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

National Cancer Institute / Coordinating Center for Clinical Trials (NCI/CCCT)

Website:
http://www.cancer.gov/about-nci/organization/ccct/other-programs/biqsfp

I. BIQSFP Application Submission and Evaluation Process

A. **BIQSFP applications are only accepted from** NCI National Clinical Trials Network (NCTN) Groups or NCI Clinical Oncology Research Program (NCORP) Research Bases.

B. **All** Integral and Real Time Integrated BIQSFP study applications **must** be evaluated by an NCI Steering Committee (SC). If an appropriate NCI SC does not exist, the study will be evaluated by an ad hoc evaluation committee.

C. **INTEGRAL** application packages must be submitted with the parent concept and will be evaluated concurrently with the parent concept.

D. **INTEGRATED** studies should be included in the parent concept as a secondary outcome and noted on the parent concept submission form.

- **Real Time (RT) INTEGRATED** studies should be submitted after the principal investigator (PI) receives notification by the CTEP or DCP Protocol Information Office (PIO) that the parent concept was approved, preferably within 3 months.
- **Non-Real Time (NRT) INTEGRATED** will be accepted only when submitted in response to a call for applications which will be issued based on funding availability.

Study Type	Application Timeline	Evaluation
INTEGRAL	**With** parent concept	NCI Steering Committee
RT INTEGRATED	**After** parent concept approval	NCI Steering Committee
NRT INTEGRATED	**Only** in response to call for applications	Ad hoc NCI review panel

E. BIQSFP applications receiving a favorable evaluation for scientific merit from the NCI Steering Committee (or the ad hoc NCI evaluation committee) will be recommended to the NCI Clinical and Translational Research Operations Committee (CTROC) for funding. CTROC approves, disapproves, and/or modifies BIQSFP applications. The respective NCTN Group or NCORP Research Base and NCI Steering Committee (or the ad hoc NCI evaluation committee) will be notified of the results of the CTROC review by the CTEP/DCP PIO.

II. Key Changes for 2020

A. Submission of NRT INTEGRATED studies has been modified (see I.D. BIQSFP Application Submission and Evaluation Process; VII.B. INTEGRATED Studies; and X.A. BIQSFP Application Package).

B. Non-randomized NCTN treatment trials with an integral study are eligible for BIQSFP funding.

C. **Cost-Effectiveness Analysis (CEA) studies are no longer eligible tor BIQSFP funding.**

D. Costs ineligible for BIQSFP funding have been clearly specified (see X.A. BIQSFP Application Package - What is Required? Detailed Budget).

III. Overview and Summary

The NCI invites NCTN Groups and NCORP Research Bases to apply for funding to support biomarker, imaging, and symptom science/quality of life (symptom science/QOL) studies. All study applications must be associated with NCI clinical trial concepts or protocols.

IV. Purpose

The NCI Clinical Trials Working Group (CTWG), as part of its Prioritization and Scientific Quality Initiatives, recommended establishing a funding mechanism and prioritization process for correlative studies and symptom science/QOL studies that are inherent in the design of a clinical trial and are not currently supported by the U10/UG1 funding mechanisms. The purpose of BIQSFP is to ensure that the most important, scientifically meritorious biomarker, imaging, and symptom science/QOL studies within appropriate NCI clinical trials can be funded and initiated in a timely manner.

Precision medicine, immunology, imaging, and QOL studies embedded in clinical trials should have the potential to modify standard of practice. The assays/tests/tools/instruments must be reliable and provide interpretable answers that are of benefit to patients. In addition, they need to lead to the validation of targets, reduction of morbidity, prediction of treatment effectiveness, enhanced clinical trial design or identification of populations that might benefit from treatment.

V. Mechanism of Support

BIQSFP is managed through the Coordinating Center for Clinical Trials (CCCT) within the NCI Office of the Director. The number of anticipated awards is contingent upon the availability of funds. Approved BIQSFP studies are funded as administrative supplements to the NCTN Group/NCORP Research Base grants.

