

## **Biomarker, Imaging, & Quality of Life Studies Funding Program (BIQSFP)**

<http://bigsfp.cancer.gov/>

### **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/>

#### **Key Dates**

Release Date: December 15, 2008; revised April 1, 2010, April 1, 2011

Submission Date: There is no specific date for parent Clinical Trial Concept and BIQSFP proposal submission to the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP). Proposals are considered for funding within 2-3 months following approval by the respective Scientific Steering Committee (SSC) or a CTEP/DCP- coordinated external review as appropriate.

Evaluation Process: SSCs (or external reviewers via CTEP/DCP if there is no appropriate SSC) evaluate and recommend the parent Clinical Trial Concept along with the Essential Biomarker, Imaging and Quality of Life Studies proposal and/or Cost-Effectiveness Analysis (CEA) endpoint, during scheduled SSC meetings for concept evaluation. **BIQSFP proposals for funding of integral and/or integrated studies or CEA must be submitted concurrently with the parent concept.** Scientifically meritorious BIQSFP proposals that are recommended by SSCs (or CTEP/DCP as applicable) are presented by NCI Program Staff to the Clinical and Translational Research Operations Committee (CTROC) for prioritization and approval at their bimonthly meetings.

Expiration Date: March 31, 2012. It is anticipated that the BIQSFP Announcement will be reissued in subsequent years.

#### **I. Key Changes with Revised Announcement:**

- A. Cost-Effectiveness Analysis (CEA) studies paired with clinical trial concepts are eligible for BIQSFP funding (see pages 5-7).
- B. Publications resulting from this Announcement should acknowledge BIQSFP support (see page 8).

#### **II. 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 (CCOP) Research Bases to apply for funding to support essential biomarker, imaging, quality of life studies with or without a CEA proposal, which are associated with clinical trial concepts. The funding support is limited to large ( $\geq 100$  patients), randomized Phase 2 concepts for therapeutic trials with a control arm and an integral study(ies). Integral and/or integrated studies associated with Phase 3 therapeutic trials, cancer prevention trials, and primary symptom management trials are eligible. Only randomized Phase 3 clinical trials are eligible for CEA proposals.

This is an "open competition" announcement with no specific receipt date. Proposals will be evaluated at the clinical trial concept stage. Meritorious proposals, approved by SSCs, or appropriate external reviewers if there is no appropriate SSC, are recommended by NCI Staff (CTEP and DCP) to the Clinical and Translational Research Operations Committee (CTROC). CTROC makes final funding recommendations. The Clinical Trials and Translational Research Advisory Committee (CTAC) annually review the approved funding portfolio, providing strategic oversight and advice.

Cost-Effectiveness Analysis (CEA) provides useful information to help health care payers manage the use of costly medical technologies in order to maximize the health of their patient populations when facing constrained budgets, and to clinicians and patients to help guide treatment decisions based on CEA's unique endpoints, perspectives, and time horizon. To be most useful to decision-makers, CEA of new cancer therapies must have maximal feasibility, be timely, and have high internal validity.

Conducting a CEA alongside a clinical trial can achieve these goals and also offers the benefit of efficiency by utilizing the existing structure of clinical trials to collect additional data for the economic analysis. It is not required that a CEA proposal be included with each clinical trial concept submitted. However, in some instances the addition of CEA may be recommended during evaluation of the clinical trial concept. The evaluation of CEA paired with Phase 3 clinical trials is the responsibility of the SSC's. CTROC makes the final funding recommendations.

### **III. Purpose**

As part of its Prioritization and Scientific Quality Initiatives, the NCI 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 purpose of the BIQSFP is to ensure that the most important, scientifically meritorious biomarker, imaging, and quality of life studies or CEA can be initiated in a timely manner in association with appropriate clinical trials.

Targeted biological studies, imaging, and quality of life studies embedded in clinical trials should have the potential to modify standard of practice. The tests/assays 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, and improve accrual and retention.

In 2010, the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) recommended the addition of Cost-Effectiveness Analysis (CEA) to the BIQSFP. The purpose of CEA is to ensure that the most important cost-effectiveness analyses can be conducted in association with appropriate NCI-sponsored clinical trials. The funding of CEA proposals will be based on the scientific merit of both the parent clinical trial concept and the CEA proposal and each must be approved by the appropriate review bodies.

