Components of a Competitive LOI –

How to Write a Strong LOI

Investigators wishing to carry out clinical trials with CTEP IND agents must initially submit a Letter of Intent (LOI), or proposal, which contains a plan for the new clinical research. To ensure that the best science moves forward and that there is the best use of NCI resources, LOIs are evaluated on the basis of a number of criteria including:

* strength of scientific rationale
* supporting preliminary data
* appropriateness of patient population
* adequacy of study design
* quality and relevance of laboratory and imaging correlatives
* ability to accrue and complete study in timely manner
* consistency with CTEP development plan
* whether it would be duplicative of other studies
* agent availability
* industry sponsor concurrence.

# Follow a “Team Science” Approach

CTEP clinical research has a strong focus on molecularly-driven studies that incorporate suitable biomarkers. Because of the complexity of this research, it is necessary to assemble individuals with different kinds of expertise and resources in order to perform the clinical and correlative components of such studies. To address this, a “Team Science” approach, in which scientists and clinicians – whether from the same or from multiple institutions - participate in both the planning and performance of the research. The principal investigator is responsible for selecting a scientific Team.

Although many Team members will be based at participating clinical sites, when appropriate, expertise from other institutions should also be sought out.

Start early and assemble the Team to help in the design. The Team should be comprised of:

* well-qualified clinicians/investigators
* preclinical/basic scientists and cancer biologists
* pathologists, translational medicine and laboratory medicine specialists
* if appropriate, imaging experts
* if appropriate, radiation therapy experts
* statisticians
* budgetary specialists and study administrators.

This Team will have input into the concepts and strategy underlying the proposed research. They will work together at every step – initially consulting upon and contributing to writing the LOI, later consulting on and contributing to writing the protocol and finally, participating in the conduct of the study. The Team should be constituted as early as possible once the general concept for the LOI is determined. Although it is possible that an individual with diverse expertise may be qualified to serve multiple roles on the Team, the intent is to get input from multiple stakeholders, each of whom brings a somewhat different perspective and strength and permits leveraging of the NCI investment in clinical, translational and biological research.

The Team should be aware that CTEP is particularly interested in research that involves:

* biomarker development, molecular profiling, pharmacodynamics, pharmacogenomics/genetics, and experimental imaging
* understanding mechanisms of primary and secondary resistance
* elucidating the increasingly complex signal transduction pathways and how these pathways interact
* novel-novel drug combinations
* special populations who have unmet medical needs
* sequential biopsies to better understand cancer biology and drug efficacy and toxicity − LOIs which do not involve tissue specimen collection may be rated with lower priority scores
* collaborations among institutions to facilitate fruitful intellectual exchanges, better science, comprehensive research (with more interesting correlatives) and rapid accrual to meet or surpass CTEP’s Operational Efficiency Working Group (OEWG) timelines for clinical research.

# Writing the Actual Letter of Intent − Critical Elements

* Be sure to check CTEP’s website for the current LOI Submission form at <http://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm>. This form must be used. Include the critical elements listed below. Clarity and brevity are desirable.

## 1) Rationale and background

* State the study rationale.
* Explain what the unmet need is.
* Explain why the patient population was chosen. Additionally, if a laboratory assay will be used to select or stratify patients, explain why. Explain how the study results could impact on future research.
* Explain why the drug or drug combination (or drug and other therapy) was chosen and any potential safety concerns with the drugs or drug combinations.
* Provide relevant preclinical and clinical information (e.g., with figures, pre-prints, or grant progress reports or applications) as well as relevant published data. Present sufficient detail to be convincing to the reviewer. Draw on Team resources!
* Provide relevant information about agents: mechanism of action, clinical and preclinical experience, ability to combine with other drugs or other modalities of treatment (e.g., radiotherapy).
* When appropriate and available, also include preclinical and clinical information about pharmacokinetics, pharmacodynamics, pharmacogenomics, molecular profiling and biomarkers. Draw on Team resources!
* Don’t cut and paste indiscriminately from material that CTEP has shared or from investigator brochures.
* Be succinct but comprehensive enough to justify the trial and to address issues that may raise reviewer concern. For example, were the preclinical studies conducted with doses of the investigational agent which led to drug levels that are achievable in man? How does the agent compare to other agents that have similar targets and what is the experience with similar agents? For combination studies, what data are there about the safety and efficacy of combination? Does the agent cross the bloodbrain barrier?

