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

http://biqsfp.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 4/1/10, 4/1/11, 4/1/12

Submission Date: There is no specific date for parent Clinical Trial Concept and BIQSFP study proposal submission to the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP).

Evaluation Process: The appropriate NCI Scientific Steering Committee (SSC) or external reviewers via CTEP/DCP if there is no appropriate SSC, evaluate and recommend the parent Clinical Trial Concept along with the Biomarker, Imaging and Quality of Life Studies proposal and/or Cost-Effectiveness Analysis (CEA) endpoint, during scheduled SSC meetings for concept review. **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. CTROC makes final funding recommendations. The Clinical Trials and Translational Research Advisory Committee (CTAC) periodically reviews the approved funding portfolio, providing strategic oversight and advice.

Expiration Date: March 31, 2013. It is anticipated that the BIQSFP Announcement will be reissued in subsequent years.

I. Key Changes with Revised Announcement:

A. INTEGRATED biomarker and imaging studies within a phase 2 treatment trial are now eligible for BIQSFP funding (see page 2).
B. The funding mechanism for approved BIQSFP studies is via NCI Administrative Supplements (see page 2).
C. Additional BIQSFP eligibility definitions have been added (see pages 3 and 7).
D. Additional detail has been added regarding integrated biomarker/imaging costs eligible for BIQSFP funding (see page 4).
E. Additional informational resources have been added regarding validation of integral biomarkers (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

biomarker, imaging, and quality of life studies with or without CEA proposals, which are associated with NCI clinical trial concepts.

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 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 clinical trial design, identify populations that may better benefit from treatment, and improve clinical trial 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.

IV. Mechanism of Support

BIQSFP is managed through the Coordinating Center for Clinical Trials (CCCT) in the NCI Office of the Director (OD).

For FY 2012-2013, BIQSFP Administrative Supplements are provided annually via the parent U10 Cooperative Agreement for the study and will be administered by CCCT in conjunction with the relevant NCI program (i.e., CCOP Research Base or Cooperative Group program). All the terms and conditions of the of the parent U10 award apply to this funding. BIQSFP Administrative Supplement recipients will be required to provide an annual progress report to CCCT.

For the FY 2012-2013 BIQSFP Announcement, the number of anticipated awards is contingent upon the availability of funds and the number of meritorious proposals submitted. NCI committed $10M to BIQSFP funding in FY 2011. Applicants may submit more than one trial concept with 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 biomarker, imaging, quality of life study, or CEA study must be approved by the appropriate review entity (SSC, CTEP or DCP) in order to be eligible for the BIQSFP funding.

V. Requirements and Definitions

A. Eligible trial types for BIQSFP funding are:

- Trials conducted by CG's and CCOP Research Bases.
- Phase 3 treatment trials with integral or integrated biomarker or imaging studies, and/or quality of life studies.
- Phase 3 cancer prevention and QOL clinical trials with integral or integrated biomarker or imaging studies, and/or QOL studies.

- Large (≥100 patients), randomized phase 2 treatment trials with integral or integrated biomarker or imaging studies.
- For CEA, the parent concept must be a randomized phase 3 clinical trial with a comparator arm.

B. **Treatment Trials** test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials. (NCI Fact Sheet 4/10)

C. **Cancer Prevention Trials** test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer. (NCI Fact Sheet 4/10)

D. **Quality-of-Life (Supportive Care) Trials** focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied. (NCI Fact Sheet 4/10)

Treatment trials are submitted to CTEP for evaluation by the appropriate NCI Disease-Specific Scientific Steering Committee.

Cancer prevention and QOL trials are submitted to DCP for evaluation by the appropriate NCI Scientific Steering Committee.

