CTEP Amendment Request Submission Policy

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TABLE OF CONTENTS

1. Amendment Request Submission - General Policy 1
1.1. What is an Amendment Request? 1
1.2. Who can Submit an Amendment Request Submission? 1
1.3. Complete Amendment Request Submissions 1

2. Draft Amendments 3

3. Amendment Approval/Disapproval 3
3.1. Amendment Review Overview 3
3.2. Amendment Approval 3
3.3. Amendment Approval with Recommendations 3
3.4. Amendment Disapproval 4

4. Withdrawing an Amendment 4
4.1. Withdrawing an Amendment 4
4.2. Withdrawing an Amendment for Further Revision 4

5. Editorial or Administrative Updates 5
5.1. What is an Editorial or Administrative Update? 5
5.2. How/when should CTEP be notified of Editorial or Administrative Updates? 6

6. Posting Amendments on the Internet 7

7. Status Updates 7

8. Activation Notice 7

9. Version and Update Dates 8
9.1. Version Date 8
9.2. Update Date 8
9.3. Version Date vs. Update Date 8
9.4. Can other Dates or a Version or Update Number appear on the Title Page of the Protocol? 10
9.5. Are the Version and Update Dates affected by modification of a local milestone date (i.e., IRB approval date, protocol activation date)? 10
9.6. Does CTEP require that all Changes be Tracked and Dated Individually within the Body of the Protocol Document? 10
9.7. Why Version and Update Dating? 11

10. How to Send Amendment Requests 11

11. Modifying Planned Accrual 11

12. IND Safety Reports vs. IND AE Action Letters 12
12.1. IND Safety Reports 12
12.2. IND AE Action Letters 12

13. Comprehensive Adverse Events and Potential Risks List (CAEPR) 12

14. CTEP or FDA Requests for Amendment 12

15. Emergency Approval of an Amendment Request 13

16. Central IRB (CIRB) Amendment Review Process 13

Appendix A: Amendment Request Submission Checklist A-1

Appendix B: Protocol Status Definitions B-1

Appendix C: Index C-1

1. Amendment Request Submission - General Policy

1.1. What is an Amendment Request?

All amendments made to protocols that are CTEP-sponsored (i.e., Cooperative Group or CTEP contract) or utilize a CTEP Investigational New Drug (IND) agent(*must* be approved by CTEP prior to implementation (see section 5 for policies regarding editorial and/or administrative change). Changes to a protocol shall be submitted to CTEP in the form of an Amendment Request. The policies regarding Amendment Requests are described below.

1.2. Who can Submit an Amendment Request Submission?

1.2.1. NCI Cooperative Groups

All Amendment Requests for NCI Cooperative Group studies *must* be routed through the Group operations office. CTEP will *not* accept an Amendment Request that has not been routed through the appropriate local channels (i.e., Cooperative Group or Cancer Center operations office). An Amendment Request that has not gone through the proper channels will be denied and forwarded to your local (i.e., Cooperative Group) operations office.

1.2.2. Other Non-Group Studies

To maintain consistency of the protocol document, CTEP will only accept Amendment Request Submissions that have been signed and approved by the Principal Investigator of a study. Co-investigators cannot submit protocol amendments. Amendment Requests that has not been signed by the Principal Investigator will be denied and returned to the submitter.

Many organizations (i.e., Cancer Centers; Consortia) require that all protocol-related correspondence be routed through a local (i.e., your organization) central operations office. Investigators are encouraged to verify and conform to any local policies or procedures regarding Amendment Request Submissions.

1.3. Complete Amendment Request Submissions

Sections 1.3.1 through 1.3.7 describe the required format and documentation for a complete Amendment Request Submission.

Appendix A: Amendment Request Submission Checklist may be used by your staff to verify that the Amendment Request is complete.

NOTE: The Amendment Request Submission Checklist is for your reference and CTEP does *not* require that the Amendment Request Submission Checklist be included with your submission.

