCAE)  $\geq 3$  or dose-interruption affecting treatment completion. Applicants must justify how the identified primary endpoint fits into one of the categories. Contact the scientific program contacts listed in the RFA to ensure endpoints are acceptable, especially if it is not a common example of one of these categories or occurs distally to cancer treatment delivered with curative or life-extending intent.

**Project Timeline and Intervention/Follow-up Period Questions**

**Q8: How long is the clinical trial and follow-up period?**

A8: The trial length and follow-up period are investigator determined but must be justified to consider the target population, cancer treatment, the selected primary endpoint, and other secondary outcomes as appropriate within the timeframe of the grant period.

**Q9: Does the RFA require each phase: prehabilitation, trial, and follow-up?**

A9: The proposed intervention may occur in prehabilitation and/or during treatment. These phases, along with the follow-up period, are investigator determined, but should be justified for the selected primary endpoint and other secondary outcomes as deemed appropriate.

**Q10: Does the range of intervention timing extend to prehabilitation-type approaches?**

A10: Yes, intervention timing may include prehabilitation-type approaches, but it is not required. The intervention timing period should be justified for the selected primary endpoint and other secondary outcomes as appropriate.

**Q11: Can recruitment occur before treatment or during the course of treatment?**

A11: Yes, the recruitment/enrollment period may occur at any time before treatment is completed and should be appropriate for the target population, cancer treatment, and selected outcomes. Recruitment after treatment completion is not permitted.

**Q12: Are collection of cancer treatment-related outcomes limited to before and/or during treatment time periods?**

A12: No. A PI may propose to follow participants beyond the completion of primary cancer treatment (for curative and life-extending intent) to capture treatment-related outcomes as deemed appropriate to the research question within the timeframe of the grant period.

**Exercise Intervention Components Questions**

**Q13: Is the exercise intervention restricted to manipulating dose or can modality be manipulated too/instead?**

A13: Any mode of exercise or combination thereof may be used/manipulated, but the exercise prescription must be fully articulated and must include the criteria for adherence to the exercise prescription.

**Q14: Can investigators take an approach comparing exercise prescription to general physical activity recommendations?**

A14: Applications proposing an exercise intervention trial, alone or in combination with medical nutrition, that only compares a general physical activity guideline (PAG) approach to a control condition are non-responsive. Trials that include a PAG approach in comparison to a fully articulated exercise prescription approach inclusive of FITT criteria are responsive.

**Q15: Do applications proposing an exercise intervention have to measure adherence to the exercise program or only physical activity?**

A15: In addition to describing elements of the exercise prescription, interventions with an exercise component must use valid measures of exercise adherence to the prescribed program and document related exercise effects (e.g., change in CRF, strength, or function). Interventions may also include general measures of physical activity, but it is not sufficient alone.

**Medical Nutrition Intervention Components Questions**

**Q16: Does a medical nutrition intervention have to manipulate macronutrients and the timing of intake?**

A16: No, studies may include a broad array of nutritional factors, including a focus on dietary patterns, macronutrients, timing of intake (e.g., intermittent fasting), body composition, and/or weight control/maintenance.

**Q17: Does a medical nutrition intervention have to take place in a hospital setting?**

A17: No, interventions must be well-measured but may take place anywhere. All proposed interventions must be justified by strong scientific evidence.

**GENERAL Requirements for Collection of Physical Activity, Diet, and Body Composition Measures Questions**

**Q18: Are measures of body composition required for studies where body composition might not be part of the protective pathway?**

A18: Yes. As a general requirement to fulfill the terms of the cooperative agreement, all studies must include at least one validated measure of body composition for the purposes of collecting common data constructs across studies for possible use in cross-site analyses.

**Q19: Are measures of physical activity required for studies where exercise is not an element of the intervention approach?**

A19: Yes. As a general requirement to fulfill the terms of the cooperative agreement, all studies must include at least one validated measure of physical activity for the purposes of collecting common data constructs across studies for possible use in cross-site analyses.

**Q20: Are measures of diet required for studies where medical nutrition is not an element of the intervention approach?**

A20: Yes. As a general requirement to fulfill the terms of the cooperative agreement, all studies must include at least one validated measure of diet for the purposes of collecting common data constructs across studies for possible use in cross-site analyses.