## 2) Hypotheses

* Succinctly state the clinical hypothesis(es) for each primary and secondary objective, including those that are primarily exploratory.

## 3) Objectives

* Provide the primary and secondary objectives.
* Verify that you have already provided a hypothesis for each objective.
* Ensure that the study design and statistical section support the objectives.

## 4) Abbreviated eligibility criteria

* Provide key inclusion criteria.
* At a minimum, inclusion criteria should include:
  + patient age
  + performance status
  + definition of adequate organ function and if abnormal organ function permitted - if yes, list abnormal organ function parameters
  + permissible and required prior therapy
  + tumor type
  + integral markers, if any.
* Exclusion criteria may include exclusion of patients taking specific concomitant medications and exclusion of patients with specific co-existing conditions.

## 5) Study design

* Succinctly describe the general study design.
* Describe randomization and stratification schemes.
* Present a user-friendly schema or flow diagram of the study if appropriate.

## 6) Treatment plan

* For each drug, state the dose level(s,) method(s) of administration, and schedule(s).
* If the research is phase 1, provide the dose escalation scheme and definitions of dose-limiting toxicities (DLTs).
* State the duration of treatment, duration of study, and duration of follow-up.
* Note: the Team may elect to combine the study design and treatment plan into one section.

## 7) Integral and integrated biomarkers

* State experience with the assay and assay methods, performance, operating characteristics, and whether the assay will be performed in a CLIA-approved laboratory.
* Use the Study Checklist for CTEP-Supported Early Phase Trials with CTEP-Supported Biomarker Assays at: http://[ctep.cancer.gov/protocolDevelopment/ancillary\_correlatives.htm](http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm).
* In lieu of completing checklist items 5-6, use the biomarker assay templates at <http://www.cancerdiagnosis.nci.nih.gov/diagnostics/templates.htm>.
* Note: if the assay result will be reported to the patient or the patient’s physician at anytime, on or off study, the assay must be performed at a CLIA-approved laboratory.
* Provide specific information, including:
  + test description
  + test methods
  + available analytic performance data, including prevalence of false positives and false negatives and clinical consequences
  + clinical decision points, i.e., cut-off points
  + name and location of laboratory conducting the assay
  + laboratory certification for assay of this complexity level (i.e., CLIA #)
  + primary person to contact about assay information.

Some or all of this information may be omitted if, and only if, reference is made to the relevant BIQSFP Application or an NCI Biomarker Template *and* the referenced documents are attached to the LOI.

* Note: for integral bioassays, FDA CDRH review will be sought to determine whether the use of the assay poses significant risk and whether formal CDRH review will be needed. If the assay has already been presented to FDA CDRH, then please denote.

## 8) Correlative studies

* List the correlative objectives. If appropriate, expand upon, but do not repeat, the information provided in the Rationale/Hypothesis section above.
* For all correlates, complete the tables in the LOI form and provide appendices with additional information about correlates. For each correlate, include the correlate’s lead PI and his/her site in the LOI form. For all correlates, provide a **letter of commitment** from the collaborating laboratory.
* For all *laboratory correlates*, state the assay, tissue or fluid source, timing of specimen collection, and whether specimen collection is mandatory or optional. For all *imaging correlates*, describe the imaging technique, organs to be scanned and timing of images, and whether performing this imaging is mandatory or optional. This information should be inserted into the appropriate tables in the LOI form.
* Add additional text in appendices. For *laboratory correlates*, state experience with the assay and assay methods, performance, operating characteristics, and whether the assays will be performed in a CLIA-approved laboratory.Justify the choice of targets and tissue/body fluid to be evaluated, and include reasons for not looking at other targets/using other assays. *For imaging correlates*, provide details about the technique, experience with the technique, image acquisition process*,* etc. Justify the use of specific imaging. Include input from the Team’s preclinical experts and the persons who will actually perform the assays!
* If funding for sample collection or for assays is being requested, provide the same information *as required for inte*gral markers.

