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

1. Introduction

All ETCTN trials must receive Cancer Therapy Evaluation Program (CTEP) approval prior to activation and enrollment. This page contains an overview of the protocol development process and the timelines to which trial conductors must adhere. 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 report of results to ClinicalTrials.gov are additional tasks of the PIO throughout the lifecycle of the protocol and will be addressed in other informational pages.

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 Principal Investigator (PI) wishes to continue development of the trial under the ETCTN, they must submit a new Letter of Intent (LOI) so that CTEP may re-evaluate if the scientific merits still apply. Further information regarding the OEWG timelines may be found on the OEWG timelines page. Once an LOI has been submitted, the progress of the trial in relation to OEWG timelines may be followed using 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 by submitting a LOI. PIs and Site Coordinators must 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copy for repeated use, as the form may be revised and can result in rejection of an LOI submission if submitted on an out of date form.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 on the LOIs/Concepts page of the CTEP website.

PIs 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 using a CTEP-held agent and submit an unsolicited LOI. A list of CTEP held agents in development may be found on the Agents/Drugs page of the CTEP website. PIs that are within 7 years of completion of fellowship training may receive additional assistance for LOI development by submitting a Career Development LOI. More information regarding the Career Development LOI process may be found on the LOIs/Concepts page of the CTEP website. Before

submitting a Career Development LOI, Early Career Investigators should contact the Investigational Drug Branch Medical Officer(s) for the intended CTEP agent(s) to schedule a preliminary conference.

The LOI must be reviewed and signed by the ETCTN grant PI prior to submission to the 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 within 400 days for new LOIs.

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:

- 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 may be scheduled to discuss steps to further develop the study (see below). Please note that the OEWG clock does not stop for issues requiring a hold.
- Provisional Approval - CTEP has approved the 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 may 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 be available in the Pharmaceutical Management Branch Online Agent Order Processing (OAOP) application.

CTEP estimates that the LOI approval stage should take about 60 days to complete. Most ETCTN studies will have the protocol authored by CTEP's Centralized Protocol Writing Support (CPWS) program in collaboration with the protocol team (e.g. PI and statistician). Once the full LOI approval letter is sent to the study team, CPWS will contact the study team with instructions and information regarding the timeline that must be followed to collaborate with the CPWS.

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 30 days to complete in order to comply with OEWG guidelines. For a protocol not authored by CPWS, CTEP strongly urges the PI to use the protocol template provided with the full LOI approval letter. The protocol must also comply with current FDA electronic submission requirements. By using the CTEP protocol template, the PI can be assured that the 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 section for Protocol Development.

Once PIO receives the protocol and finds that the submission is complete, it will be reviewed by CTEP's internal PRC. 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 conference call to discuss the review of the protocol and further protocol development. 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 Page. Additionally, if the PI is new to CTEP, the Pharmaceutical Management Branch (PMB) will contact the PI with instructions on how to register as a CTEP PI (for more information, visit the Registration and Credential Repository page).

Once all outstanding issues for the protocol have been resolved, CTEP will issue an approval on hold letter and will forward the protocol to the Food and Drug Administration (FDA) if the study is being filed to a new CTEP held Investigational New Drug (IND) and the NCI Central Institutional Review Board (CIRB) for simultaneous review. The PI (or CPWS team) will be instructed to complete the CIRB application and submit it directly to the CIRB. For further information regarding CIRB processes, refer to ETCTN NCI CIRB Initiative Information Page.

The protocol is also sent to NCI's Clinical Trials Reporting Office (CTRO) by PIO in order to 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 issues full approval of the protocol, and CTEP concurs with any CIRB stipulations, CTEP will submit the protocol and consent to the FDA (if it was not previously submitted as part of the IND filing process). Once FDA receipt is confirmed, a study specific template Delegation of Tasks Log (DTL) is approved by CTEP, the Rave build is complete, and other regulatory checks (e.g., drug supply, IND activation) are completed by CTEP, the final approval letter is issued to the PI. For more information about creation of a template DTL, refer to the DTL Template Browser Help (for LPOs) on the Cancer Trials Support Unit members' website. 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 Data Mapping Utility reporting are accurate.

CTEP estimates that the protocol approval stage will take approximately 120-280 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. For ETCTN trials, the attestation statement requirements included below have been met, per CTEP approval. The Lead Protocol Organization (LPO) must attest to the following conditions in the 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 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 (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.
- The study is CIRB reviewed or 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 or regarding OEWG timelines, contact the PIO:

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

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

- CTSU Regulatory Help Desk: 1-866-651-CTSU (2878); CTSURegHelp@coccg.org; CTSU Help Desk hours are 9:00 am – 6:00 pm EST Monday-Friday (excluding holidays)

For questions about the CTSU website and protocol posting, contact the CTSU Help Desk:

- CTSU Help Desk: 1-888-823-5923; CTSUContact@westat.com; CTSU Help Desk hours are 9:00 am – 6:00 pm EST Monday-Friday (excluding holidays)

For questions about the NCI CIRB, contact the CIRB Help Desk:

- CIRB Help Desk: 888-657-3711 or ncicirbcontact@emmes.com

For questions related to agent ordering or study team registration issues, contact the PMB:

- PMB Contacts: (240) 276-6575; pmbafterhours@mail.nih.gov