Supplements to UM1 grants for NCI's Early Therapeutics Clinical Trials Network (ETCTN) to support biomarker assay development for incorporation into ETCTN studies

Key Dates
Release Date: October 1, 2017
Request Receipt Date: Rolling submission, but no later than June 1, 2018
Earliest Anticipated Start Date for Awards: December 1, 2017

Purpose

The National Cancer Institute (NCI) announces the opportunity for supplemental funding for UM1 grants supporting the Experimental Therapeutics Clinical Trials Network (ETCTN) to promote biomarker assay development for application in clinical studies in the ETCTN. The goal of these supplements is to support the development of validated biomarker assays that can be incorporated as endpoints into ETCTN studies to demonstrate target engagement, mechanism of action, mechanisms of resistance, or to enhance patient selection in subsequent studies. The long-term goal is to accelerate the development of NCI-IND agents to improve the outcome of cancer therapy.

Note that the purpose of this supplement program is to support the development of new fit-for-purpose biomarker assays for use in ETCTN trials. These supplement awards are not expected to support the performance of the assay in trials. Investigators will need to seek other funding sources for these efforts and are encouraged to consult CTEP staff to discuss options.

Background

The NCI's Experimental Therapeutics Development Program sponsored by the Cancer Therapy Evaluation Program (CTEP) in the Division of Cancer Treatment and Diagnosis (DCTD) has contributed to the clinical development of many anticancer agents. This Program has the unique ability to quickly take advantage of new scientific opportunities to promote therapeutic innovations. It melds partnerships with pharmaceutical companies developing novel agents with specialized clinical trial expertise found in academic medical centers to leverage development of a particular agent or novel agent combinations. NCI accepts new agents into its portfolio through the NCI's Experimental Therapeutics (NExT) program, and develops Collaborative Research and Development Agreements (CRADAs) with pharmaceutical companies and academic investigators. Through the ETCTN, NCI creates a drug development plan (DDP) that includes phase 1 and phase 2 studies which are an essential part of the CTEP drug development process. The phase 2 program investigators provide access to disease-oriented clinics in clinical sites, and expertise in conducting phase 2 studies. These studies are designed to provide a sufficiently unequivocal signal of clinical benefit to justify definitive large multi-institutional phase 3 trials designed to demonstrate improved outcomes and change the standards of practice.

The current ETCTN consists of 12 UM1 grantee Lead Academic Organizations and their affiliates committed to conducting studies of NCI-IND agents with a phase 1 emphasis. These UM1 grantees have incorporated a separate ETCTN Phase 2 Program that had consisted of 7 contract holders at major academic medical centers and their affiliates. The ETCTN provides the major clinical trials infrastructure and laboratory support to conduct complex early phase trials in its partnerships with industry. The ETCTN phase 1 and phase 2 programs have mechanisms to support sites for investigator effort and patient accrual to ETCTN studies.

Biomarker incorporation into early clinical trials of novel agents is an essential component of the overall drug development process. These biomarkers, which are measured on biological samples obtained from patients enrolled in clinical trials, may demonstrate target engagement, mechanism of action of the novel agent, mechanisms of resistance to the novel agent, or may be designed to enhance patient selection in subsequent studies. Biomarkers often originate in the research laboratory but require additional refinement to demonstrate fitness-for-purpose in the context of a clinical study. This validation process can involve development of standard operating procedures for the performance of the assay, specification and control of pre-analytic variables, demonstration of accuracy using standards or calibrators, and demonstration of reproducibility. The feasibility of the application of a validated test

Eligible Institutions

All funded affiliates of the ETCTN are eligible to apply.