VI. Eligibility

A. Applications must be associated with the following types of trials conducted by NCTN Groups or NCORP Research Bases and reviewed by NCI Steering Committees:

- Randomized phase 2 or phase 3 **treatment** trials
- Randomized phase 2 or phase 3 **prevention** trials
- Randomized **symptom science/supportive care** clinical trials
- **Non-randomized phase 2 or phase 3 treatment trials** (integral studies only)

B. Trial Types

- **NCI Treatment Trials** test the effectiveness of new cancer treatments or new ways of using existing cancer treatments in people who have cancer. The treatments tested may include drugs, vaccines, approaches to surgery or radiation therapy, or combinations of treatments including immunotherapy modalities.
- **NCI Cancer Prevention Trials** are studies involving healthy people. In most prevention trials, the participants either do not have cancer but are at high risk for developing the disease or have had cancer and are at high risk for developing a new cancer or recurrence. These studies look at cancer risk and ways to reduce that risk.
- **NCI Symptom Science/Quality of Life Trials** test interventions to improve the quality of life of cancer patients, especially those who have side effects from cancer and its treatment, such as fatigue, pain, infection, nausea and vomiting, sleep disorders, depression, and other cancer and treatment related symptoms and toxicities.

Further details on the preceding definitions can be accessed below:
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/types.

VII. Integral and Integrated Studies

Two types of studies embedded in NCTN or NCORP trials are eligible for consideration – INTEGRAL and INTEGRATED.

A. **Integral Studies** are assays/tests/tools/instruments that must be performed in order for the trial to proceed or to support the primary analysis. Integral studies are inherent to the design of the trial and must be performed on all participants, usually in real-time. **Integral studies have the highest funding priority.**

Examples of integral studies include the following:

- Tests to establish eligibility for the trial or direct treatment assignment in a treatment, imaging, prevention or symptom science trial. Note that in rare instances a biomarker may be needed for stratification of randomization, but this use requires strong justification. One example of strong justification for biomarker-stratified randomization is that the biomarker is strongly prognostic and the trial is very small or biomarker prevalence is so low that there is a risk that the arms will become substantially unbalanced with respect to the biomarker. Another example is when separate accrual goals are needed for different biomarker-defined subgroups. This need could arise when a biomarker has prevalence extreme relative to 50% and accrual may need to continue longer in some subgroup in order to have adequate statistical power to address a treatment question specific to that subgroup.
- Trial endpoints based on functional imaging or molecular characterization.

B. **Integrated Studies** are intended to clinically validate markers, imaging tests, or symptom science/QOL tools/instruments for possible use as an integral marker in future trials or in clinical practice. Integrated studies should test a specific hypothesis with a preplanned statistical design and are not hypothesis-generating or exploratory. The assays/tests/tools/instruments need to have already been analytically validated. Integrated studies must be included in the protocol as secondary outcomes.

- **Real Time (RT) Integrated Studies** need the assays/tests/tools/instruments to be performed and/or assessed in real time during the trial. For studies with assays/tests/tools/instruments that can be conducted non-real time but require funding for the collection or real time processing of biospecimens, please consult with a CTEP medical officer (for treatment concepts), DCP program staff (for symptom science/QOL concepts), and/or with the Cancer Imaging Program (CIP) medical officer (if an imaging study is proposed), to determine eligibility prior to submitting an RT integrated study application.

  RT integrated studies should be submitted after the principal investigator (PI) receives notification by the CTEP or DCP PIO that the parent concept was approved, preferably within 3 months.

- **Non-Real Time (NRT) Integrated Studies** do not require real time processing or testing of specimens. For example, NRT integrated assays/tests/tools/instruments can be performed later on specimens, patient scans, or patient tools/instruments collected as part of the clinical trial and the results are not needed for trial eligibility, stratification, or treatment assignment. NRT Integrated study applications will be accepted only when submitted in response to a call for applications, which will be issued based on funding availability.

Examples of integrated studies include the following:

- Studies to establish clinical validity or clinical utility for assays/imaging tests/tools/instruments that are completely "locked down," e.g., a prospective-retrospective study (Simon et al., J Natl Cancer Inst 101:1446-52, 2009).
- Studies to confirm aspects of a biomarker or imaging test that has already demonstrated some degree of clinical validity and promise for future integral use but requires confirmation of certain aspects, e.g., confirmation of a cut point to be applied to a continuous marker value for use in a future clinical trial.
- Symptom science/QOL studies to validate tools/instruments in understudied populations, such as pediatrics and adolescent/young adults, experiencing disease or treatment related symptoms, such as chemotherapy induced peripheral neuropathy, fatigue, and pain.

