

BIOMARKER STUDY Evaluation Guidelines

Purpose and Background

As part of its Prioritization and Scientific Quality Initiatives, the Clinical Trials Working Group (CTWG) of NCI recommended establishing a funding mechanism and prioritization process for essential correlative biomarker studies that are incorporated into the fundamental design of a clinical trial. The objective of this initiative is to ensure that the most important biomarker studies can be initiated in a timely manner in association with clinical trials.

Biological studies embedded in clinical trials often lead to scientific observations that validate targets, reduce morbidity, predict treatment effectiveness, facilitate better drug design, identify populations that may better benefit from treatment, improve accrual and retention, and ultimately lead to change in the standard of practice. Support for timely and important studies during the clinical trial concept development phase will ensure timely development of effective, informative and high impact clinical trials.

The primary purpose of this funding mechanism is to support integral and/or integrated biomarker studies embedded in large (≥ 100 patients), randomized phase 2 treatment trials or in any randomized phase 3 clinical trials conducted by NCI National Clinical Trials Network (NCTN) groups and NCI Community Oncology Research Program (NCORP).

Biomarker Studies

Two types of essential biomarker studies are eligible – Integral and Integrated.

BIQSFP proposals for funding of **INTEGRAL** biomarker studies must be submitted concurrently with the parent concept. **INTEGRATED** biomarker study applications **must be submitted after parent concept approval and must be received within four months** of notification of parent concept approval.

Integral studies - Defined as assays 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. Studies that will be conducted in the future on stored specimens are **not** eligible for supplemental funding, except if the results are critical to the stated primary or secondary objectives of the trial.

Integral studies will have the highest priority.

Eligible categories of integral studies and examples are as follows:

- Tests to establish eligibility – e.g., ERCC-1 to determine protocol eligibility for patients with gastric cancer.
- 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

BIOMARKER STUDY Evaluation Guidelines

patients to a study arm; eradication of the bcr-abl clone in CML to determine whether to continue treatment.

Integrated Studies – Defined as assays that are clearly identified as part of the clinical trial from the beginning and are intended to identify or validate assays or markers that are planned for use in future trials. Integrated studies in general should be designed to test a hypothesis, not simply to generate hypotheses. The number of integrated assays performed should be sufficient to obtain scientifically valid outcomes during the trial and include complete plans for specimen collection, laboratory measurements, proposed cutpoints, and statistical analysis. One example would be predictive biomarker assays that are measured either in vitro or in vivo where the assay result is not used for eligibility, treatment assignment, or treatment management in the current trial.

Criteria for Review of Biomarker Studies

Prioritizing and evaluating criteria for essential biomarker studies will include:

- The strength of the preliminary data for feasibility, utility, and performance characteristics including cutpoints
- The potential of the assay to change practice and have high impact on patient care (e.g., the impact of the assay itself or the change of therapy indicated by the results of the trial)
- The ability of the assay to yield well defined and validated interpretations that will guide decision-making
- The extent of standardization of the assays 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 assay

Clinical assays 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. 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. Based on the strength of the information presented and your scientific judgment, you will be asked to rate your level of enthusiasm for the study on a five-point scale from High to Mild.

BIQSFP submissions should include a completed Study Checklist for each assay. The elements in the Study Checklist are listed below. The application should include a response to these elements.

Biomarker, Imaging, & QOL Studies Funding Program (BIQSFP)

***'16 Study Checklist for Clinical Trials with
BIOMARKER ASSAYS for Treatment/Symptom Science/Supportive Care Studies***

INSTRUCTIONS: For INTEGRAL assay, respond to Items 1-6, 8.
For INTEGRATED assay, respond to Items 1, 2, 4-8.

Please submit a response to each of the criteria below and complete one Study Checklist for each biomarker endpoint. The Proposal Package must also include a budget at the time of submission that clearly details the Direct and Indirect costs of the requested funding. The budget for the project should use the standard PHS 398 budget form (<http://grants.nih.gov/grants/funding/phs398/phs398.html>) along with a narrative justifying each requested cost. The Budget packet must include a completed NIH biosketch form for each study PI. Form SF424 can be found at: <http://grants.nih.gov/grants/funding/424/index.htm#format>. Additional information on the new biosketch requirements can be found at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-024.html>.

NOTE: INTEGRATED biomarker study applications must be submitted after parent concept approval but prior to protocol activation. Subsequent NCI prioritization and approval for funding will be decided by CTROC after evaluation of the INTEGRATED study(s) by the respective NCI Steering Committee (SSC).

1. For an integral or integrated assay, indicate the role(s) of the biomarker assay 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) who are being considered for conducting the assay(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:
 - A. Specify the analyte(s), technical platform, and sources of assay components (e.g., reagents, chips, and calibrators).
 - B. Describe the specimens, and anticipated methods for specimen acquisition, fixation or stabilization and processing.
 - C. Describe the scoring procedures and type of data to be acquired
 - quantitative/ continuously distributed
 - semi-quantitative/ordered categorical
 - qualitative/non-ordered categorical
5. Provide data on the clinical utility of the integral/integrated assay as it will be used in the trial:

BIOMARKER STUDY Evaluation Guidelines

- A. Provide background information that justifies the use of this assay 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, specify the cutpoint(s) and describe how these will be used in the trial). Provide the rationale for the cutpoint(s) selected. What proportion of subjects is expected to have values above and below the proposed assay value cutpoints? What magnitude of effect (e.g., treatment benefit) or outcome (e.g., prognosis) is expected for patients with assay 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 results.
6. Provide data on the analytical performance of the assay.
 - A. For *in vitro* tests, describe the current status of studies defining the accuracy, precision, reportable range, reference ranges/intervals (normal values), and failure rate of the assay as it is to be performed in the trial (e.g., performance of test on specimens intended to be used in the clinical trial). Describe the use of positive and negative controls, calibrators, and reference standards for 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_CLIA_Brochures.asp). Applicants are encouraged to submit a laboratory Standard Operating Procedure (SOP) as an appendix, to support validation of the assay(s) being proposed.
 - B. If the assay 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.
 - C. Provide turn-around-time for reporting assay results to the clinical PI (for INTEGRAL studies).
 7. For an **INTEGRATED** study, provide justification for the assay to be completed in real time (if applicable).
 8. The Budget Justification should include a description of potential cost-sharing approaches for the assay (e.g., billing to third-party payers, partial funding from commercial partners, choosing between academic vs. commercial labs, etc.) along with justification for the costs of academic vs. commercial laboratories.

8/08,3/09,3/10,3/11,3/12,4/13,11/13,12/14,12/15

**Please complete and return the attached
BIOMARKER STUDY EVALUATION TEMPLATE.**

Thank you.