Amendment Requests that are incomplete will be placed on-hold and the site contacted to submit the missing information. The Amendment Request will *not* be processed or reviewed by CTEP until all required documentation is submitted. If all documentation is not received within seven days, the Amendment Request will automatically be disapproved.

1.3.1 Amendment Request Cover Letter

The Amendment Request Cover Letter shall identify by page and section each change made to a protocol document. All changes shall be described in a point-by-point format (i.e., Page 3, section 1.2, replace 'xyz' and insert 'abc'). Page numbers should reflect the clean, unmarked copy of the protocol document. When appropriate, a brief justification for the change should be included.

1.3.2 New Version Protocol Document

A revised, unmarked (without handwritten notes or highlights) copy of the protocol document that accurately reflects the Amendment Request Cover Letter. The following must be included with the protocol document:

1.3.2.1 All protocol attachments listed in the Table of Contents regardless of whether any changes occurred to these sections.

Exception: If the Case Report Forms (CRFs) are identified in the Table of Contents and the amendment does not affect the CRF, you do *not* need to include the CRF in the Amendment Request Submission packet. The Amendment Request Cover Letter should indicate that no changes were made to the CRFs.

1.3.2.2 The entire Informed Consent regardless of whether any changes occurred to this document.

1.3.3 Supporting Documents

Ancillary supporting documentation as required (i.e., IRB approval for addition of a new institution to a non-Cooperative Group study), should be provided.

1.3.4 Version Date

The protocol title page shall include a Version Date that reflects the most recent Amendment Submission to the study (see section 9.1 for more information on Version Dates).

1.3.4.1 Version Dating throughout Protocol Document

Local (i.e., your organization) policy may require inclusion of a Version Date associated with each individual change *throughout* the protocol document. (NOTE: CTEP only requires a Version Date on the protocol cover page.) If local policy requires inclusion of Version Dates throughout the protocol document, then the date changed for each line item *must* be included in the Amendment Request Cover Letter. Example:

- Page 5, section 2.1: Has been changed from "PK samples will be sent to 123 Main St., Anytown, USA" to "PK samples will be sent to 456 Broadway, Anytown, USA. This change was made effective ##/##/####."

1.3.5 Update Date

If your organization takes advantage of CTEP's Administrative/Editorial Update policy (see section 5), the protocol title page *must* include an Update Date to reflect the date of the most recent change to the study (see section 9.2 for more information on Update Dates).

1.3.6 CTEP or FDA Request for Change

If the amendment is in response to a CTEP or Food and Drug Administration (FDA) request for change, the CTEP or FDA request shall be included by the Principal Investigator or Study Chair as part of the Amendment Request Submission packet, or referenced in the Amendment Request Cover Letter.

1.3.7 Optional

In addition to the above, you may include a revised copy of the protocol with all changes specified in the Amendment Request Cover Letter highlighted throughout the document utilizing a word-processing program.

2. Draft Amendments

CTEP will *not* accept a draft of a proposed amendment. There shall be no indication anywhere in the protocol document that it is a draft (i.e., document stamped 'draft'). Documents stamped 'draft' will be returned to the investigator without CTEP review.

3. Amendment Approval/Disapproval

3.1. Amendment Review Overview

Amendments are approved or disapproved by CTEP and most IRBs as a packet. Each line item of an amendment is reviewed on its individual merit. Approval of an amendment requires acceptance of each individual change included in the Amendment Request Submission. Therefore, amendment approval is an all or nothing proposition.

3.2. Amendment Approval

If CTEP finds all protocol changes acceptable, an 'Amendment Approval' letter will be sent to the Principal Investigator or their designee. Once the approval letter is received, the changes can be distributed to the study participants.

3.3. Amendment Approval with Recommendations

Occasionally CTEP staff will provide recommendations for future changes along with the Amendment Approval letter. These recommendations are suggestions for future amendments. There is no requirement for any action. The site may elect to resubmit another amendment to address the suggested changes or they may elect to ignore the recommendation.

