STATISTICAL EVALUATION TEMPLATE

Evaluator's Name:

Date of Evaluation:

Concept/BIQSFP ID Number and Title:

Instructions for BIQSFP Statistical Evaluators: You have been asked to provide a statistical evaluation of the BIQSFP study associated with the attached phase 2 or phase 3 clinical trial concept. Please complete one (1) Statistical Evaluation Template for each biomarker, imaging, and symptom science/QOL study. There could be more than one BIQSFP application (e.g., multiple biomarker or biomarker and imaging, and/or QOL) associated with a single clinical trial, and each should be submitted on a separate BIQSFP form.

Your responsibilities consist of evaluating the statistical aspects of the proposed study by providing written comments on this form in response to the specific questions that follow the evaluation criteria below.

Please use the attached *BIQSFP Proposal Package* in completing your evaluation. In addition to the information contained in the BIQSFP application, some sections of the parent trial concept such as *Section 10* (*Statistical Considerations*), correlative science sections, or protocol Statistical Considerations (Section 13) may be relevant to the proposed BIQSFP studies.

After completing this form, please save it to a new file, attach the form to an e-mail message referencing the concept/BIQSFP number, and forward the email to the CTEP, DCP, CCCT, or EMMES Program Staff who requested this evaluation from you. Submit your response at least 5 business days preceding the study evaluation conference call/meeting, so that all perspectives may be shared, and your written comments viewed by other evaluators of this study. You will likewise be provided access to the written comments of the other evaluators.

Key evaluation criteria:

A. Whether the study is integral, real time integrated, non-real time integrated, or exploratory

Based on the definitions provided below, evaluators should assess whether the proposed study is *integral*, *real time integrated*, *non-real time integrated*, or *exploratory*. Integral studies have highest priority for BIQSFP funding. Exploratory studies are not eligible for BIQSFP funding.

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.

Integrated Studies are intended to clinically validate markers, imaging tests or tools, or symptom science/QOL 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 (please see the definition of "exploratory" below). 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 or tests, including imaging scans and/or symptom science/QOL tools/assessments, to be performed and/or assessed in real time during the trial. Real time studies may also involve special sample collection or processing and cannot be stored and batched for analysis later.

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 at a later time on patient scans or specimens collected as part of the clinical trial, and the results are not needed for trial eligibility, stratification, or treatment assignment.

Exploratory studies include studies characterizing novel assays/tests/tool/instruments as pathways to suggest new therapeutic or interventional approaches that might be worthy of further investigation. Studies are also considered exploratory when they aim to test preliminary hypotheses or to further refine such hypotheses in situations where background data in the specific disease type or therapeutic context are limited.

B. Specification of assay/test/tool/instrument procedure

For BOTH integral and integrated studies, statistical evaluators should assess whether the assay or imaging test has been specified in sufficient detail in the BIQSFP documents. For biomarker assays, this specification should include preanalytical requirements for specimen collection, description of the technical protocol, reagents, positive and negative controls, scoring methods, and cutpoints, as applicable. For imaging assessments, the specification should include a description of patient preparation procedures, image acquisition and processing protocols, and interpretation criteria, as applicable. For symptom science/QOL tools/instruments, the specification should include minimum important difference (MID) or metric for clinically significant change. The submission should include symptom science/QOL scoring instructions as an appendix, to support validation of the tool/instrument(s) being proposed.

C. Adequacy of information provided about the analytical (technical) performance of the assay/test/tool/instrument procedure

Statistical evaluators are requested to provide comments about whether sufficient documentation of acceptable analytical (technical) performance has been provided. The BIQSFP documents should provide information about accuracy, precision, reportable range, reference ranges/intervals (normal values), limit of detection, limit of quantification, and failure rate of the assay/test/tool/instrument, as applicable, and in the context of how the procedure is to be performed in the trial (e.g., performance of test on the types of specimens or patients expected in the clinical trial and/or whether the specimens will be batched for analysis or analyzed in real-time).

The statistical evaluators should consider whether performance metrics have been clearly defined and sufficient information has been provided about the numbers and types of specimens (or subjects) involved in the analytical (technical) performance studies. Details should include the distribution of assay/test/tool/instrument measurements in the specimens or subjects studied in the performance assessment (e.g., how many were positive versus negative for the biomarker) and descriptions of the replication schemes used for precision and reproducibility evaluations.

