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

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 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.

Imaging Studies

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

BIQSFP proposals for funding of **INTEGRAL** imaging studies must be submitted concurrently with the parent concept. **INTEGRATED** imaging study applications **must be submitted after parent concept approval and must be received within four months (16 weeks)** of notification of parent concept approval.

Integral studies - Defined as imaging 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. Studies that will be conducted in the future on stored images 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., imaging assessment of hypoxia for trials of drugs effective in hypoxic tissues such as tirapazamine
- Tests to assign patients to a treatment arm of a trial, including surrogate endpoints for assignment of treatment during a trial – e.g., 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 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. The number of integrated tests performed should be sufficient to obtain scientifically valid outcomes during the trial and include complete plans for patient preparation, procedures, analysis, interpretation of results, scoring procedures, expected distribution of the imaging study results in the study population, etc. (See *IMAGING STUDY Checklist* below). One 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 Imaging Studies

Prioritizing and evaluating criteria for essential imaging studies will include:

- The strength of the preliminary data for feasibility**,** 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 test as to be transferable to the non-research setting
- The adequacy of the process for image acquisition and processing including feasibility data
- A description of potential cost-sharing approaches that can be developed with entities that would eventually commercialize the test

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 test. 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)

'14 Study Checklist for Large Randomized Phase 2 and Any Phase 3 Trials with IMAGING TESTS

INSTRUCTIONS: Please submit a response to each of the criteria below and complete one Study Checklist and the Form PHS 398 Grant Budget Worksheets for each Imaging endpoint.

NOTE: One-time INTEGRATED imaging study applications must be submitted after parent concept approval and must be received within four months (16 weeks) of notification of parent concept approval. Subsequent NCI prioritization and approval for funding will be decided by CTROC after evaluation of the INTEGRATED study(s) by the respective SSC.

1. Indicate the role of the imaging test in the trial and whether it is INTEGRAL or INTEGRATED:
   A. Eligibility criterion
   B. Assignment to treatment
   C. Stratification variable
   D. Risk classifier or predictive and prognostic markers
   E. Response assessment
   F. Other (describe in detail):

2. Identify the specific individual(s) or imaging departments/sites that are being considered for conducting the imaging test for the trial.

3. Describe the imaging test:
   A. Specify the imaging devices or imaging agents.
   B. 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

4. Provide data on the clinical utility of the integral/integrated imaging test as it will be used in the trial:
   A. Provide background information that justifies the use of this imaging test result as a part for this trial. For example, if the integral imaging test 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 imaging study results 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 imaging cutpoints? What

magnitude of effect (e.g., treatment benefit) or outcome (e.g., prognosis) is expected for patients with imaging results above and below the proposed cutpoint(s)?

D. Describe under what conditions treating physicians and or patients will be able to access the imaging test results.

5. Provide data on the analytical performance of the imaging test.
   A. Describe the known performance characteristics of the imaging test. State and justify the limits of acceptable performance. Describe the use of positive and negative controls, calibrators, and reference standards for the imaging test.
   B. If the imaging test will be performed at more than one site, describe how inter-facility variability in the measurements 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 imaging test results.

6. Provide the type and number of scans. Indicate if the scan is standard of care (SOC) or investigational: e.g., 300 MRIs (SOC): 100 patients x 3 per patient; 200 FDG PET/CTs (investigational for the proposed indication/time point): 100 patients x 2 per patient; 100 F-MISO PET/CTs (investigational): 100 patients x 1 per patient.

7. The Budget Justification should include:
   A. Site/scanner qualification costs (usually done prior to patient enrollment in multi-center trials).
   B. Technical costs for each type of scan (including facility use, scanner time costs, etc.).
   C. Professional costs for each type of scan (*including cost for local radiologists / nuclear medicine physicians to interpret the images*).
   D. Image transfer costs (*includes network costs, shipping/mailing costs if physical media is used for transport*).
   E. Central imaging review costs (*if central review is performed*) for each type of scan.
   F. Real time image review costs (*if applicable*) for each type of scan.
   G. Image quality assurance costs (*additional data QA costs on top of basic interpretation or central review costs*).
   H. Imaging agent and contrast material costs, for each type of scan: (*if imaging agent costs can be further broken down into categories such as agent manufacturing, transport, or storage costs, please provide those*).
   I. Image storage costs (*includes costs for long term storage of imaging data, archiving, back-up systems, etc.*).
   J. Statistical support costs (*can include costs for services such as a contracted statistical center).*
   K. Salary support costs (*e.g. investigators, imaging technologists, research coordinators, study nurses, research assistants, etc.*).

4/13,11/13

Please complete the attached IMAGING STUDY EVALUATION TEMPLATE.

Thank you.