C. Studies Ineligible for BIQSFP Funding

- Studies that are not embedded in an eligible trial type (e.g., phase 1 concepts, ETCTN trials, observational studies, Cancer Care Delivery Research (CCDR) studies, etc.)
- Biomarker and imaging studies still within the discovery phase or pre-clinical development stage focusing on assay/test development
- Studies proposing to use assays/tests that have not been analytically validated
- Studies considered exploratory or hypothesis-generating
- Studies eligible for DCP Cancer Control accruals or other DCP or DCTD funding
- Studies that include assays, tests, tools, or instruments that are standard of care and normally reimbursed by third-party payers
- CEA studies and studies involving financial hardship measures
- Studies proposed more than 6 months after the primary results are reported

VIII. Statistical Requirements for BIQSFP Study Applications

The statistical analysis section should be developed in consultation with a biostatistician who is familiar with the specific trial data elements relevant to the proposed BIQSFP study. All BIQSFP applications should include a thorough statistical section addressing the key points described below.

A. Measurements

- A list or description of the laboratory or imaging-based biomarkers or symptom science/QOL measurements essential to the proposed integrated of integral study must be provided.
- The timepoints at which these measurements will be taken (e.g., prior to initiation of study treatment, after four cycles of therapy, at progression, etc.) should be stated.
- Separate documents describing the characteristics and performance of the tests or assessment tools should be provided in accordance with the checklists indicated as required in section X.A. "Study Checklist."

B. Endpoints

Precisely define the clinical endpoints involved in the analysis. For time-to-event outcome variables, this definition should indicate what constitutes an "event" (e.g., disease progression, death due to cancer, death due to any cause, etc.).

C. Case Selection

Whether the BIQSFP study will involve all patients from the parent trial, or only a subset, should be specified. If only a subset, then the case selection process, including inclusion/exclusion criteria, stratification, matching, or any other algorithms (e.g., adaptive selection) to be used must be described.

D. Statistical Analysis Plan

A statistically rigorous analysis plan should be provided to describe how the primary or secondary objectives will be addressed. The statistical analysis plan should be described in sufficient detail so that another qualified individual with access to the data would be able to reproduce the analysis. Type of information needed will often include, but is not limited to, the following:

- Transformations, normalizations, cut-points, or categorizations applied to variables, and justification for their use
- Algorithms needed to combine measurements into any indices or risk scores that will be used
- Statistical methods to be used for the primary analyses (e.g., stratified or unstratified log-rank test, Cox proportional hazards regression, conditional or unconditional logistic regression, Receiver Operating Characteristic curve analysis, etc.)
- If evaluation of whether a study biomarker or imaging test adds to information provided by standard clinical or pathologic variables is planned, then a list or description of the variables initially considered for inclusion in a multivariable model should be provided along with any planned variable selection strategies)
- Multiple-testing adjustment methods (e.g., Bonferroni, Holm-Bonferroni, Benjamini-Hochberg FDR control, etc.)
- Quantitative criteria to be met to establish whether clinical utility has been demonstrated or further investigation of the biomarker or imaging test is warranted

E. Justification for Sample Size

Based on the stated primary objectives and corresponding statistical analysis plan, sample size or power estimates should be provided to justify the number of assays/tests/tools/instruments proposed. The rationale should include a clear explanation (or cited reference) for the method of sample size or power calculation along with a statement of all assumptions required to perform that calculation. An independent statistician should be able to reproduce the estimates from the information provided in the application.

Typically, sample size or power estimates will require assumptions about the following:

- Anticipated distribution of biomarker or imaging test values in the targeted population(s) (e.g., marker positivity rate if the marker is dichotomous)
- Expected percentage of successful assays or evaluable images (based on anticipated rates of technical failures, degraded or insufficient biospecimens, patient noncompliance, etc.)
- Event rates or number of events anticipated for the cases included in the primary analysis
- Expected differences in outcomes or magnitudes of associations (e.g., hazard ratio or other “effect” size)

These assumptions and estimates need to be supported by preliminary data or previous studies, which should be described either in this section or in the background section.

IX. Evaluation Criteria

It is not intended that any priority is assigned to one criterion over another but rather that applications are evaluated based on the totality of the information and strength of the supporting data and analytical plan.

