# Study Checklist for CTEP-Supported Early Phase Trials with BIOMARKER ASSAYS

**INSTRUCTIONS: For INTEGRAL assay, respond to Items 1-7.**

**For INTEGRATED assay, respond to Items 1-3 and 5-7.**

**Please submit a response to each of the criteria below and complete one Study Checklist** **for each Biomarker endpoint. Incomplete checklists will not be accepted.**

1. Name of marker and use in the trial (e.g., integral, integrated, or exploratory)1, 2 :
2. For an integral or integrated assay, indicate the role(s) of the biomarker assay in the trial1, 2:
   1. Eligibility criterion
   2. Assignment to treatment
   3. Stratification variable
   4. Risk classifier or score
   5. Other (*please describe in detail here*):
3. List the laboratory(ies) (including institution(s)) in which the proposed assay will be performed and identify the laboratory head or principal investigator1.
4. Integral laboratory assays used for clinical decision-making must be performed in a CLIA-certified facility. For such assays, provide the lab’s CLIA number that is performing the integral biomarker study(ies) and the expiration date of the certificate.
5. Describe the assay:
   1. Specify the analyte(s), technical platform, and sources of assay components (e.g., reagents, chips, and calibrators).
   2. Describe the specimens, and anticipated methods for specimen acquisition, fixation or stabilization, and processing. Provide justification for the timing of specimen collection.
   3. Describe the scoring procedures and type of data to be acquired:

* quantitative/continuously distributed
* semi-quantitative/ordered categorical
* qualitative/non-ordered categorical

1. Provide data on the analytical performance of the assay.
2. 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. 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>
3. 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.
4. Provide data on the clinical utility of the integral/integrated assay as it will be used in the trial:
5. Provide background information that justifies the use of this assay result as a marker for this trial. State the hypothesis and rationale for utilizing the biomarker, with supporting preclinical and clinical data, when available. 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, explain how the magnitude of the association or effect will be measured and provide power calculations for any statistical tests that are planned.

1. Describe the expected distribution of the biomarker in the study population. Justify the number of patients and specimens to determine feasibility and to demonstrate that the studies are likely to produce interpretable results.
2. 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)?
3. Describe the conditions under which treating physicians and or patients will be able to access the biomarker assay results.

**Notes:**

* + 1. This should match the information in the current Biomarker Table for the study.
    2. If the biomarker will have multiple uses in the trial (e.g., integral – eligibility, integrated – looking for resistance mutations), please list both uses and purposes in your answers to Question #1 and #2.

**BRC Study Checklist Instructions**

*Attached is the Study Checklist for CTEP-supported Early Phase Clinical Trials with Biomarker Assays. The purpose of the Study Checklist is to provide CTEP with detailed information about the analytical and clinical performance of each integral or integrated assay proposed for your trial that requires BRC Review. This information will be used by the CTEP Biomarker Review Committee (BRC) to evaluate whether these assays are fit-for-use in a human clinical trial.* ***Submission of this checklist is mandatory for BRC Review.***

**General Instructions:**

* A separate Study Checklist is required for each assay that has been identified as requiring BRC Review. Note: a requirement for BRC Review will be identified in the Biomarker Table in the CTEP-issued LOI Response Letter for the trial.
* The Study Checklist should be completed by the laboratory that will perform the assay.
* Ideally, assay validation will have been completed prior to submission of the Study Checklist. However, if not, we ask that you provide as much information as you can to enable appropriate evaluation of the assay.
* **The BRC Study Checklist will be rejected if data is not provided to support answers to Questions #6-7.**
* **All information submitted in the study checklist will be kept confidential.**

**Step-by-Step Instructions for Questions #5-7:**

* + For Question #5: Detailed description of the assay
  + If a formal SOP exists, it should be submitted along with the Study Checklist to the BRC. **Please note that if an SOP is submitted, it is still necessary to provide a written answer to Question #5 in the Study Checklist, itself.**
  + For Part A provide details about the technical components of the assay, including sources of critical reagents (e.g., antibody vendor and catalog number).
  + For Part B describe methods and justify the timing of specimen collections.
  + For Part C provide details about the planned analysis: scoring methods, controls, gating or image segmentation
  + For Question #6: Analytical performance of the assay
    - Laboratory data (copied into the checklist or sent as a separate document) and/or relevant publications should be provided in support of answers to #6.
  + **Please note, that if publications or a formal validation report are submitted, it is still necessary to provide a written answer to Question #6 in the Study Checklist, itself. Additionally, please clarify how the publication or validation report supports your answer by referencing the relevant figures and/or tables in the Study Checklist.**
  + If published data is cited, please provide a pdf of the publication.
  + If unpublished data is presented, please provide complete labels and legends for figures and tables.
  + The data provided should be from the laboratory that will perform the assay.
  + Ideally, the data provided will be in the tissue/tumor type relevant to the trial.
  + For multiplex assays (e.g., gene panel, protein array) please specify the primary analyte for which pre-analytic and analytic considerations will be optimized and which will be reported for the analysis set forth in the statistical plan for the trial. It is understood that additional analytes will be evaluated and may contribute important information. However, for the purpose of BRC review these evaluations will be considered exploratory. The checklist responses and supporting information will be reviewed to determine that at least the primary analyte will be measured in a manner that is fit for purpose.
    - Study Checklists are often rejected for missing necessary information in answers to Question #6. The examples below are not meant to be a complete list and additional information may be needed depending upon the assay that is being submitted for BRC review.
    - For Part A: describe the analytical performance of the assay
    - What is the assay’s accuracy, precision and reportable range? What are the reference intervals/range (normal values) for the expected patient population?
    - If possible, please provide sample data of results within the expected range, along with the positive and negative controls.
    - Identify any critical preanalytical variables or assay limitations (e.g., analyte stability, requirement for freshly cut slides etc.)
    - For integral biomarkers state the turn-around time and assay failure rate.
    - For pharmacodynamic biomarkers provide data to demonstrate that the assay can reproducibly measure the relevant effect. The data should demonstrate that the assay can detect a change in a signal in the expected range.
  + For Part B: for an assay that will be performed at a single site, please provide data on reproducibility within a run, between runs and across operators. For an assay that will be performed at multiple sites, please follow the Study Checklist instructions.
  + For Question #7:
  + For Part A, the background information should be limited to what is relevant to the proposed study and should be presented succinctly but with sufficient detail to enable evaluation by the reviewers. Avoid indiscriminate cutting-and-pasting from investigator brochures, trial solicitations, or other CTEP communications.
  + For Part B, describe and justify the expected size of the effect of interest (e.g., extent of correlation, pharmacodynamic response). The analytic performance of a fit-for-purpose assay (e.g., sensitivity, precision, dynamic range) will be sufficient to detect this signal, if it exists, over and above background sources of variability.
  + For Part C, provide data if available, to justify the cut points described.
  + **Please note, that if publications are submitted, it is still necessary to provide a written answer to Question #7 in the Study Checklist, itself. Additionally, please clarify how the publication supports your answer by referencing the relevant figures and/or tables in the Study Checklist.**