The above information is necessary for proper interpretation of the reported analytical (technical) performance results. The requirement for information on analytical performance also applies to a commercially-available assay/test/tool/instrument. Regardless of whether a biomarker assay is a laboratory developed test or is a commercially available kit, the analytical performance study description should provide supporting data to establish that the test performance has been evaluated in the laboratory that will be performing the assay for the clinical trial, and according to the same technical protocol (including specimen preanalytical factors). The same is applicable for imaging tests and/or symptom science/QOL tools/instruments.

D. Pre-specified hypotheses, intended role, and supporting data

Pre-specified hypotheses and aims and a clear intended role for the assay/test/tool/instrument (including "image-based biomarker") measurement in disease management, with supporting data from prior studies, should be provided in the BIQSFP documents. Statistical evaluators should comment on the statistical robustness of the supporting data considering factors such as and the design and analysis of the studies that generated those data. The supporting data need to be of sufficient strength and quality to justify the proposed investigation of the assay/test/tool/instrument in an integrated study or its proposed use in the execution of the parent concept (integral assay/test/tool/instrument).

E. Statistical considerations

The BIQSFP documents must also include a detailed statistical plan, which should provide 1) a clear statement of the clinical endpoints and the biomarker/imaging/symptom science/QOL measurements involved in the analysis, 2) a description of the statistical analysis methodology used along with underlying assumptions, and 3) a justification for the number of patients to be studied and assays/tests/tools/instruments to be performed in order to establish that the study is

sized to permit scientifically and clinically meaningful conclusions.

For integral assays/tests/tools/instruments that are an inherent part of the trial design (e.g., only patients whose tumors overexpress the integral protein biomarker are eligible for entry into the trial and for randomization to treatment), the biomarker or imaging hypothesis is intimately tied with the treatment question and will have been reviewed already as part of the review of the treatment objectives of the parent clinical trial. However, if the statistical evaluators have any concerns about the adequacy of the background data supporting the use of the biomarker in the proposed manner, they are encouraged to comment.

In addition, any concerns regarding feasibility and logistics associated with aspects such as turnaround time, communicating with patients/physicians, and implementation of the trial should be addressed here.

If the BIQSFP study involves a comparison of assays/tests/tools/instruments, a statistical plan should be provided which describes how assay/test/tool/instrument superiority will be determined.

Evaluator Comments:

1. Based on the definitions provided under review criterion A and on your evaluation of the objectives of the BIQSFP study, would you categorize this study as INTEGRAL*or INTEGRATED*, or EXPLORATORY as defined above? Please provide a brief explanation for your answer.

2. Is the assay/test/tool/instrument sufficiently described (see review criterion B) and standardized to enable meaningful and well-defined quantifications of the underlying biomarker?

   Strengths:
   Weaknesses:

3. Is the analytical or technical performance of the measurement procedure (e.g., specificity, sensitivity, reliability, accuracy, as applicable) sufficiently well documented in the BIQSFP proposal (see review criterion C), and does it meet sufficiently high-performance standards that you judge it to be fit for the purpose for which it is to be used in the study?

   Strengths:
   Weaknesses:

4. Is the underlying scientific objective of the assay/test/tool/instrument well-defined, feasible, achievable, and amenable to statistical evaluation? Are the underlying scientific question and hypothesis clearly stated and adequately supported by results from previous studies?

   Strengths:
   Weaknesses:

5. Comment on the adequacy and appropriateness of the statistical design and analysis plan for addressing the stated study hypotheses considering aspects such as case selection, timing of measurements, choice of clinical endpoints, sample size and power, and the statistical analysis approach.

   Strengths:
   Weaknesses:

6. Based on the strength of the information presented and your scientific judgment, please indicate your level of enthusiasm for the study:

High				**Low**
1	2	3	4	5

   SCORE: _____

7. Please comment on the attached Budget and Justification if there are any issues relevant to the statistical design or analysis methods. Provide recommendations if needed.

8. Please list any KEY QUESTIONS that the study Principal Investigator could address, which might change your recommendation regarding the BIQSFP proposal.

It is understood that by agreeing to assist in this evaluation, you have no conflicts of interest with this concept. In addition, all unpublished information, reports, and discussions are strictly confidential.