A. Biomarker and Imaging Studies

Clinical laboratory or imaging tests that are used to assign or significantly modify a patient’s treatment in the proposed clinical trial must have undergone rigorous analytic validation and sufficient clinical validation to warrant inclusion in a clinical trial. Laboratory assays must be performed in CLIA-accredited facilities (if they are reported to the patient or their physician) and comply with FDA regulations (e.g., determination of need for an investigational device exemption (IDE)). Prioritization and evaluation criteria include the following:

- Strength of the preliminary data for both test utility and performance characteristics including cut points
- Adequacy of statistical plans, including sample size/power, appropriateness of assumptions and methods, and justification for subset analyses (if planned)
- Potential of the test to change practice and have high impact on patient care (e.g., the impact of the test itself or through its impact on therapeutic management strategy and outcome as will be demonstrated by results of the trial)
- Ability of the test to yield well-defined and validated interpretations that will guide decision-making
- Extent of standardization of the assays/tests/tools/instruments as to be transferable to the non-research setting
- Adequacy of the process for specimen collection or image acquisition or analysis including feasibility data
- Description of cost-sharing with entities that would eventually commercialize the test

Information regarding validation of integral biomarkers can be found at NCI's Cancer Diagnosis Program (CDP) website: https://cdp.cancer.gov/resources/drdr/default.htm

For additional explanations and definitions related to biomarker assays, see **Performance Standards Reporting Requirements for Assays in Clinical Trials** accessed below: http://cdp.cancer.gov/scientific_programs/pacct/PACCT_Assay_Standards_Document.pdf

B. Symptom Science/QOL Studies

Most symptom science/QOL studies (which use previously validated tools/instruments) should be submitted for DCP Cancer Control accruals. However, scientifically meritorious symptom science/QOL studies may be considered for BIQSFP funding when the collection of data requires funding beyond the usual Cancer Control funding. Both integral and integrated symptom science/QOL studies are eligible for BIQSFP funding.

The application should include a letter from DCP indicating that the proposed costs exceed allowable DCP funding and that DCP has agreed that the study should be considered for BIQSFP funding. DCP will provide this letter to the NCORP Research Base for the application

Prioritization and evaluation criteria include:

- The potential to impact patient morbidity and quality of life with clinically meaningful benefit
- The potential to move science forward 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 collection
- A statistical plan with adequate power for testing the symptom science/QOL study hypothesis(es)
- Tools/instruments are reliable, valid, and appropriate to the population of interest or are in the process of validation

X. BIQSFP Application Package Preparation

All resources needed for completion of the BIQSFP Application Package can be found on the following BIQSFP website: https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp. The site also includes the BIQSFP Guidelines, Frequently Asked Questions (FAQs), Application Checklists, Budget and Budget Justification information, and Program Contacts.

A. BIQSFP Application Package - What is required?

- Parent concept application forms can be accessed below:
  - **CTEP** (https://ctep.cancer.gov/protocolDevelopment/docs/Concept_Submission.docx)
  - **DCP** *NCORP Clinical Trials Document Submission Worksheet v3.1* (https://prevention.cancer.gov/sites/default/files/uploads/clinical_trial/NCORP-Clinical-Trials-DSW-02272017.docx)

- Cover letter signed by the NCTN Group/NCORP Research Base Chair indicating submission of a biomarker, imaging, or symptom science/QOL application in response to the 2020 BIQSFP Guidelines. The cover letter should include:
  - Title(s) of the BIQSFP project(s) (Each biomarker/assay/test/tool/instrument should be considered a distinct project and have it's own title)
  - Principle Investigator of the BIQSFP project(s)
  - Title and protocol number of the parent clinical trial concept associated with the biomarker, imaging, and/or symptom science/QOL application
  - Brief description of the project indicating whether it is **integral, RT integrated,** or **NRT integrated**
  - Type of study(s) proposed (i.e., biomarker, imaging, and/or symptom science/QOL)
  - Total budget requested for each project
  - Duration of each project

- Detailed budget
  - Total composite budget that details the costs (direct and indirect) for *each* biomarker, imaging, and/or symptom science/QOL study, including cost per case or cost per patient and the total number of cases or patients to be tested.
  - Use the PHS 398 Form (http://grants.nih.gov/grants/funding/phs398/phs398.html)
  - Include a narrative justifying each requested cost: Budget Justification.
  - Covered BIQSFP costs may include, but are not limited to, procurement of and completion of research assays on blood or tissue, central pathology or image reading, and shipping.
  - Investigators are encouraged to explore options for reducing the cost of assays/tests/ tools/instruments to be supported by BIQSFP funding, perhaps by billing third party payers, obtaining partial funding from commercial partners, or choosing the lowest priced laboratory.
  - The signature of the institutional business official is not required at the time of initial submission of the total composite budget. Institutional approval and sign-off is required once the final funding has been approved by the NCI.
  - **Costs ineligible for BIQSFP funding include the following**:
    - Salary for the PI of the clinical trial/study and/or NCTN Group/NCORP Research Base leadership
    - Meeting travel costs
    - Presentation or publication costs
    - Cost-of-living/inflationary increases
    - Costs already covered under the U10/UG1