Application Instructions

Applications should identify the test to be developed and the steps that will be undertaken to validate the test prior to its incorporation into ETCTN clinical studies. The application should explain the importance of the test in the context of the early clinical development of specific agents in the NCI-CTEP portfolio (NCI-IND agents). Applications for these supplements must propose to analytically and/or clinically validate an existing assay using human specimens in a clinical laboratory into a diagnostic assay that can be used in an ETCTN trial. The primary elements for achieving the research objectives are:

- Existing assay: an assay that has been reduced to practice in human tissues. An assay may be from discovery research or based on the scientific investigator's interests but should have essentially completed analytical validation (see below). The clinical use of the assay within a specific disease must be clearly stated and defined.
- Clinical laboratory: a laboratory that provides assay results that either assist in medical decision-making or test postulates or mechanisms of action of clinical, prevention or cancer control treatments or interventions. Assays that support medical-decision-making need to be performed in Clinical Laboratory Improvement Act of 1988 (CLIA)-certified laboratories. Assays to test postulates or mechanisms should conform to Good Laboratory Practice (GLP) or ISO 17025 standards in order to assure that the data generated by the assay are of sufficient quality as to be useful in clinical trials and justify sample collection.
- Molecular diagnostic: a marker measured in a validated assay that is associated with a clinical endpoint in a pre-defined clinical context or situation that yields usable information about prognosis or response to a clinical intervention for treatment, prevention or control of cancer.

Project Characteristics

- The project must focus on assays whose marker or classifier is likely to be used in ETCTN trials to develop NCI-IND agents. However, there does not need to be a commitment to a particular trial.
- The project should use technologies already in use or soon to be approved for use in clinical laboratories since this is not a technology development FOA.
- Since the analysis of samples from patients is an objective (see below) the project can include sample acquisition from patients enrolled on ETCTN trials.

Assay Pre-requisites and Preliminary Data: The applicant must have an assay using human specimens that may be derived from discovery research or the result of previous hypotheses or biological or clinical rationale. The assay may be a multiplex assay or a classifier but must be able after conversion to a clinical assay to be performed in a clinical trial. The assay must be near the end of analytical validation with fine-tuning of cut-offs or thresholds for a positive assay result left for clinical validation. It is expected that the following metrics will have been achieved during analytical validation of the assay:

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity including interfering substances
- Reportable range of test results for the test system
- Reference intervals (normal values) with controls and calibrators
- Harmonization of analytical performance if the assay is to be performed in multiple laboratories
- Establishment of appropriate quality control and improvement procedures
- Any other performance characteristic required for test performance with determination of calibration and control procedures.

Preliminary data should define the current status of the assay as well as justify support for optimization and usability in a clinical trial.

Objectives for the Biomarker Development Supplement: The objectives for completion of the clinical validation of assays may include:

- Definition of the sensitivity and specificity of the assay result with the defined clinical endpoint within the described clinical context of use
- Estimation of the prevalence of the marker within subjects or patients for the intended clinical context
- Establishment of an appropriate cut-off or threshold for the assay using appropriate statistical analysis
- Demonstration of the association of the result of the assay with a clinical endpoint (e.g., survival, response, disease presence or absence) in samples from patients that have been treated or exposed to a uniform intervention or observation for treatment, prevention or cancer control trials

Investigators' Team

The projects proposed for this FOA will necessitate multi-disciplinary interaction and collaboration among scientific investigators, clinicians, statisticians and clinical laboratory scientists and staff. Therefore, in addition to the PD/PI, the Investigators' Team should include the following participants:

- *Clinical Investigator:* Investigator(s) who define the intended clinical context of use for the marker and its assay and will oversee their incorporation into a potential trial –likely to be oncologist(s) who treat patients but may be a translational scientist.
- *Clinical Laboratory Staff:* Staff who will perform the translation of the assay into a clinical assay. The staff may work in a CLIA-certified clinical laboratory but do not need to do so if the assay is not intended to be used for medical decision-making. In that case the assay is likely to be for hypothesis or mechanism of action testing and the clinical laboratory staff and their laboratory need to be aware of Good Laboratory Practices and/or ISO 17025 standards and perform to that level of quality but not necessarily be certified. In any case, the clinical laboratory staff need to be aware of the Westgard rules.
- *Statistician:* A statistician familiar with the needs of marker studies should be part of the team, when power calculations need to be provided for assessing the use of the assay and its marker within the intended clinical context.

Commercial Developer (optional): While not necessary for all projects, successful assays will need to be distributed and supported. Therefore, collaboration with a commercial partner who will support the distribution and commercialization of the assay is encouraged, but not required.

Terms and Conditions of Funding and Allowable Costs

The budget should justify all the direct and indirect costs. A maximum of $100,000 in direct costs will be available for each supplement. The award period will be for 1 year. Funds may be carried over to subsequent years.