**Q21: What is the minimum number of assessment timepoints required if a measure of body composition, diet, or physical activity is only being proposed for the purpose of fulfilling a general requirement as opposed to being integral to an intervention approach?**

A21: Assessments conducted only to fulfill general requirements for physical activity, diet, and body composition must be measured at pre-intervention baseline and at one or more post-intervention timepoints.

**Pilot Project and Steering Committee (SC) Questions**

**Q22: Should possible pilot projects emanating from common data in the consortium be described?**

A22:

(U01 Applications): No, U01 applications should not describe any future pilot projects. With submission, applicants acknowledge and agree to the terms of the cooperative agreement, which describe possible pilot projects, but they should not be proposed at the time of application. Please note that applications are required to reserve \$35,000 per year for future pilot projects, which will be decided upon in conjunction with the consortium.

(U24 Applications): No, U24 applications should not describe any pilot project but should list possible avenues for pilot project research. The ENICTO consortium structure provides the opportunity to pool data across research sites, collect new data, and pursue research questions collectively that could not be pursued by individual U01 research sites. Therefore, U24 applicants should list the areas/possible directions for which pilot studies are anticipated.

**Q23: Who approves pilot projects?**

A23: The ENICTO Steering Committee must approve the use of collective data for pilot projects and the use of funds set aside for these purposes.

**Q24: Who is on the Steering Committee?**

A24: The ENICTO Steering Committee consists of one PI from each U01 awardee, the Coordinating Center (CC) awardee, and one NCI representative. Each Steering Committee member has one vote.

**Q25: What does the Steering Committee do?**

A25: The ENICTO Steering Committee determines scientific priorities, activities, and the use of funds dedicated for cross-site pilot projects. The Steering Committee should work together to maximize shared resources. Details on the composition and functions of the Steering Committee are provided in Section VI. Award Administration Information, Terms and Conditions of Cooperative Agreement, “Areas of Joint Responsibility.”

**Other Application Components Questions**

**Q26: Can investigators have a foreign component and plan to recruit survivors in foreign countries?**

A26: Foreign components are allowed for U01 applications; however, they are not allowed for U24 applications. The PI should carefully consider how the nature of the foreign involvement impacts the trial approach, significance, and translational potential of the project.

**Q27: Are applications based solely on animal studies allowed?**

A27: No, they may be cited as part of the rationale but are not sufficient for this RFA.

**Coordinating Center (CC) Questions**

**Q28: Will the coordinating center be involved in participant recruitment activities (e.g., will there be a general recruitment and enrollment plan that all U01 projects sites must follow or draw from)?**

A28: No. All U01 projects should propose their individual recruitment, enrollment, and retention plan specific to their project. The CC could conceivably be involved in the collection of recruitment plans across U01 sites, track strategies employed, and relative success.

**Q29: Will the coordinating center use an NCI data reporting platform or repository?**

A29: Applicants for the CC should propose their plan to create and/or integrate data collection platforms as deemed appropriate to the data needs and structure of the ENICTO consortium.

**Questions During Webinar**

**Q30: Would cancer patients shortly after completion of all treatment be an acceptable population to target as part of this RFA? If so, what is a reasonable post-treatment timeline?**

A30: Studies may follow patients after treatment completion, but patients must be recruited before treatment begins or during the course of treatment.

**Q31: Are New Investigators (NI) and Early Stage Investigators (ESI) eligible to apply, and if so, will NI and ESI statuses be considered during review?**

A31: Yes, New and Early Stage Investigators are eligible and will be considered as appropriate by NCI policy.

**Q32: Is time to begin adjuvant therapy after surgery an acceptable primary endpoint?**

A32: Yes, with a justification of the importance of the endpoint.

**Q33: Is it acceptable to propose studies with complementary or alternative medicine?**

A33: Yes, with justification as to how the intervention meets the exercise and medical nutrition intervention definition within the RFA, describing the biological rationale for the approach and the relevance to an appropriate treatment-related endpoint.

