ETCTN
Experimental Therapeutics Clinical Trials Network
Team Driven. Cancer Therapy Focused.
National Cancer Institute at the National Institutes of Health

TRIAL DEVELOPMENT
Intended for those involved with the development of ETCTN trials

Steps for Developing an ETCTN Trial Concept from Letter of Intent (LOI) to Study Activation

1. Introduction

All ETCTN trials must receive Cancer Therapy Evaluation Program (CTEP) approval prior to activation and enrollment. This information sheet contains an overview of the protocol development process and the timelines that trial conductors must adhere to. CTEP's Protocol Information Office (PIO) manages the entire protocol development process. While an investigator may receive informal communication from various members of CTEP staff and contractors, all official approval and disapproval letters will come from CTEP PIO.

Amendment changes, monitoring, correspondence, and receipt of a final published report are additional tasks of the PIO throughout the lifecycle of the protocol and will be addressed in other information sheets.

All trials conducted under the ETCTN will adhere to Operational Efficiency Working Group (OEWG) timelines. The milestones at various points in the protocol development process are suggested guides, but if the OEWG deadline date is reached prior to protocol activation, then the protocol is automatically disapproved. If a PI wishes to continue development of the trial under the ETCTN, they must submit a new LOI so that CTEP may re-evaluate if the scientific merits still apply. Further information regarding the OEWG timelines may be found here: http://ctep.cancer.gov/protocolDevelopment/OEWG.htm. Once your LOI has been submitted, you can follow the progress of your trial in relation to OEWG timelines via the secure access tab at the top of the CTEP website homepage.

2. LOI Submission

For most early phase CTEP trials, protocol development begins with the submission of a clinical study via a Letter of Intent (LOI). Principal Investigators and Site Coordinators are urged to use the most current LOI form on the CTEP website rather than downloading a local copy for repeated use, as the form may be revised and can result in rejection of an LOI submission if submitted on an out of date form. More in-depth information regarding filling out the LOI form and submitting a competitive LOI may be found here: http://ctep.cancer.gov/protocolDevelopment/docs/competitive_loi.docx.

Principal Investigators may be asked to submit an LOI in response to an approved Project Team Member Application (PTMA) or may have a novel idea for a trial utilizing a CTEP-held agent and submit an unsolicited LOI. A list of CTEP held agents in development may be found here:

http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm. Principal Investigators that are within 7 years of completion of fellowship training may receive additional assistance for LOI development by submitting a Career Development LOI (CrDl). More information regarding the CrDl process may be found here: http://ctep.cancer.gov/protocolDevelopment/letter_of_intent.htm#instructions.

The LOI must be reviewed and signed by the ETCTN grant PI prior to submission to CTEP PIO. Once received by PIO, the LOI will be reviewed by CTEP's Investigational Drug Branch (IDB), the Protocol Review Committee (PRC), and may be reviewed by the NCI Biomarker Review Committee (BRC) if integral or integrated biomarkers are used in the trial or if there is a request for NCI funding for patient sample collection. Review of the LOI at PRC marks the starting of the OEWG clock. From this point, the trial must be activated and open to patient accrual with a target of 210 calendar days, and with an absolute deadline of 450 days.

LOI Outcomes- Once the LOI is reviewed, there are several possible outcomes. The PI and grant PI will receive a decision letter with explicit follow-up instructions depending on the decision below:

- Administrative or Scientific Disapproval- An administrative disapproval is given if the study is duplicative of ongoing studies in CTEP's portfolio, if the pharmaceutical collaborator decides not to supply the investigational agent, or for other non-scientific reasons. A scientific disapproval is given if there are scientific deficiencies in the LOI that CTEP does not believe can be rectified with a revised LOI. There is no further action for the PI to take upon receipt of a disapproval letter.
- On Hold- There are outstanding scientific questions that require resolution before CTEP approval may be given to the LOI. Instructions in the letter should be followed for resubmission. At this time, a conference call will be scheduled to discuss steps to further develop the study (see below). Please note that the OEWG clock does not stop for any hold issues.
- Provisional Approval- CTEP has approved your LOI and has now sent it to the pharmaceutical collaborator so that they may review the LOI and agree to supply drug. A conference call for outstanding issues will be scheduled at this point (see below).
- Full Approval- Once the LOI has been reviewed and approved by the pharmaceutical collaborator, PIO will send a full approval letter. The approval letter will include either an agent specific template or instructions on how to download the generic protocol template. Other agent specific information will also be sent with the approval letter, such as a Comprehensive Adverse Events and Potential Risks (CAEPR) list. The Investigator Brochure will also be sent at this point via a separate email from the Pharmaceutical Management Branch (PMB).

CTEP estimates that the LOI approval stage should take about 60 days to complete.

Conference calls - Once an LOI reaches a status of either on hold, provisional approval, or full approval, a conference call will be set up by CTEP for the investigators and CTEP reviewers to discuss what issues must be addressed in order for the LOI to be approved (for those on hold), as well as any items that may need clarification or discussion for the purposes of writing the protocol. The purpose of the conference calls is to ensure that both sides are in agreement and to avoid unnecessary back and forth between CTEP and the investigators.