### **IV. Mechanism of Support**

BIQSFP is managed through the Coordinating Center for Clinical Trials (CCCT) in the NCI Office of the Director. New concepts to be considered for BIQSFP funding are evaluated and prioritized by the appropriate SSC and by DCP and CTEP Program Staff with CTROC making the final funding recommendation. Approved BIQ studies are supported through subcontracts established between those institutions receiving the BIQSFP awards and Science Applications International Corporation-Frederick, Incorporated (SAIC-F). It is anticipated that BIQSFP 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 the 2011 Announcement, the number of anticipated awards is contingent upon the availability of funds and the number of meritorious proposals submitted. However, NCI committed \$10M to BIQSFP funding in fiscal year 2010. Applicants may submit more than one trial concept with essential biomarker, imaging, quality of life studies or a CEA, provided they are scientifically distinct. However, both the scientific merit of the parent clinical trial concept and the merit of the essential biomarker, imaging, quality of life study, or CEA must be approved by the appropriate review entity (SSC, CTEP or DCP) in order to be eligible for the BIQSFP funding.

## V. Requirements and Definition

### Eligible trial types for BQSFP funding are:

- Trials conducted by CG's and CCOP Research Bases.
- Large ( $\geq 100$  patients), randomized Phase 2 concepts for therapeutic trials with a control arm and an integral study(ies).
- Phase 3 therapeutic trials with integral or integrated 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.
- For CEA, the parent concept must be a randomized Phase 3 clinical trial with a comparator (control arm).

## VI. Essential Biomarker and Imaging Studies

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

**A. Integral studies** - Defined as tests that must be performed in order for the trial to proceed. Integral studies are inherent to the design of the trial from the onset and must be performed in real time for the conduct of the trial. Integral biomarkers require a CLIA-certified lab.

***Integral studies have the highest funding 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

**B. 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.

### C. Criteria for Review of Essential Biomarker and Imaging Studies

Prioritization and evaluation criteria 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 (e.g.; 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

Clinical assays that are used to assign or significantly modify a patient's treatment in the concurrently proposed clinical trial must have seen rigorous analytic validation and sufficient clinical validation to warrant inclusion in a clinical trial. Such assays will ordinarily be performed in CLIA-accredited laboratories and may need FDA review as well.

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

## VII. Essential Quality of Life (QOL) Studies

**A. QOL studies can be integral or integrated** and should be part of the clinical trial design from the beginning, conducted in real time. They are intended to inform on treatment options and side effects, and/or validate: patient-reported outcome data; QOL assessment tools; 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.

**B. Eligible categories of essential quality of life 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 2 or 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 such as:

- Studies that provide "objective" correlates to self-report measures that are not easily supported through 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 quality of life trial. Examples of studies in this category include, but are not limited to: 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, quality of life 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 is 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.

### **C. Criteria for Review of Quality of Life Studies**

Prioritization and evaluation criteria include:

- The potential to impact patient morbidity or quality of life with clinically meaningful benefit
- The potential to move science forward in cancer related quality of life 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 quality of life 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

### **VIII. Essential Cost-Effectiveness Analysis (CEA) Studies**

The CEA evaluation criteria are intended to help guide the selection of cancer clinical trials that warrant additional funds for a CEA. The CEA study should be a secondary endpoint of the parent concept. SSCs evaluate CEA proposals paired with clinical trial concepts through their concept evaluation and prioritization process. SSCs will make use of ad hoc CEA expert(s), including resources available at the NCI, to evaluate CEA proposals included in clinical trial concepts.

#### **Criteria for Review of CEA Proposals**

Researchers should consider pairing a CEA proposal to phase 3 clinical trials when the following conditions are met:

- The results of a Phase 3 clinical trial are expected to substantially influence clinical practice.
- The cost-effectiveness study would be of high impact judged by substantial budget implications for health care systems, either in terms of overall cost savings or added costs to the system.
- It is feasible to conduct a high quality CEA as part of the clinical trial. Specific issues to consider include:
  - The comparator (control arm) should be relevant to current clinical practice.

- The trial should be of sufficient duration, with respect to follow-up of patient outcomes, that consequences of interest to economic evaluation can be captured either directly or through modeling.
- There is reasonable statistical power for the key cost-effectiveness analysis.
- Because of high cost, there is a reasonable degree of uncertainty regarding the outcome of the CEA even if the clinical outcome favors the experimental treatment.

CEA proposals included in Phase 3 clinical trial concepts should be developed by CGs and CCOP Research Bases. When CGs and CCOP Research Bases choose to submit a CEA proposal, this must be submitted with the Phase 3 parent clinical trial concept.