3.4. Amendment Disapproval

In the event that CTEP finds one or more of the line items of an Amendment Request Submission unacceptable, the entire amendment will be disapproved. The Disapproval Letter will include a brief justification that identifies which line item(s) was not acceptable and why. The site can resubmit a new amendment that:

- Corrects the issues described in the Disapproval Letter.
- Provides additional justification to support the original request.
- Includes all line items that CTEP found acceptable, less the line items that CTEP specifically disapproved.

The revised amendment will be treated as a new Amendment Request Submission and therefore must include all the appropriate documentation (see section 1.3) including a new Version Date, and, if required, a new Update Date shall be inserted on the protocol title page (see sections 9.1 and 9.2). To streamline the review process, CTEP would recommend that the site briefly describe how the amendment was revised. Although the revised amendment will be treated as a new document, CTEP will attempt to minimize unnecessary duplicative reviews whenever possible.

On occasion, CTEP may contact an investigator or their designee to clarify and/or correct a minor issue or discrepancy rather than sending a formal Disapproval Letter. In this case, a new complete Amendment Request Submission is not required. The site shall make the change and resubmit the corrected protocol. A new Version Date, and, if required, a new Update Date shall be inserted on the protocol title page (see sections 9.1 and 9.2).

4. Withdrawing an Amendment

4.1. Withdrawing an Amendment

Any amendment that has been submitted to CTEP and that is still in the review process may be withdrawn by the Principal Investigator or their designee. The request for withdrawal must be made in writing. NOTE: Once an amendment has been approved by CTEP, it cannot be withdrawn. In the event that a site requires that a previously approved amendment be revised, then they must submit a new Amendment Request that conforms to the policies and procedures outlined in this document to further modify the protocol document.

4.2. Withdrawing an Amendment for Further Revision

If the Principal Investigator or their designee identifies that an amendment, that has been submitted to and is currently still being reviewed by CTEP (i.e., CTEP has not approved or disapproved the amendment), requires further changes, the site has two options:

First, the site may contact CTEP's Protocol and Information Office (PIO) (PIO@ctep.nci.nih.gov) and request that the original amendment be withdrawn. The site may then resubmit a new amendment with whatever corrections or additions that were identified in the Amendment Request Cover Letter (see section 1.3.1). A new Version Date and, if required, a new Update Date shall be inserted on the protocol title page (see sections 9.1 and 9.2). Although the revised amendment will be treated as a new document, CTEP will attempt to minimize unnecessary duplicative reviews whenever possible.

If acceptable to your local IRB, the second alternative is to wait for final approval of the original amendment and then submit a second amendment for CTEP review. Once CTEP approval has been obtained for both amendments, the site may combine the changes described in the Amendment Request Cover Letters into a single document to notify their investigators and/or IRBs.

NOTE: Once an amendment has been approved by CTEP it cannot be withdrawn. In the event a site desires to reverse an amendment that has previously been approved by CTEP, they must submit a new Amendment Request Submission as per standard procedure to request further modification to the study.

5. Editorial or Administrative Updates

5.1. What is an Editorial or Administrative Update?

Editorial or administrative updates are those changes to a protocol document, including the Informed Consent, that do *not* affect the scientific intent of the study, study design, patient risk, or human subject protection. Editorial or administrative updates can be made *without* prior CTEP or CIRB review and approval. Investigators should follow local IRB policy and procedures regarding editorial or administrative updates. The protocol title page should reflect the latest Update Date and, if required, the Version Date (see section 9.1 and 9.2).

Any change to the protocol document or Informed Consent that affects the scientific intent, study design, patient safety, or human subject protection is considered an amendment, and therefore *must* be approved by CTEP and your IRB prior to implementation.

Examples of conditions that CTEP considers editorial or administrative updates are:

- Typographical correction, except if the change results in a change in patient risk (i.e. change eligibility from < to > XYZ; or change dose from mg to mcg).
- Rephrasing a sentence or section to add clarity as long as the change does *not* affect the scientific intent, study design, patient risk, or human subject protection.
- Reformatting the document as long as the change does *not* affect the scientific intent, study design, patient risk or human subject protection.
- Address, telephone, or e-mail changes, except changes to the Principal Investigator or Protocol Chair contact information.

