Biomarker, Imaging and Quality of Life Studies Funding Program

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH) (http://www.nih.gov/)

Components of Participating Organizations
National Cancer Institute (NCI) (http://www.nci.nih.gov/)

Title: Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP)

Key Dates

Release Date: December 15, 2008

Submission Date: There is no specific date for submission of the concept along with the BIQSFP proposal to the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP). It is anticipated that proposals will be considered for funding within 4-6 months following approval by the respective Scientific Steering Committee (SSC).

Evaluation Process: SSCs will evaluate and recommend Clinical Trial Concept along with the Essential Biomarker, Imaging and Quality of Life Studies, in accordance with current procedures, during scheduled SSC meetings for concept evaluation. NCI Program Staff will recommend concepts to the Clinical and Translational Research Operations Committee (CTROC) for prioritization at their scheduled meetings. The Clinical Trials Advisory Committee (CTAC) will make final recommendations to the NCI Director.

Expiration Date: December 14, 2009. It is anticipated that the BIQSFP will be reissued in subsequent years.

Overview and Summary

The Division of Cancer Treatment and Diagnosis (DCTD) and the Division of Cancer Prevention (DCP), National Cancer Institute (NCI), invite funded Cooperative Groups (CGs) and funded Community Clinical Oncology Program (CCOPs) Research Bases, to apply for funding to support essential biomarker, imaging and quality of life studies which are associated with clinical trial concepts (phase 3 therapeutic trials and cancer prevention trials) and primary symptom management trial concepts. This is an “open competition” announcement with no specific receipt date and proposals will be evaluated at the clinical trial concept stage. Meritorious concepts, approved by Scientific Steering Committees (SSCs), will be recommended by NCI Staff (CTEP and DCP) to the Clinical and Translational Research Operations Committee (CTROC) for prioritization across disease sites and symptoms. Final recommendations will be made by the Clinical Trials Advisory Committee (CTAC). Up to 25 percent of the total funds may be available for supporting meritorious quality of life studies associated with the approved clinical concepts.

Purpose

As part of its Prioritization and Scientific Quality Initiatives, the Clinical Trials Working Group (CTWG) recommended establishing a funding mechanism and prioritization process for essential correlative studies and quality of life studies that are incorporated into the fundamental design of a clinical trial and are not currently supported by the U10 funding mechanism. The objective of this initiative is to ensure that the most important biomarker, imaging, and quality of life studies can be initiated in a timely manner in association with late phase clinical trials.

Targeted biological studies and quality of life studies embedded in clinical trials should have the potential to inform the standard of practice. The studies must be reliable and provide interpretable answers that are of benefit to patients leading to scientific observations that validate targets, reduce morbidity, predict treatment effectiveness, facilitate better drug design, identify populations that may better benefit from treatment, improve accrual and retention.

The primary purpose of this funding mechanism is to support biomarker, imaging, and quality of life studies that are integral to or integrated with phase 3 clinical trials conducted by the CGs and CCOP Research Bases.

Mechanism of Support

BIQSFP will be managed through the Coordinating Center for Clinical Trials (CCCT). New concepts to be considered for BIQSFP funding will be evaluated and prioritized by the appropriate SSC and by DCP and CTEP Program Staff with CTAC making the final recommendation. Selected BIQ studies will be supported through sub-contracts established between those institutions, receiving the BIQSFP awards and Science Applications International Corporation-Frederick, Incorporated (SAIC-F). SAIC-F will be providing support to the BIQSFP including making payments. It is anticipated that the funding will be renewed in subsequent years, pending the availability of funds. The NCI Director will determine the funding level on a yearly basis.
For this announcement, the number of anticipated awards is contingent upon the availability of funds and the number of meritorious proposals submitted. NCI intends to commit at least $5 million in total costs in calendar year 2009. Applicants may submit more than one trial concept with essential biomarker, imaging, and quality of life studies provided they are scientifically distinct. However, both the scientific merit of the parent clinical trial concept and the merit of the essential biomarker, imaging and quality of life studies must be approved by the appropriate review committee (SSC, CTEP or DCP) to be eligible for the funding.

Requirements and Definition

Eligible trial types are:

- Phase 3 therapeutic trials with essential biomarker or imaging studies, and/or quality of life studies
- Phase 3 cancer prevention trials with essential biomarker or imaging studies, and/or quality of life studies

- Primary symptom management trials with essential biomarker or imaging studies, and/or quality of life studies

Essential Biomarker and Imaging Studies

Two types of essential biomarker and imaging studies are eligible – integral and integrated

Integral studies - Defined as tests that must be performed in order for the trial to proceed. Integral studies are inherent in the design of the trial from the onset and must be performed in real time for the conduct of the trial.

Integral studies will have the highest priority.