- BIQSFP Checklist -- Submit the appropriate checklist based on the type of application: (https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp)
  - **Integral Biomarker:** A separate document (no more than 5 pages per assay) is required describing the characteristics and performance of **each** biomarker assay test proposed for funding and its role in the trial. Applicants should follow the *Study Checklist for Integral Biomarker Assays*.
  - **Integrated Biomarker:** A separate document (no more than 5 pages per assay) is required describing the characteristics and performance of **each** biomarker assay test

proposed for funding and its role in the trial. Applicants should follow the *Study Checklist for Integrated Biomarker Assays*.

- **Integral Imaging:** A separate document (no more than 5 pages per imaging study) is required describing the characteristics and performance of **each** imaging test proposed for funding and its role in the trial. Applicants should follow the *Study Checklist for Integral Imaging Tests*.
- **Integrated Imaging:** A separate document (no more than 5 pages per imaging study) is required describing the characteristics and performance of **each** imaging test proposed for funding and its role in the trial. Applicants should follow the *Study Checklist for Integrated Imaging Tests*.
- **Symptom Science/QOL:** A separate document (no more than 5 pages per instrument) is required describing the characteristics and performance of **each** measure that validates a symptom science/QOL assessment and/or an instrument proposed for funding and its role in the trial. Applicants should follow the *Study Checklist for Symptom Science/QOL Assessments.*

- Standard Operating Procedures (SOP) -- Applicants are encouraged to submit an SOP(s) as an appendix when the SOP informs on precision, accuracy, and specificity needed for validation of the assay(s), imaging tests or symptom science/QOL tools/instruments being proposed.

- NIH Biosketch -- Include a completed NIH biosketch form for each study PI. Information on the biosketch requirements can be found at: https://grants.nih.gov/grants/forms/biosketch.htm

B. A complete **Application Package** as a **PDF** must be emailed to the relevant Program office. Applications must reference "BIQSFP" in the subject line of the email.

Email NCTN Group BIQSFP applications as noted below:

NCI CTEP Protocol Information Office - PIO@ctep.nci.nih.gov
cc: Margaret Mooney, MD, MBA - mooneym@ctep.nci.nih.gov
BIQSFP mailbox – NCIBIQSFP@mail.nih.gov

Email NCORP Research Base BIQSFP applications as noted below:

NCI DCP Protocol Information Office - ncidcppio2@mail.nih.gov
cc: Worta McCaskill-Stevens, MD, MS - wm57h@nih.gov
BIQSFP mailbox – NCIBIQSFP@mail.nih.gov

XI. Conditions for Funding

BIQSFP studies are funded via Administrative Supplements to the parent U10/UG1 Cooperative Agreement for the study and are administered by CCCT in conjunction with the appropriate NCI program (e.g., CTEP or DCP). All the terms and conditions of the of the parent U10/UG1 award apply to this funding. This includes adherence to the NIH data sharing policy, even if BIQSFP study results are negative. https://grants.nih.gov/grants/policy/data_sharing/

Funding is restricted to the approved project and dependent on continuance of the clinical trial and adequate progress on the BIQSFP-funded study. Carryover requests must receive written approval from the relevant NCI program official.

A progress report for each funded BIQSFP study must be included with the parent grant's noncompeting renewal. The progress report should indicate the number of

assays/tests/tools/instruments completed in the previous budget period, the number of patients screened, and/or the number of patients enrolled, as appropriate for each study. Please refer to the BIQSFP website for guidance regarding the type of information that the yearly progress report should include. It should also identify any problems with the BIQSFP study or enrollment in the trial.

Any requested changes to the study budget (e.g., the sample size increased or additional tests were added during protocol development, the cost of the test increased, etc.) should be described in the budget narrative and require BIQSFP program approval.

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 should be directed to the following NCI Program Staff:

For CTEP Trials:

Margaret M. Mooney, MD, MBA
Chief, Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
9609 Medical Center Drive
Room 5W-412
Bethesda, MD 20892-9737
For non-USPS mail (FedEx, UPS, etc.)
Rockville, MD 20850-9737
Phone: 240-276-6560
Email: mooneym@ctep.nci.nih.gov

For DCP Trials:

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For non-USPS mail (FedEx, UPS, etc.)
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Phone: 240-276-7075
Email: wm57h@nih.gov

Direct questions regarding prioritization, evaluation, and administrative supplements to:

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