  Note: CTEP should be notified through the FDA form 1572 of any change in address for any investigator (principal or co-investigator) identified on the title page of a study that utilizes a Pharmaceutical Management Branch (PMB)-supplied agent.
- Addition/deletion of physician co-investigators to studies that do *not* utilize a PMB-supplied agent.
- Addition/deletion of non-physician co-investigators to any trial.

- Addition/deletion of an institution to a CTEP U10 Cooperative Group 'Group-wide' study.
- Standardization of protocol language inconsistencies, as long as the change does *not* affect the scientific intent, study design, patient risk or human subject protection.

Protocol changes that do *not* meet the above examples of conditions should be considered amendments and therefore *must* be submitted and approved by CTEP in the form of an Amendment Request prior to implementation. To add further clarity, the following protocol changes are considered amendments and therefore require prior CTEP approval:

- Typographical correction that may affect patient safety (i.e., change eligibility from < to > XYZ; change dose from mg to mcg, or risk, regardless of whether risk is increased or decreased). See emergency approval (see section 15) regarding expedited approval of emergent changes required to ensure patient safety.
- Addition/deletion of an institution to a CTEP U10 Cooperative Group 'limited institution' study if the participants are individually named on the title page of the study.
- Addition/deletion of physician co-investigators to studies that utilize a PMB-supplied agent.
- Rephrasing a line or section that results in a change of scientific intent, study design, or affects human subject protection.
- Reformatting the document that results in a change of scientific intent, study design, or affects human subject protection.
- A change of Protocol Chair or Principal Investigator.
- A change of institution for the Principal Investigator or any physician co-investigator on a study with a PMB-supplied agent.
- The addition/deletion of a Cooperative Group to an intergroup study.
- A change in accrual targets.

5.2. How/when should CTEP be notified of Editorial or Administrative Updates?

CTEP may be informed of editorial or administrative updates, in one of three ways. The first two methods are preferred because they will reduce everyone's workload. CTEP should be informed, through the Amendment Request Submission process of editorial or administrative updates within at least one-year of the modification:

- Batch – All editorial or administrative updates for a given study during the year can be assembled together and reported at one time.
- Combine with scientific, study design, or human subject protection amendments – Editorial or administrative updates can be incorporated into an amendment that relates to scientific or human subject protection issues.

- PRN – As the changes occur, an editorial or administrative update can be submitted to CTEP.

When an editorial or administrative update is formally submitted to CTEP, it is considered an Amendment Request and must comply with all guidelines for an Amendment Request Submission (see section 1). Editorial and administrative amendments will receive an expedited CTEP review.

6. Posting Amendments on the Internet

Only CTEP-approved amendments may be posted on the Internet for general notification of their membership and participants for implementation. Exception: editorial or administrative updates (described above) may be posted on the Internet without prior CTEP or CIRB approval. Prior to CTEP approval, amendments may only be distributed in a limited manner to those individuals that are required to review and assess the requested changes. Alternatively, drafts of amendments may be posted for organization-wide review and consideration as long as it is clearly identified as draft and that the changes cannot be implemented until CTEP approval has been obtained.

7. Status Updates

Status changes are not amendments per se. CTEP should be notified regarding any change in protocol status in a timely fashion. In general, CTEP would recommend that status changes not be incorporated with other protocol changes (amendments). CTEP would recommend that investigators utilize the CTEP PIO Status Update Form (available from the Forms page of the CTEP Web site) to notify the NCI of protocol status changes. Other forms of communication are acceptable, (i.e., e-mail) as long as they use the CTEP terms and definitions for protocol statuses. All Clinical Data Update System (CDUS) submissions should be consistent with the latest protocol status notification. The CTEP terms and definitions for protocol status are located in Appendix B.