Eligible categories of integral studies and examples are as follows:

- Tests to establish eligibility – e.g., *in vitro* assessment of HER2 for trials of anti-HER2 agents in diseases where HER2 testing is investigational, or imaging assessment of hypoxia for trials of drugs effective in hypoxic tissues such as tirapazamine
- Tests for patient stratification – e.g., measurement of 18qLOH and MSI for assignment of risk in stage 2 colon cancer
- Tests to assign patients to a treatment arm of a trial, including surrogate endpoints for assignment of treatment during a trial – e.g., Oncotype DX test to assign breast cancer patients to a study arm; eradication of the bcr-abl clone in CML to determine whether to continue treatment; FDG-PET scan after initial course of therapy to assess early response to determine whether to continue treatment
- Non-reimbursable imaging tests to measure a primary endpoint or to stratify patients based on imaging response – e.g. PET scans for non-Hodgkin's lymphoma response to chemotherapy

Integrated Studies – Defined as tests that are clearly identified as part of the clinical trial from the beginning and are intended to identify or validate assays or markers and imaging tests that are planned for use in future trials. Integrated studies in general should be designed to test a hypothesis, not simply to generate hypotheses. Integrated studies are tests performed in real time and include complete plans for specimen collection, laboratory measurements and statistical analysis. One example would be predictive marker assays that are measured either *in vitro* or *in vivo* on all cases but where the assay result is not used for eligibility, treatment assignment or treatment management in the current trial; a second example would be the use of an imaging test to detect biologic modification of the target but where the image is not used as a primary study endpoint.

Criteria for Review and Prioritization of Essential Biomarker and Imaging Studies

Prioritizing and evaluating criteria for essential biomarker and imaging studies will include:

- The strength of the preliminary data for both test utility and performance characteristics
- The potential of the test to change practice and have high impact on patient care (i.e., the impact of the test itself or the change of therapy indicated by the results of the trial)
- The ability of the test to yield well defined and validated interpretations that will guide decision-making
- The extent of standardization of the tests as to be transferable to the non-research setting
- The adequacy of the process for specimen collection and processing including feasibility data
- A description of potential cost-sharing approaches that can be developed with entities that would eventually commercialize the test

It is not intended that any priority or particular level of merit should be assigned to one criterion over another but rather the proposals should be evaluated based on the totality of the information and strength of data.

Essential Quality of Life Studies

QOL studies should be part of the clinical trial design from the beginning, conducted in real time and are intended to inform on treatment options and side effects, and/or validate: patient – reported outcome data; quality of life assessment tools; and biomarker and imaging tests of pathophysiology that may be used for decision making in future trials. Currently, the Division of Cancer Prevention funds quality of life studies that obtain information for use in patient-physician decision making or to help the patient prepare for and interpret the treatment experience. Examples of this include studies where differences between treatments in survival or other disease-related endpoints are expected to be minimal or when treatment arms represent very different treatment scenarios. Assessments include, but are not limited to, qualitative data, toxicity impact, convenience, psychosocial outcomes and function.

Eligible categories of essential QOL studies and examples are:

- Studies to obtain additional information for use in patient–physician decision making or to help the patient prepare for and interpret the treatment experience when the collection of QOL data requires resources beyond the usual cancer control credits or per case reimbursement

- Studies that validate measures previously tested in smaller studies. QOL measures that have been piloted in smaller studies and are supported by preliminary data require full validation in a phase 3 trial. This includes evaluating patient reported outcomes (PRO) as complementary adjuncts to clinician assessed outcomes for measuring toxicity (e.g., adverse events as measured by Common Toxicity Criteria). In addition, there have been

advances in the PRO measurement field with the integration of modern measurement theory for the development of brief, precise, and valid PRO measures. These advancements will allow an examination of the benefits of integrating these measures, including electronic data capture, into clinical trials. Examples of studies that fall into this category include: computer-based testing; experience sampling; and multiple brief symptom assessment (as opposed to infrequent and lengthier assessment) used in symptom assessment

There is growing interest in the role of objective measures such as biomarkers, imaging studies, and measures of activity such as pedometers and actigraphs that can further inform symptoms, QOL assessments and selected patient reported outcomes.

- Studies that provide "objective" correlates to self-report measures that are not easily supported though funding for clinical trials. Concurrent collection of an "objective" test along with a performance measure provides stronger data when following patients on a symptom management or QOL trial. Examples of studies in this category include: enhancing patient self-report of fatigue or physical function with objective actigraphy; and neuropsychological testing in studies of cognitive effects from therapy, or in following patients with brain tumors or metastases

- Studies that are predictive correlative measures with testable hypothesis(es) and a high likelihood to give validated interpretations. Correlative measures to predict morbidity, safety, pathophysiologic mechanisms of symptom expression, and /or treatment efficacy and genetic determinates of symptom expression, QOL endpoints and treatment efficacy need support. Examples of these study measurements include but are not limited to: cytochrome P450 metabolism; cytokine analyses; pharmacokinetic studies for drug interactions; neuroendocrine studies, and fMRI for cognitive changes

Each category is of equal priority, however in general, higher consideration will be placed on concepts that: are scientifically grounded and well developed; use well validated and reliable measures; and are likely to have the largest impact on clinical practice.