VI. Biomarker and Imaging Studies

Two types of 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., ERCC-1 to determine protocol eligibility for patients with gastric cancer 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., FLT3/ITD ratio for assignment of pediatric AML 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 where third-party payers would not cover the cost

- 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 on patients during the trial and include complete plans for specimen collection, laboratory measurements, proposed cutpoints, 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 Biomarker and Imaging Studies

Prioritization and evaluation criteria include:

- The strength of the preliminary data for both test utility and performance characteristics including cutpoints
- 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 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 will 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. Quality of Life (QOL) Studies

QOL studies can be integral or integrated tests, assays, and/or tools. They must be part of the clinical trial design from the beginning (assessments conducted while the trial is open). They are intended to inform on treatment options and side effects by validating the biological and functional clinical correlates of patient–reported outcome (PRO) data. These may also include biomarker assays and imaging tests that may be used for decision making in future trials.

Currently, DCP funds quality of life studies that obtain information for use in patient-physician decision making that help the patient prepare for and interpret the treatment experience. Examples of this DCP support may 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 may include, but are not limited to, qualitative data, toxicity impact, convenience, psychosocial outcomes and function.

A. Eligible categories of quality of life studies and examples include:

- QOL 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).
- Studies in the PRO measurement field with the integration of modern measurement theory for the development of brief, precise, and valid PRO measures. These advancements provide an examination of the benefits of integrating these measures, including electronic data capture, into clinical trials. Examples of studies that fall into this category may include: computer-based testing, experience sampling, and multiple brief symptom assessment (as opposed to infrequent and lengthier 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 measures that validate PRO data 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 may include: enhancing measures that validate 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" measures with testable hypothesis(es) and a high likelihood to give validated interpretations, and 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. Examples of these study measurements may include: cytochrome P450 metabolism; cytokine analyses; pharmacokinetic studies for drug interactions; neuroendocrine studies, and fMRI for cognitive changes.

B. 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 quality of life correlative study hypothesis(es)
- Measures that are reliable, valid and appropriate to the population of interest
- Feasibility of proposal such that completion can be accomplished efficiently and in a reasonable time frame

VIII. Cost-Effectiveness Analysis (CEA) Studies

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 (e.g., societal, clinical, or third-party), and time horizon (e.g., within trial or long-term survivorship). 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 review of the clinical trial concept.

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 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.

IX. Studies Ineligible for BIQSFP Funding

- Studies that do not meet the definitions for eligible trials [e.g., phase 1 concepts, small (<100 patients) randomized & all non-randomized phase 2 concepts, studies involving toxicity screens on animals].
- Studies that are still within the discovery phase or pre-clinical development stage focusing on assay development.
- Studies that can be conducted in the future on stored specimens (retrospective studies), except if the results are critical to the stated primary or secondary objectives of the trial.
- Studies eligible for DCP Cancer Credits.
- Cohort studies, screening studies, or longitudinal observational studies.

- Studies that include assays, tests, or tools that are standard of care and normally reimbursed by third-party payers.

Exceptions

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 or integrated component, and/or cancer prevention or QOL 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.

X. BIQSFP Budget Preparation & Submission

- All BIQSFP study 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 study proposals submitted.
- 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.
- Covered BIQSFP costs may include but not be limited to serial research biopsies for tissue analysis, procurement of and completion of research assays on blood or tissue, central pathology or image reading, and shipping.
- Costs for the PI of the clinical trial concept/study and/or Cooperative Group/CCOP leadership are not covered under the BIQSFP program.

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).
  - Brief description of the project indicating whether the study(s) is integral or integrated.
  - Type of study(s) proposed (biomarker, imaging, quality of life, and/or CEA).
  - Total budget figure requested for each project (biomarker, imaging, QOL, CEA).
  - Duration of the study.
- Detailed budget as described in the **BIQSFP Budget Preparation & Submission** section (above).
- The parent clinical trial concept with the biomarker, imaging, QOL, 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 *Study Checklist for Large, Randomized Phase 2 or Phase 3 Trials with 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 Assays in Clinical Trials** at: http://www.cancerdiagnosis.nci.nih.gov/scientificPrograms/pacct/PACCT_Assay_Standards_Document.pdf.