**Q34: For applicants with strong research in either exercise or nutrition, is it acceptable to submit an application focused only on one (either exercise or nutrition)? Do measures of the other still need to be included, even if not the focus of the intervention?**

A34: As outlined in the RFA, it is a requirement to include at least one measurement of exercise or nutrition. Investigators focused on exercise must include at least one measurement of diet. Investigators focusing on diet or nutrition must include a measure of physical activity.

**Q35: Does NCI envision patient advocates being involved in the ENICTO consortium, and if so, at what level – individual U01 sites or the Coordinating Center?**

A35: Yes, but involvement and extent are up to the investigators and as justified in the application. NCI would encourage patient advocate involvement at whatever level is appropriate for an individual site or for the coordinating center, as often as possible to the extent it makes sense for the study.

**Q36: What does the RFA require with regard to inclusion of biomarkers? Is inclusion of measures of body composition, fitness, and diet sufficient? Or are additional mechanistic biomarkers required?**

A36: Inclusion requirements per the RFA must be met. If including specific biomarkers, investigators must provide a justification for the inclusion of biomarkers and why they are important for the study.

**Q37: Is there an expectation that responses to the U01 will include a single trial or would multiple trials within one response be considered?**

A37: NCI anticipates most applications will involve a single primary trial with an identified treatment-related outcome as a primary endpoint and a patient-reported outcome as a secondary outcome. Multiple trials within an application would be considered, though the rationale for multiple trials must be clearly stated and consider that multiple trials would be more demanding in terms of power, and cost/budget cap.

**Q38: Will there be more than one application receipt date for this RFA?**

A38: At present, there is only one receipt date.

**Q39: For U01 proposals, should investigators clearly identify patient populations they want to study? But ultimately will it be a consortium decision on the final protocol that will be implemented across sites?**

A39: Yes, patient populations should clearly be identified. The consortium may provide input, but there will not be a final protocol instituted across all studies. Investigators should clearly convey their protocol and justification for conducting their own trial.

**Q40: Will prevention of cancer treatment-related weight gain be considered a severe outcome and eligible for this RFA?**

A40: Possibly, but investigators must focus on cancer survivors enrolled prior to or in conjunction with cancer treatment, and they must justify how a particular level of weight gain

meets accepted criteria as a cancer-treatment related severe adverse event. Weight gain alone is not sufficient as an end point, as justification must be provided for a severe adverse event.

**Q41: Will the consortium alter funded awards/projects to ensure common outcomes and/or data elements?**

A41: No. These are all independent projects, but they all must contain required common elements (e.g., measures of diet, physical activity, and body composition). Post-award, the Coordinating Center will identify strategies to harmonize data elements and only where possible suggest specific common measurements.

**Q42: Can fatigue can be considered a treatment-related outcome only if it is grade 3 or higher?**

A42: Yes. Fatigue must be severe, e.g. CTCAE = 3 or higher to qualify as a severe event.

**Q43: Can the serious adverse events come from the [PRO-CTCAE](#), and if so, are there particular questions that must be included?**

A43: Yes, severe adverse events can come from PRO-CTCAE, but there are no mandatory questions that must be included. However, they must be relevant to the cancer treatment under consideration and as justified by the strength and stability of the proposed intervention.

**Q44: Is preliminary data required for this application?**

A44: Yes, [Section IV](#), sub-section C of RFA-CA-21-031 describes required preliminary data, and information concerning preliminary data is also provided in [Section V](#) scoring criteria.

**Q45: Does the budget application need to set aside money for potential future pilot studies?**

A45: Yes, the budget section specifies that funds must be set aside in years 2 through 5. The \$35,000 per year must be represented on the submitted budget.

**Q46: Is the intent of the RFA to elicit well-powered Phase 3 trials of interventions with strong preliminary evidence, or are novel hypothesis-driven approaches preferred?**

A46: This is not specifically an either/or question. NCI is looking for hypothesis driven, well-powered trials, that are well justified (e.g., with good evidence for the translational research phase) and that identify one of the required primary endpoints.

**Q47: Is it acceptable for medical nutrition interventions to include both dietary patterns and nutritional supplements (e.g., protein powder, vitamin D, omega-3 fatty acids, etc.)?**

A47: Yes, this is acceptable, as long as investigators have a process, hypothesis support, and strong justification for how the intervention would impact treatment-related outcomes.