Criteria for Review and Prioritization of QOL Studies

Prioritizing and evaluating criteria for essential QOL studies will include:

- The potential to impact patient morbidity or QOL with clinically meaningful benefit
- The potential to move science forward in cancer related QOL by adding critical knowledge
- The strength of the preliminary data supporting the hypothesis(es) to be tested and methods proposed
- A clearly defined process for data and specimen collection
- A statistical plan with adequate power for the primary symptom management and/or QOL correlative study hypothesis(es)
- Measures that are reliable, valid and appropriate to the population of interest

- Feasibility of proposal addressed such that completion can be accomplished efficiently in a reasonable time frame

Preparation of Budgets

All proposals for the BIQFSP must include a budget at the time of submission that details the entire costs **(Direct and Indirect)** of the biomarker, imaging and/or QOL studies. For a concept that contains more that one biomarker, imaging and/or quality of life study, a separate and clearly distinguishable budget must be provided for each study as well as a total composite budget for the entire cost of the project. The budgets for the project should use the **BIQSFP Cost Estimate Worksheet** (see attached) along with a narrative justifying each requested cost.

Proposal Package

What is required:

- A cover letter signed by the CG/CCOP Chair and the Business Official of the Institution indicating submission of a biomarker, imaging and/or quality of life study in response to the BIQFSP announcement. The cover letter should include: the title(s) of the project(s); a brief description of the project indicating whether the studies are integral or integrated; and the type of study(s) proposed (biomarker, imaging or quality of life)

- A detailed budget as described in **Preparation of Budgets** (above)

- The parent trial concept (phase 3 treatment, prevention, or symptom management) with the BIQ study embedded (for evaluation by SSCs or where appropriate CTEP or DCP)

A separate document describing the characteristics and performance of each biomarker and imaging assay proposed for funding, and its role in the trial. Applicants should refer to the **Concept Checklist for Phase 3 Trials with Essential Biomarker Assay/Imaging Assays** (see attached) for instructions on what information is needed. This section is not to exceed five (5) pages for each assay or test. If both integral and integrated studies are proposed within the same concept being submitted, each study will require a separate document as indicated above. For additional explanations and definitions, investigators are also encouraged to visit **Performance Standards Requirements for Essential Assays in Clinical Trials** at: http://www.cancerdiagnosis.nci.nih.gov/pdf/PACCT_Assay_Standards_Document.pdf

A complete **Proposal Package**, including a cover letter by the Principal Investigator of the Cooperative Group or CCOP Research Base and Cost Estimate Worksheet (s), must be emailed via. pdf attachment to the relevant Program office. The NCI contractor will coordinate the processing of all proposals once the NCI has recommended an award.

CCOP Research Base proposals must be e-mailed to:

Lori Minasian, M.D. - minasilo@mail.nih.gov
cc: Ann O'Mara, Ph.D. - omaraa@mail.nih.gov

Cooperative Group proposals must be e-mailed to:

Elise Kreiss, MBA - kreisse@mail.nih.gov
cc: Margaret Mooney, M.D. - mooneym@ctep.nci.nih.gov

E-mail submissions must reference "BIQSFP" in the Subject line.

To Be Considered Responsive

Embedded biomarker, imaging and QOL studies that do not meet the definitions for eligible studies, or are still within the discovery phase or pre-clinical development stage (e.g., phase 1 and 2 concepts, studies involving toxicity screens on animals), or are retrospective in nature, or that focus on assay development are not considered responsive. Studies that can be conducted in the future on stored specimens will not be eligible for funding, except if the results are critical to the stated primary or secondary objectives of the trial.

While the primary purpose of this funding is for newly developed concepts, in some circumstances, phase 3 protocols and primary symptom management protocols that are still in development may be considered for the BIQFSP if they are of exceptional clinical importance and address the evaluation criteria, and Performance Standards. It is recommended that these be discussed with CTEP or DCP Program Staff prior to submission to determine eligibility.

Terms and Conditions for Funding

All the terms and conditions of the of the parent U10 award apply to this funding.

Funding will be restricted for the purpose of the approved project. Similarly, any carryover requests for this award will be limited to the approved project unless written approval is obtained in advance by the relevant NCI program official.