Additional information regarding validation of integral biomarkers can be found at NCI's Cancer Diagnosis Program (CDP) website: **http://www.cancerdiagnosis.nci.nih.gov/diagnostics/templates.htm**

For BIQSFP study proposals containing assays that are not fully developed, applicants can refer to NCI's Clinical Assay Development Program (CADP) website for guidance regarding assay validation: **http://cadp.cancer.gov**.

C. Quality of Life: A separate document is required describing the characteristics and performance of each measure that validates a QOL assessment and/or an instrument proposed for funding, and its role in the trial. Applicants should refer to the *Study Checklist for Randomized 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 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 *Study Checklist for Randomized Phase 3 Clinical Trials with a Comparator 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.

E. 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:
Worta McCaskill-Stevens, MD, MS - wm57h@nih.gov
cc: Ann O'Mara, Ph.D. - omaraa@mail.nih.gov

Cooperative Group proposals must be e-mailed to:
NCI CTEP Protocol Information Office - PIO@ctep.nci.nih.gov
cc: Margaret Mooney, M.D. - mooneym@ctep.nci.nih.gov

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

XI. Terms and Conditions for Funding

BIQSFP Administrative Supplements are provided annually via the parent U10 Cooperative Agreement for the study and will be administered by CCCT in conjunction with the relevant NCI program (i.e., CCOP Research Base or Cooperative Group program). 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. Funding is dependent on continuance of the clinical trial protocol and adequate progress.

XII. 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".

XIII. 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 M. 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

For DCP:

Worta J. McCaskill-Stevens, MD, MS
Acting Chief
Community Oncology and Prevention Trials Research Group
Head, Breast Cancer Prevention
Head, Minority-Based Community Clinical Oncology Program
Division of Cancer Prevention
6130 Executive Blvd., EPN 2026
Bethesda, Md. 20892
301-496-8541
301-496-8667
Email: wm57h@nih.gov

Ann M. 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

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

Questions regarding the prioritization, evaluation, and Administrative Supplements funding processes should be directed to:
Raymond A. 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

Questions regarding the subcontracting process 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
Frederick National Laboratory for Cancer Research
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
Email: seidelg@mail.nih.gov

Questions regarding Cost-Effectiveness Analysis should be directed to:
O. Wolf Lindwasser, Ph.D.
Program Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
6120 Executive Blvd, Suite 300
Bethesda, MD 20892-7227 (mail)
Rockville, MD 20852 (courier)
O: 301-443-6792
F: 301-480-1522
Email: wolf.lindwasser@nih.gov

Study Checklist for Large Randomized Phase 2 and Any Phase 3 Trials with 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 Study Checklist and the BIQSFP 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 study(ies) 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, and 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 above).

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** .

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.

Study Checklist for Randomized Phase 3 Trials with Quality of Life Components

INSTRUCTIONS: Please submit a response to each of the criteria below. Please complete one Study 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. For each instrument, identify whether it is INTEGRAL or INTEGRATED.

5. Describe any included *objective* correlates that enhance the patient-reported outcomes data (e.g. actigraphy, imaging, pulse ox, etc).

6. Identify any *biomarker or imaging* correlates of the patient-reported outcome measure(s) that will be collected (e.g., molecular, protein, other assays or tests).

7. Explain how patient non-compliance, missing data and/or early death may impact the analysis.

8. How will visually challenged, non-English speaking patients be accommodated when completing the instrument(s)?

9. Describe the procedures for data collection and data monitoring including the training of data collection personnel.

Study Checklist for Randomized Phase 3 Clinical Trials with a Comparator 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

Date:	**Check One:** ☐ **BM**_____ ☐ **Imaging**_____ ☐ **QOL**_____ ☐ **CEA**
	Check One: ☐ **Total Composite Budget** ☐ **Annual Budget**

PERIOD OF PERFORMANCE	FROM	THROUGH
	(date of award)	(12 months after date of award)

DIRECT LABOR

LABOR CATEGORY	HOURLY RATE	ANNUAL # OF HRS	TOTAL ANNUAL 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**

3/11,2/12