## **X. BIQSFP Budget Preparation & Submission**

All BIQSFP proposals must include a budget at the time of submission that clearly details the costs (**Direct and Indirect**) for each of the biomarker, imaging, quality of life, and/or CEA proposals submitted. In addition, a total composite budget must be provided for the entire cost of the BIQSFP project. The budgets for the project should use the **BIQSFP Cost Estimate Worksheet** (see attached) along with a narrative justifying each requested cost.

### **A. BIQSFP 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, quality of life, and/or CEA study in response to the BIQSFP 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; the type of study(s) proposed (biomarker, imaging, quality of life, and/or CEA); the total budget figure requested for each project (biomarker, imaging, QOL, CEA); and the duration of the study.
- A detailed budget as described in **Preparation of BIQSFP Budgets** (above)
- The parent clinical trial concept with the BIQ and/or CEA study embedded (for evaluation by SSCs or where appropriate, CTEP or DCP)

**B. Biomarker and Imaging:** A separate document is required describing the characteristics and performance of each biomarker assay and imaging test proposed for funding, and its role in the trial. Applicants should refer to the *Concept Checklist for Large, Randomized Phase 2 or 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 BIQSFP Proposal Package as indicated above. For additional explanations and definitions, investigators are also encouraged to visit **Performance Standards Reporting Requirements for Essential Assays in Clinical Trials** at:

[http://www.cancerdiagnosis.nci.nih.gov/scientificPrograms/pacct/PACCT Assay Standards Document.pdf](http://www.cancerdiagnosis.nci.nih.gov/scientificPrograms/pacct/PACCT_Assay_Standards_Document.pdf).

**C. Quality of Life:** A separate document is required describing the characteristics and performance of each QOL component and/or instrument proposed for funding, and its role in the trial. Applicants should refer to the *Concept Checklist for Large, Randomized Phase 2 or Phase 3 Trials with QOL Components* (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 BIQSFP Proposal Package as indicated above.

**D. Cost-Effectiveness Analysis:** A separate document is required describing the rationale and justification of the CEA proposal for funding. The CEA proposal should be a secondary endpoint of the parent study. Applicants should refer to the *Concept Checklist for Randomized Phase 3 Clinical Trials with a Control Arm and Cost-Effectiveness Analysis (CEA) Component(s)* (see attached) for instructions on what information is needed. This section is not to exceed five (5) pages.

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.

**CCOP Research Base proposals must be e-mailed to:**

Lori Minasian, M.D. - [minasilo@mail.nih.gov](mailto:minasilo@mail.nih.gov)

cc: Ann O'Mara, Ph.D. - [omaraa@mail.nih.gov](mailto:omaraa@mail.nih.gov)

**Cooperative Group proposals must be e-mailed to:**

NCI CTEP Protocol Information Office - [PIO@ctep.nci.nih.gov](mailto:PIO@ctep.nci.nih.gov)

cc: Margaret Mooney, M.D. - [mooneym@ctep.nci.nih.gov](mailto:mooneym@ctep.nci.nih.gov)

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

**XI. To Be Considered Responsive**

Embedded biomarker, imaging, quality of life, and/or CEA proposal 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 concepts, small (<100 patients) randomized & all non-randomized Phase 2 concepts, or studies involving toxicity screens on animals], or are retrospective in nature, or focus on assay development are not considered responsive. Studies that can be conducted in the future on stored specimens are not eligible for funding, except if the results are critical to the stated primary or secondary objectives of the trial. For BIQSFP study proposals containing assays that are not fully developed, applicants can refer to the Cancer Assay Development Program (CADP) website for guidance regarding assay validation: <http://cadp.cancer.gov>.

While the primary purpose of this funding is for newly developed concepts, in some circumstances, large randomized Phase 2 and any Phase 3 protocols with an integral component, and primary symptom management protocols that are still in development may be considered for the BIQSFP 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. In general, the priority for consideration in these circumstances would be for studies requiring integral markers.

**XII. Terms and Conditions for Funding**

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

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

The NCI contractor, SAIC-Frederick (SAIC-F), will coordinate the processing of all proposals once the NCI has recommended an award. Quarterly invoices/progress reports must be submitted to SAIC-F for payment of approved BIQSFP funds. An annual Protocol Progress Report addressing the BIQSFP award is to be submitted with the annual progress report of the parent U10 award.