8. Activation Notice

The Principal Investigator or Protocol Chair shall notify CTEP when a study is ready to be activated. An active study is defined as a study that is open to accrual. An Activation Notice is an administrative means to notify CTEP of the change in status; formal CTEP approval of such a notice is not required prior to actual activation of the study. CTEP strongly discourages the incorporation of other changes in an Activation Notice, but a site may still include them if they so choose.

If a site incorporates other changes, including administrative and editorial changes with the Activation Notice, the document will be treated as an Amendment Request Submission. Therefore, the study *cannot* be activated or any changes implemented until CTEP has approved the amendment. CTEP would recommend that sites take advantage of the Administrative or Editorial Update policy and *not* include changes that meet these guidelines with the Activation Notice. If a site takes advantage of CTEP's Administrative or Editorial Update policy, they may activate their studies without delay and in parallel make whatever administrative or editorial changes necessary without prior CTEP approval.

9. Version and Update Dates

9.1. Version Date

The Version Date is the day that reflects the most recent Amendment Submission to CTEP. The Version Date shall approximate the date the amendment was submitted to CTEP or the CIRB. The Version Date, though, may be assigned by some other mechanism as per local policy (i.e., the date the Principal Investigator or Study Chair approved amendment). CTEP and others (i.e., Institutional Review Board [IRB], Central IRB [CIRB], Cancer Trials Support Unit [CTSU], local institutions) will use the Version Date to identify the latest edition of a protocol document. The Version Date, including the month, day, and year (i.e., Version: ##/##/####), shall be clearly identified on the protocol title page. The Version Date is required on the protocol title page for all original protocol submissions and all revisions and amendments. If a protocol requires further modification based on comments received during the review process, then the Version Date shall be modified to reflect the most recent Amendment Request Submission.

9.2. Update Date

If your organization takes advantage of CTEP's Administrative/Editorial Update policy (see section 5), the protocol title page *must* include an Update Date. If your organization chooses *not* to take advantage of CTEP's Administrative/ Editorial Update policy, you are *not* required to include the Update Date on the protocol title page. The Update Date reflects the most recent change to a protocol document. The Update Dates must be adjusted whenever a protocol document is modified. The Update Date shall be clearly identified on the protocol title page and include the month, day, and year (i.e., Update: ##/##/####). The Update Date is intended to allow ready identification of a study that has been modified since the last CTEP review.

9.3. Version Date vs. Update Date

Version Dates are adjusted whenever an Amendment Request is submitted to CTEP. Update Dates are adjusted whenever a site modifies a protocol document. Therefore:

- Version Date = Amendment Submission
- Update Date = Protocol modification

NOTE: The Update Date is only required of those sites who take advantage of CTEP's Administrative/Editorial Update policy (see section 5). If you elect to submit all protocol changes to CTEP, including Administrative and Editorial Updates, then by definition the Version and Update dates will be analogous (Version Date ~/= Update Date). Therefore, if your organization chooses *not* to take advantage of CTEP's Administrative or Editorial Update policy, you are *not* required to include the Update Date on the protocol title page.

A Version Date must change whenever an Amendment Request is submitted to CTEP. The Version Date shall always reflect the last Amendment Request submission to CTEP. The Version Date will change whenever an Amendment Request is submitted to

CTEP regardless of the nature of the change (i.e., editorial, administrative, scientific, safety, etc.).

If a site utilizes CTEP's Administrative/Editorial Update policy, then the protocol title page must contain an Update Date as well as a Version Date. The Update Date is adjusted whenever the protocol document is modified regardless of the nature of the change (i.e., editorial, administrative, scientific, safety, etc.).

Version and Update Dates shall be adjusted independently of one another based on the policy described above. If local policy requires that the Update Date be modified whenever the Version Date is adjusted, then local policy should be followed.

The following scenario provides an example regarding how to use Version and Update Dates.

