Biomarker & Imaging Study Evaluation Guidelines

Biomarker & Imaging Studies Funding Program

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 and imaging 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 and imaging studies can be initiated in a timely manner in association with clinical trials.

Biological and imaging 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 and imaging studies embedded in large (≥100 patients), randomized phase 2 treatment trials or in any randomized phase 3 clinical trials conducted by the Cooperative Groups (CG's) and Community Cancer Oncology Program (CCOP) Research Bases.

Biomarker and Imaging Studies

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

Integral studies - Defined as tests that must be performed in order for the trial to proceed. Integral studies are inherent 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 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

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 and statistical analysis. One example would be predictive marker assays that are measured either *in vitro* or *in vivo* on all cases but where the assay result is not used for eligibility, treatment assignment, or treatment management in the current trial; a second example would be the use of an imaging test to detect biologic modification of the target but where the image is not used as a primary study endpoint.

Criteria for Review of Biomarker and Imaging Studies

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

- The strength of the preliminary data for feasibility**,** utility, and performance characteristics including cutpoints
- 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 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. Based on the <u>strength</u> of the information presented and your <u>scientific judgment</u>, 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/test. The elements in the Study Checklist are listed below. The application should include a response to these elements.

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.

Please complete the attached BIOMARKER & IMAGING STUDY EVALUATION TEMPLATE.

Thank you.