### **XIII. Publication of BIQSFP-Funded Studies**

Upon completion of BIQSFP-funded studies, publications should acknowledge the funding source as follows:

*“This clinical study was supported in whole or in part by funding from the Biomarker, Imaging, & QOL Studies Funding Program (BIQSFP) awarded by the National Cancer Institute”.*

### **XIV. Inquiries**

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

#### **For CTEP:**

Margaret Mooney, M.D.  
Chief  
Clinical Investigations Branch  
National Cancer Institute  
Building EPN Room 7025  
6130 Executive Blvd  
Bethesda, MD 20892  
Phone: 301-496-2522  
Fax: 301-402-0557  
Email: [mooneym@ctep.nci.nih.gov](mailto:mooneym@ctep.nci.nih.gov)

#### **For DCP:**

Lori Minasian, M.D.  
Chief  
Community Oncology and Prevention Trials Research Group  
National Cancer Institute  
Executive Plaza North Room 2017  
6130 Executive Blvd  
Bethesda, MD 20892  
Phone: 301-496-8541  
Fax: 301-496-8667  
Email: [minasilo@mail.nih.gov](mailto:minasilo@mail.nih.gov)

Ann O'Mara, Ph.D.  
Program Director  
Community Oncology and Prevention Trials Research Group  
National Cancer Institute  
Executive Plaza North Room 2017 - 7340  
6130 Executive Blvd  
Bethesda, MD 20892-7340  
Phone: 301-496-8541  
Fax: 301-496-8667  
Email: [omaraa@mail.nih.gov](mailto:omaraa@mail.nih.gov)



**Questions regarding cancer imaging studies:**

Lalitha K. Shankar, MD, PhD  
Chief, Clinical Trials Branch  
Cancer Imaging Program  
Division of Cancer Treatment and Diagnosis  
National Cancer Institute  
6130 Executive Blvd., Room 6056  
Bethesda, MD 20892-7412  
Phone: 301-496-9531  
Email: [shankerl@mail.nih.gov](mailto:shankerl@mail.nih.gov)

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

Raymond Petryshyn, Ph.D.  
Program Director  
Coordinating Center for Clinical Trials  
National Cancer Institute  
Executive Plaza South Suite 300  
6120 Executive Blvd  
Bethesda, MD 20892  
Phone: 301-594-1216  
Fax: 301-480-0485  
Email: [petryshr@mail.nih.gov](mailto:petryshr@mail.nih.gov)

**Questions regarding the payment or subcontracting process (SAIC-Frederick) should be directed to:**

Geoffrey D. Seidel, RN, BSN, MS (Contractor)  
Clinical Project Manager II, Program Director  
Support to Coordinating Center for Clinical Trials  
National Cancer Institute, Office of the Director  
SAIC-Frederick, Inc.  
Clinical Monitoring Research Program  
National Cancer Institute at Frederick  
National Institutes of Health  
6120 Executive Boulevard, Suite 300  
Bethesda, MD 20892-7227  
O: 301-496-5748  
F: 301-480-1522  
[seidelg@mail.nih.gov](mailto:seidelg@mail.nih.gov)

**Concept Checklist for Large Randomized Phase 2 with a Control Arm and any Phase 3 Trials with Essential Biomarker Assays / Imaging Tests**

**INSTRUCTIONS:** For **INTEGRAL** assay/test, respond to Items 1-5.  
 For **INTEGRATED** assay/test, respond to Items 4-5 and 6b.

**Please submit a response to each of the criteria below and complete one Concept Checklist and the BQSFP Cost Estimate Worksheet for each Biomarker and/or Imaging endpoint.**

1. For an integral or integrated 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 test(s) for the trial.
  
3. Integral laboratory assays used for clinical decision-making must be performed in a CLIA-certified facility. Provide the lab's CLIA number that is performing the integral biomarker concepts and the expiration date of the certificate.
  
4. Describe the assay or imaging test:
  - A. Specify the analyte(s), technical platform, and sources of assay components (e.g., 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).
  
5. Provide data on the clinical utility of the integral/integrated 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 a 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 biomarker assay/imaging test results.
6. 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 as it is to be performed in the trial. 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. Describe any critical preanalytic variables. For guidance on regulatory requirements for laboratory assays please visit: [http://www.cms.gov/CLIA/05 CLIA Brochures.asp](http://www.cms.gov/CLIA/05%20CLIA%20Brochures.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.