- *Baseline*: Study approved on July 1, 2003. Title page reflects a Version Date and Update Date of 7/1/03.
  - Version Date – 7/1/2003
  - Update Date – 7/1/2003
- *Administrative/Editorial Update*: On July 25, 2003, the PI notices that the statistician's phone number is incorrect on the title page of the protocol. Rather than submit an amendment to CTEP, the PI elects to take advantage of CTEP's Administrative or Editorial Update policy. The PI corrects the statistician's phone number and changes the Update Date to reflect the date of the change (i.e., 7/25/03). Since the change was not submitted to CTEP, the Version Date remains unchanged (7/1/03).
  - Version Date – 7/1/2003
  - Update Date – 7/25/2003
- *Administrative/Editorial Update*: Over the course of the next few months, the PI makes several other minor modifications to the protocol that match the criteria within the Administrative or Editorial Update policy (ex. reformatting; typo correction; etc.). Whenever he modifies the protocol, he also adjusts the Update Date. The last Administrative change occurs on 10/31/03.
  - Version Date – 7/1/2003
  - Update Date – 10/31/2003
- *Amendment Submission without any new protocol modification*: In December, the PI decides to notify CTEP regarding all the changes that have occurred to the study during the previous 5 to 6 months. No additional changes have occurred to the study since October 31. The PI prepares an Amendment Request Submission packet that details each of the changes that occurred over the last six-months in a point-by-point fashion. In addition, he modifies the Version Date to reflect that the changes (i.e., 12/15/03) have been submitted to CTEP via the Amendment Request process. Since no additional protocol changes have occurred since the last protocol modification, the Update Date should remain unchanged.
  - Version Date – 12/15/2003
  - Update Date – 10/31/2003

- *Amendment Submission with new changes*: In March, the PI decides to adjust the treatment regimen based on Adverse Events that have been reported on the study. He prepares an Amendment Request Submission packet as per the SOP, including adjustment of both the Version and Update Dates to reflect when the Amendment Request was submitted to CTEP (the Version Date) and when the study was modified (the Update Date).
    - Version Date – 3/15/2004
    - Update Date – 3/15/2004

9.4. Can other Dates or a Version or Update Number appear on the Title Page of the Protocol?

Based on local (i.e., your organization) policy, other dates, milestones (i.e., CTEP approval, IRB approval, activation, amendment effective date, etc.), and version numbers (a sequential number that identifies the latest amendment) *may* be included on the title page of the study. The Version Date and Update Date shall be clearly identified to distinguish them from any other dates on the title page of the protocol.

9.5. Are the Version and Update Dates affected by modification of a local milestone date (i.e., IRB approval date, protocol activation date)?

No, if local (i.e., your organization) policy requires the inclusion of other dates, (i.e., CTEP approval, IRB approval, activation, etc.) on the protocol title page, you should *not* modify the Version or Update Dates as these other milestone dates are changed. For example, if local policy requires recording the IRB approval date on the protocol title page:

- Record the IRB approval date, on the protocol title page of the study once IRB approval has been obtained.
- Do *not* modify the Version or Update Dates to reflect the recording of the IRB approval milestone.

All other changes should result in either a change to the Version or Update Date or both.

9.6. Does CTEP require that all Changes be Tracked and Dated Individually within the Body of the Protocol Document?

CTEP does *not* require that all editorial and administrative changes be dated individually within the body of the protocol document. CTEP requires that the protocol title page reflect the most recent Version Date. If your organization takes advantage of CTEP's Administrative or Editorial Update policy, the protocol title page *must* also include the Update Date.

If local (i.e., your organization) policy requires dating of individual editorial or administrative updates within the body of the protocol:

- For editorial or administrative updates:
    - Note date of change in the body of the protocol.

- Modify the Version and/or Update Dates on the protocol title page.

- For editorial or administrative updates when submitted with an Amendment Request:
  - The Version Date shall be modified to reflect the most recent Amendment Request Submission.
  - The Amendment Request Cover Letter *must* include the date the change took place for each line item. For example:
    - Page 5, section 2.1: Has been changed from "PK samples will be sent to 123 Main St., Anytown, USA" to "PK samples will be sent to 456 Broadway, Anytown, USA. This change was made effective ##/##/####."