## 9) Projected accrual

* Provide a realistic projected accrual rate. Do not overstate projected accrual rates. Document that the projected accrual rate is realistic by citing accrual to similar completed and ongoing trials in the same or similar patient population.
* Note any competing studies and projected completion dates.
* If accrual rates are likely to be slow, seek collaborations with other institutions prior to writing the LOI. Trials that do not accrue according to reasonable timelines risk closure.

CTEP encourages investigators to establish collaborations that will result in both fewer study closures for failure to meet accrual goals and in earlier trial completion.

## 10) Endpoints/Statistical considerations

* Explicitly state:
* the null and alternative hypothesis(es) for the primary objective(s)
* sample size
* type 1 and 2 errors
* impact on future studies.
* Provide analysis plans for both primary and secondary objectives, including for each correlative. Provide this information, even if the analysis will only be descriptive.
* Include information about which statistical tests will be applied.
* State the projected accrual rate and ensure that the accrual goals are realistic and achievable with current resources.

## 11) References

* Provide references for data which are cited in the text data as well as references for key background/concepts.
* Verify all references.

# LOI Review Process

The Principal Investigator and Study Team should:

* Complete the “LOI Submission Form.”
* Review the LOI content for consistency and clarity.
* Submit the LOI to CTEP’s Protocol and Information Office at [pio@ctep.nci.nih.gov](mailto:pio@ctep.nci.nih.gov).

Once received at CTEP, you can expect that:

* The Investigational Drug Branch (IDB) of CTEP will conduct a Review and Priority Scoring of Clinical and Laboratory Components for:
  + scientific rationale
  + quality of the clinical plan, for example, appropriateness of study design
  + importance of the proposed trial for the further development of the agent, improving scientific understanding of the target and the disease, and/or for providing meaningful patient benefit
  + relevance and appropriateness of correlative studies
  + statistical plan appropriateness
  + feasibility
  + determination of whether the trial is a good use of government resources
  + determination of whether the research is duplicative with other ongoing or proposed studies.

Remember that a quality LOI is likely to benefit from the input of Team Science members!

* A Review of the LOI will also occur at a CTEP Protocol Review Committee (PRC) meeting by the agent-oriented Investigational Drug Branch (IDB,) the disease-oriented Clinical Investigations Branch (CIB), and, as appropriate, the Cancer Imaging Program, the Radiation Research Program, the Cancer Diagnosis Program, the Biometrics Research Branch (statistical plan), the Clinical Trials Monitoring Branch (informed consent, auditing, data reporting), the Pharmaceutical Management Branch (agent description, agent inventory, distribution), and the Regulatory Affairs Branch (regulatory compliance and interactions and agreements with industry collaborators).
* CTEP will send a LOI response letter to the investigator, indicating that CTEP either disapproves or provisionally approves the LOI. If CTEP’s review is favorable, final approval will be contingent on the industry sponsor’s agreement to supply drug.
* If an investigational laboratory assay will be used for an integral biomarker, FDA CDRH review will be sought to determine whether the use of the assay poses significant risk and whether formal CDRH review will be needed.
* CTEP will request a conference call to discuss and to resolve potential issues related to the LOI.

Approximately 1/3 of submitted LOIs receives final approval from CTEP and the industry partner. If your LOI is approved, you have up to 60 days to submit a protocol. Refer to the CTEP website for the most current program information, guidelines, forms, and funding opportunities.

Thank you and good luck!