**Concept Checklist for Large Randomized Phase 2 and any Phase 3 Trials  
with Quality of Life Components**

**INSTRUCTIONS:** Please submit a response to each of the criteria below. Please complete one Concept Checklist and the BIQSFP Cost Estimate Worksheet for each QOL endpoint.

1. State the HRQOL (health-related quality of life) hypothesis(es) and its scientific foundation. Specify the study endpoint(s).
2. Identify the HRQOL instrument(s) to be used to test each hypothesis, the basis for choosing each instrument, and the timing of the assessments.
3. For each instrument document its validity, reliability, and responsiveness in the selected patient population. Specify the minimum important difference (MID) or metric for clinically-significant change.
4. Describe any included *objective* correlates that enhance the patient-reported outcomes data (e.g., actigraphy, imaging, pulse ox, etc).
5. Identify any *biomarker* correlates of the patient-reported outcome measure(s) that will be collected (e.g., molecular, protein, other assays).
6. Explain how patient non-compliance, missing data and/or early death may impact the analysis.
7. How will visually challenged, non-English speaking patients be accommodated when completing the instrument(s)?
8. Describe the procedures for data collection and data monitoring including the training of data collection personnel.

**Concept Checklist for Randomized Phase 3 Clinical Trials with a Comparator (Control Arm) and Cost-Effectiveness Analysis (CEA) Component**

**INSTRUCTIONS:** Please submit a response to each of the elements below and complete the BIQSFP Cost Estimate Worksheet.

1. Describe and justify the perspective of the CEA.
2. Explain the situations in which the outcomes of the clinical trial could substantially change clinical practice.
3. Describe the potential implication(s) of different outcomes of the trial on overall costs to the health care system, in terms of costs saved or costs added.
4. Briefly describe and justify the CEA study terms of:
  - a) Trial population (in relationship to treatment population in community practice)
  - b) Intervention(s) and control therapy selected for the CEA
  - c) Question or hypothesis posed
  - d) Measure(s) of outcome for the CEA
  - e) Method of estimating costs
  - f) Modeling approach proposed (if appropriate)
  - g) Approach to characterizing uncertainty analysis
  - h) The time horizon and discount rates of the CEA. If the time horizon of the CEA exceeds that of the trial, describe the extrapolation or modeling approach that will be used.
5. Describe any threats to the external validity of the study in relation to community practice.

**BIQSFP Cost Estimate Worksheet**

<b>Date:</b>							<b>Check One:</b> <input type="checkbox"/> <b>BM</b> _____ <input type="checkbox"/> <b>Imaging</b> _____ <input type="checkbox"/> <b>QOL</b> _____ <input type="checkbox"/> <b>CEA</b>						
							<b>Check One:</b> <input type="checkbox"/> <b>Total Composite Budget</b> <input type="checkbox"/> <b>Annual Budget</b>						
<b>PERIOD OF PERFORMANCE</b>							<b>FROM</b>			<b>THROUGH</b>			
							(date of award)			(12 months after date of award)			
<b>DIRECT LABOR</b>													
LABOR CATEGORY		HOURLY RATE	ANNUAL # OF HRS	TOTAL ANNUAL SALARY	FRINGE %	FRINGE AMOUNT	TOTAL DIRECT LABOR						
						<b>SUBTOTAL DIRECT LABOR</b>							
<b>OTHER DIRECT COSTS</b>													
<b>CONSULTANT/SUBCONTRACT COSTS</b>													
<i>(List names and services to be provided - attach agreement and pricing)</i>													
<b>EQUIPMENT</b>													
<i>(Provide description and price for each item)</i>													
<b>SUPPLIES</b>													
<i>(Provide itemized list with prices)</i>													
<b>PATIENT CARE COSTS</b>													
<i>(List procedure and detailed cost information)</i>													
<b>OTHER DIRECT COSTS</b>													
<i>(Provide itemized list with prices)</i>													
						<b>SUBTOTAL OTHER DIRECT COSTS</b>							
						<b>TOTAL DIRECT COSTS</b>							
						<i>(Subtotal Direct Labor + Other Direct Costs)</i>							
<b>INDIRECT COSTS OR OVERHEAD ( )%</b>													
<i>(May only be applied to non-patient care related costs)</i>													
						<b>TOTAL COSTS</b>							
						<i>(Total Direct costs + Indirect Costs)</i>							
<b>SIGNATURE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION</b>							<b>Date</b>						
<i>(Institutional Business Official)</i>													