A separate progress report addressing the BIQFSP award is to be submitted with the annual progress report of the parent U10 award.

Inquiries

Questions regarding responsiveness of the proposed studies to the BIQFSP should be directed to the one of the following NCI Program Staff:

Margaret Mooney, M.D.
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For DCP:

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Questions regarding the prioritization and evaluation process should be directed to:

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Fax: 301-480-0485
Email: petryshr@mail.nih.gov

Concept Checklist for Phase 3 Trials with Essential Biomarker /Imaging Assays

1. For an integral assay, indicate the role(s) of the biomarker assay or imaging test in the trial:
   - A. Eligibility criterion
   - B. Assignment to treatment
   - C. Stratification variable
   - D. Risk classifier or score

E. Other (describe in detail):

2. Identify the specific individual(s) and laboratory(ies) (or imaging departments) who are being considered for conducting the assay(s) or imaging tests for the trial. **Note**: Laboratory assays used for clinical decision-making must be performed in a CLIA-certified facility.

3. Describe the assay or imaging test:

A. Specify the analyte(s), technical platform, and sources of assay components (i.e., reagents, chips, calibrators), imaging devices or imaging agents.

B. Describe the specimens, and anticipated methods for specimen acquisition, fixation or stabilization and processing. For imaging tests, describe any patient preparation procedures, as well as the procedures for imaging, analysis and interpretation of the results.

C. Describe the scoring procedures and type of data to be acquired
--quantitative/ continuously distributed
--semi-quantitative/ordered categorical
--qualitative/non-ordered categorical

D. If cutpoints will be used, specify the cutpoint(s) and describe how these will be used in the trial (also, see 4C, below).

4. Provide data on the clinical utility of the assay or imaging test as it will be used in the trial:

A. Provide background information that justifies the use of this assay or imaging test result as an integral marker for this trial. For example, if the integral marker will be used as a stratification or treatment-determining variable, data supporting its prognostic or predictive association with a main trial endpoint should be described or referenced.
Note: If the trial objectives include an evaluation of the association of the integral marker with a new clinical endpoint or factor not previously studied, the statistical section of the concept should explain how the magnitude of the association or effect will be measured and provide power calculations for any statistical tests that are planned.

B. Describe the expected distribution of the biomarker in the study population.

C. If cutpoints will be used, provide the rationale for the cutpoint(s) selected. What proportion of subjects is expected to have values above and below the proposed assay or imaging test value cutpoints? What magnitude of effect (e.g., treatment benefit) or outcome (e.g., prognosis) is expected for patients with assay or imaging test results above and below the proposed cutpoint(s)?

D. Describe under what conditions treating physicians and or patients will be able to access the assay results.

5. Provide data on the analytical performance of the assay or imaging test.

A. For *in vitro* tests, describe the current status of studies defining the accuracy, precision, reportable range, reference ranges/intervals (normal values), turn-around time and failure rate of the assay <u>as it is to be performed in the trial</u>. For imaging tests, describe what performance characteristics are known. State and justify the limits of acceptable performance. Describe the use of positive and negative controls, calibrators, and reference standards for either

imaging or clinical assays. For guidance on regulatory requirements for laboratory assays please visit:
http://www.cms.hhs.gov/CLIA/05_CLIA_Brochures.asp

B. If the assay or imaging test will be performed at more than one site, describe how inter-laboratory variability in the measurements listed in 5A above will be assessed. Describe how these sources of variation will be minimized to maintain performance at all sites within acceptable limits and to prevent drift or bias in assay or imaging test results.

BIQSFP Cost Estimate Worksheet

					PERIOD OF PERFORMANCE	
					FROM	**THROUGH**
					date of award	"x" months after date of award
DIRECT LABOR						
LABOR CATEGORY	HOURLY RATE	# OF HRS.	TOTAL SALARY	FRINGE %	FRINGE AMOUNT	TOTAL DIRECT LABOR
					SUBTOTAL DIRECT LABOR	
OTHER DIRECT COSTS:						
CONSULTANT/SUBCONTRACT COSTS *(List names and services to be provided - attach agreement and pricing)*						
EQUIPMENT *(Provide description and price for each item)*						
SUPPLIES *(Provide itemized list with prices)*						
PATIENT CARE COSTS *(List procedure and detailed cost information)*						
OTHER DIRECT COSTS *(Provide itemized list with prices)*						
SUBTOTAL OTHER DIRECT COSTS						
TOTAL DIRECT COSTS (Subtotal Direct Labor + Other Direct Costs)						
INDIRECT COSTS OR OVERHEAD ( )% *(May only be applied to non-patient care related costs)*						
TOTAL COSTS (Total Direct costs + Indirect Costs)						
SIGNATURE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Institutional Business Official)*						**Date**