3. Initial Protocol Submission

CTEP expects that the initial protocol authoring should take about 60 days to complete to comply with OEWG guidelines. CTEP strongly urges the PI to use the CTEP protocol template provided to minimize the revision process. The protocol must also comply with current FDA electronic submission requirements. By using the CTEP protocol template, the PI can be assured that his/her protocol submission will not be returned for administrative reasons. The initial protocol submission must also be accompanied by the sample Informed Consent and a Protocol Submission Worksheet (PSW). All of these documents may be found on the CTEP website under the tab for Protocol Development.

Once PIO receives the protocol and finds that the submission is complete, it will be scheduled for the PRC. The PI will receive an acknowledgement letter from PIO with the tentative review date. After the review, the PI and the protocol development team will receive a Consensus Review of CTEP's comments and a meeting request for a teleconference to discuss the review of the protocol and further protocol development. The consensus review will also include a Track Changes version of the protocol originally submitted with the CTEP requested changes in the protocol document. This is to cut down on revision time, and the PI is required to use this version of the protocol going forward. Most protocols require one or two revisions after PRC review. The steps for revisions are outlined in the "ETCTN Protocol Revision and Amendment Process Information Sheet." Additionally, if the PI is new to CTEP, the PMB will contact the PI with instructions on how to register as a CTEP PI and will be instructed to complete an FDA Form 1572 for CTEP PMB (for more information, please see the "ETCTN Person Registration and CTEP Identity and Access Management (CTEP-IAM) Information Sheet").

Once all outstanding issues for the protocol have been resolved, CTEP will issue a final on hold letter and will forward the protocol to the FDA if this study is being filed to a new CTEP held IND and then NCI Central Institutional Review Board (NCI CIRB) for their review, once the FDA completes review. The PI will be instructed to complete the CIRB application and submit it directly to the CIRB. For further information regarding CIRB processes, please consult the "ETCTN NCI CIRB Initiative Information Sheet."

The protocol is also sent to NCI's Clinical Trials Reporting Office (CTRO) by PIO so that they can register the trial in ClinicalTrials.gov and obtain an NCT number.

During CIRB review, Theradex, which manages the Clinical Trial Monitoring Service (CTMS) for the ETCTN, including the network's data management activities, will develop the patient enrollment forms in the Oncology Patient Enrollment Network (OPEN) and build the study database in Medidata Rave.

Once CIRB approves the protocol, CTEP submits the protocol to the FDA. Once FDA receipt is confirmed, the final approval letter is issued to the PI. At this time, the protocol may proceed to activation if all requirements are met (see Section 4). PIO will also send a coding letter to the site to ensure that the codes that are used in Medidata Rave and Clinical Data Update System (CDUS) reporting are accurate.

CTEP estimates that the protocol approval stage will take approximately 90-150 days to complete.

4. Protocol Activation

Protocol activation is defined by CTEP as the date when the first patient is eligible to be enrolled in a trial and is the final milestone under the OEWG guidelines. The Lead Protocol Organization must attest to the following conditions in the Cancer Trials Support Unit (CTSU) Regulatory Support System (RSS) to activate the study:

- All agreements that support trial activation are in place.
- Any correlative science issues are resolved.
- One of the following IND scenarios holds true:
    - The protocol has been submitted to an effective ['approved'] IND, as described below-
        - An IND goes into effect (1) 30 days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold OR (2) on earlier notification by FDA that the clinical investigations in the IND may begin [21 CFR 312.40]
        - CTEP will be responsible for providing the IND / IDE# for all trials conducted under CTEP-sponsored INDs.
        - The LPO will be responsible for providing the IND / IDE# in the RSS for all trials with IND/IDE sponsors other than CTEP.
    - The study fulfills all of the criteria for an IND-exempt study as described in 21 CFR 312.2(b)(1) (and Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer [CDER and CBER/FDA])
- Study agent(s) ready for distribution to enrolling site (if applicable).
    - Applicable to LPO sponsored INDs only
- Initial and essential Case Report Forms (CRFs) are ready.
- Databases that support patient enrollment / receipt of initial study form data are deployed.
- At least one site IRB approval corresponding to the latest version of the trial has been received and documented as 'Complied' by the CTSU. For ETCTN trials, this will be satisfied by NCI CIRB approval.

5. For Questions and Support

For questions about submitting protocol-related documents to CTEP, please contact PIO:

- PIO Help Desk: PIO@ctep.nci.nih.gov

For questions regarding the OEWG timelines, please contact the CTEP Project Managers:

- CTEP Project Managers: ncicteppmt@mail.nih.gov

For questions regarding trial activation, please contact the CTSU Regulatory Help Desk:

- CTSU Regulatory Help Desk: 1-866-651-CTSU (2878); CTSURegulatory@ctsu.coccg.org