**Q48: Does this study require a single Institutional Review Board (IRB), or is each U01 considered a separate trial with their own IRB?**

A48: As each study is an independent trial requiring a single therapy, each would require its own IRB.

**Q49: What is the expected sample size for the proposed clinical trial(s)?**

A49: The expected sample size depends on the investigator's endpoint, the documented

expected impact of the intervention, and the power for each trial. There is not a sample size requirement.

**Q50: What documents are allowed in the appendix for these clinical trials?**

A50: General requirements can be found in the RFA. Please remember that reviewers are not required to read appendix items, so please ensure all vital components are included in the body of the application.

**Q51: Is NCI interested in ensuring a diversity of cancer sites/populations for this RFA? In other words, should investigators avoid focusing on common cancers?**

A51: Each investigator will approach this RFA differently. Applications will likely be based on an investigator's experience, as individuals must justify what they are proposing, to which selected population, and why the cancer site(s) was chosen. Investigators will make this determination themselves. NCI is ultimately looking to add information that currently does not exist concerning the effect of exercise and/or medical nutrition on cancer treatment-related outcomes, so this could be pursued in a novel question to a common cancer. However, diversity in cancer site is acceptable as well.

**Q52: Under "Funds Available," the RFA states that NCI intends to commit up to \$1 million in FY22 to fund one U24 award. If investigators have \$875,000 in direct costs, can they utilize their DHHS approved F&A (facilities and administrative costs, aka indirect costs or overhead) rate, which would take the total costs above \$1 million, or are the maximum total costs allowed \$1 million?**

A52: The budget must be commensurate to the work proposed. Though it may not exceed \$875,000 in direct costs, investigators may apply their negotiated rate in calculating total costs.

**Q53: Can the intervention be "food is medicine" interventions such as medically tailored meals and produce prescription programs?**

A53: NCI is interested in medically nutrition tailored interventions, with concrete justifications of how an intervention influences a treatment-related outcome as the primary endpoint and include a patient-reported outcome as a secondary outcome as described in the [RFA-CA-21-031](#). If investigators have specific questions related to their proposal, feel free to contact the scientific leads.

**Q54: Is one Patient-Reported Outcome (PRO) to be listed as the primary PRO or is more than one PRO acceptable?**

A54: More than one PRO can be acceptable as a secondary outcome (e.g., the primary PRO) but selected PRO outcomes must be adequately powered and be distinct from the required primary endpoint or endpoints as described in the RFA.

**Q55: Does the PRO need to be a mediator/mechanism of the primary treatment-related outcome?**

A55: This is not a requirement, though it may sense and fare better during review since an approach should generally be well justified for the outcomes selected.

**Q56: Can the U01 support multiple PIs for a transdisciplinary team?**

A56: Yes. NCI always accepts multiple PIs. However, there is a revised minimum level of effort [policy](#) that must be met.



**Q57: For data sharing, does NCI have a data repository platform, or should the Coordinating Center application plan to make de-identified data available on their own platform?**

A57: The Coordinating Center should propose this work. The Coordinating Center can incorporate other platforms, but one of their tasks is to create or integrate platforms for data reporting and sharing.

**Q58: Are nutritional supplements and micronutrients considered responsive?**

A58: This depends on the intervention and whether investigators are looking at reported treatment outcomes, as well as whether they can justify the supplements and the micronutrients. If investigators have specific questions related to their proposal, feel free to contact the scientific leads.

**Q59: If investigators have an MPI team, would all travel request funds be made to the Steering Committee?**

A59: Travel funds to attend one in-person steering committee a year should be included within the applicant's budget as described in the RFA-CA-21-031 and RFA-CA-032. Travel requests are not made to the steering committee, although it is conceivable that a pilot project to be considered by the steering committee could include travel in a budget.

**Q60: Can NCI confirm that total funding for the U01 is \$875,000 with a cap of \$35,000 for a clinical trial for years 2-5/each year and explain the rationale for the trial cap?**

A60: The budget cap for U01 projects is \$875,000 in direct costs, of which \$35,000 per year in years 2 – 5 for consortium pilot projects must be reflected in yearly and cumulative budgets. Given the total budget NCI approved for the entire program, NCI leadership determined the project/application cap to reasonably accomplish the scope of work as described in each RFA.