Supplement Award Application Procedures

1. **Cover Letter**
   A cover letter should accompany each application and include the following:
   a. Request for an administrative supplement to support the project
   b. Title of the supplement
   c. UM1 grant number
   d. Contact information for the LAO PI and the project leader
   e. Signatures of the LAO PI and the authorized institutional official

2. **Application**
    a. Standard PHS 398 (pgs 1-5)
        i. Item 2: check yes and provide the title indicated in the cover letter, 1.b.
        ii. Item 7A-8B, denote the direct and total costs for the project. Direct costs may not exceed $100,000.
        iii. The authorized organization representative must sign the face page.
        iv. Include a detailed budget description.
        v. Provide NIH biographical sketches for the P30 principal investigator.

3. **Summary of the Project**. On 10 pages or less describe:

Specific Aims: Describe the specific aims of the research project.

Research Strategy: Organize the Research Strategy in the sections identified below:

1) Background and Significance (recommended length: 1-2 pages)

- Define the cancer problem to be addressed, including the marker and its assay and how they fit the intended clinical context in which they will be used.
- Provide the biologic or discovery research rationale for the marker and its importance.
- Outline the proposed assay and its marker and its potential for affecting the intended clinical context in treatment, prevention or cancer control trials.

2) Preliminary Data (Note: This should be provided by the laboratory that will perform the assay development.)

- Describe and provide data to illustrate the current state of analytical validation of the assay in human specimens within the intended clinical context, including the current reagents and technologies and types of specimens that the assay will use (e.g., fresh frozen or formalin-fixed tissue, serum or plasma)
- Describe the status of analytical validation for each of the pre-requisites described in Section I above.

3) Approach

- Plans for additional optimization of analytical validation primarily limited to establishing thresholds or cut-offs for assay
- Plans to accrue specimens to perform clinical validation of assay including identification of the clinical resource or trial that will provide specimens, documentation of appropriate availability and pre-approvals to get specimens (i.e. indication that the repository holder identifies availability of specimens and that there is an appropriate process to get the specimens with reasonable certainty)
- Provision of a statistical power analysis that defines the number of specimens needed
- Plan for clinical validation of the assay within the intended clinical context of use
- Plans to address regulatory requirements needed to get assay into clinical trial
- Identification of Potential Pitfalls and Alternative Approaches to overcome obstacles to clinical validation of the assay
- Plans to address the regulatory issues regarding use of the marker in clinical trials and its assay within its intended clinical context. This includes the possibility of controlling intellectual property, evaluation of the significant risk of the assay and marker within the clinical context of a clinical trial and plans for collaboration with commercial entities to support the assay if it is successful.

4) Milestones and Timeline

- The applicant and the clinical laboratory staff must propose milestones for clinical validation.

Justification of Staff: Attach CV of named individuals. Note that in order to qualify for a supplement, a name of an individual must be proposed at the time of submission.

Application Submission

Applications may be submitted at any time after October 1, 2017. The grantee's Authorized Organizational Representative, on behalf of the PD(s)/PI(s) of the parent award, must submit the request for supplemental funds via email to the ETCTN Phase 2 Science Officer (Jeffrey.Moscow@nih.gov) with a note of concurrence with the entire supplement request package attached to the email.

Review Criteria

Applications will be reviewed by the NCI/CTEP program staff for the potential to produce an important validated biomarker assay for subsequent incorporation into ETCTN studies.

Awards

Awards will be based on responsiveness to the aims of this announcement and the availability of funds.

Reporting Requirements/Deliverables

Information on what has been accomplished via the administrative supplement during the funding period should be included in the progress report for the parent UM1 grant. Terms of award may also include milestones that will periodically be reviewed with the grantee by the CTEP program staff to provide assistance to the grantee, and to ensure progress toward a validated assay that is approvable by the BRC for incorporation into an ETCTN study.

Questions

Please contact Dr. Jeffrey Moscow (Telephone: 240-276-6565 Email: jeffrey.moscow@nih.gov) for questions related to the ETCTN or Dr. Tracy G. Lively (Telephone 240-276-5944 Email: livelyt@mail.nih.gov) for questions related to BRC review.