9.7. Why Version and Update Dating?

Substantial delays and confusion are frequently encountered because of the inconsistent approach to amendment numbering and dating. This confusion often results in delays in amendment reviews and approval. The problem stems from the inability of all parties to effectively track the 'active' version of an amendment or protocol. It is common for amendments to go through multiple iterative review cycles until approved. The allowance of investigators to make minor modifications to their studies without prior CTEP approval via the Administrative/Editorial Update Policy further complicates the version control issue. The Update Dates are intended to allow ready identification of a study that has been modified since the last CTEP review. Without appropriate version control, the amendment review process is often very cumbersome. A heightened awareness of this issue has resulted from the involvement of the CIRB and CTSU in the amendment review and approval process.

10. How to Send Amendment Requests

CTEP strongly recommends that all Amendment Request Submissions be sent via e-mail to the PIO (PIO@ctep.nci.nih.gov). All appropriate documentation for the Amendment Request *must* be included in the e-mail (see section 1.3). The preferred format is Microsoft Word®, but CTEP will accept most major file formats including Corel WordPerfect®, Portable Document Format (PDF), and ASCII.

Amendment Requests should *not* be sent via multiple different mechanisms (i.e., e-mail, express courier, U.S. mail, etc.), as this will cause delays in processing times.

11. Modifying Planned Accrual

If the study accrual goals are modified, then the appropriate sections of the protocol document (i.e., the statistical section) should modified accordingly. In addition, revised race and ethnicity targets corresponding to the new accrual goals must be provided. The CTEP Protocol Submission Worksheet (PSW) should be used to provide the revised race and ethnicity accrual targets.

12. IND Safety Reports vs. IND AE Action Letters

CTEP informs investigators of Adverse Events (AE) observed with a CTEP IND agent(via two different mechanisms, IND Safety Reports and IND AE Action Letters. The requirement for amending studies differs between the two types of notifications.

12.1. IND Safety Reports

IND Safety Reports keep investigators apprised of those expedited adverse event reports that have been filed to the FDA by CTEP. Investigators are requested to file a copy of the report with their protocol and to send a copy to their IRB according to local IRB policy and procedure. CTEP does *not* require that the protocol and/or Informed Consent document be modified based on an IND Safety Report(.

12.2. IND AE Action Letters

IND AE Action Letters(are issued by CTEP for serious AEs that warrant a change in the Informed Consent document and/or protocol. The letter will specify if accrual to the protocol is to be suspended until the revision is made and whether previously enrolled patients, who are still on study, require reconsenting. Investigators are provided a timeframe (typically 30 days) for which to submit an Amendment Request to CTEP's Protocol and Information Office. To assure patient safety, investigators should forward the IND AE Action letter to local IRBs and co-investigators prior to submission of the formal amendment to CTEP and the IRB.

13. Comprehensive Adverse Events and Potential Risks List (CAEPR)

The *Comprehensive Adverse Events and Potential Risks* list (CAEPR) represents a summary of *all* expected and potential Adverse Events (AE) for a CTEP IND agent.(It will include human data, when available, and may include pertinent animal data. It is written using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 language. The AEs considered expected for reporting purposes (the former Agent Specific Expected Adverse Event List [ASAEL] items) will be contained within the CAEPR but will be highlighted (using bold and italic text). The CAEPR list will be sent to the Principal Investigator or Study Chair as part of the Letter of Intent (LOI) or Concept approval packet for studies that utilize a CTEP IND agent. The CAEPR list should be inserted into the protocol in its entirety. It should not be altered in any way.

The CAEPR list serves as the basis for AEs that should be included in the Informed Consent.

The Informed Consent may not need to include all the events in this list, but should include the reported AEs that are appropriate for the specific treatment regimen and patient population involved. (Note: For Phase 1/2 trials involving investigational agents with limited safety data, all reported adverse events from the list must be included.)

14. CTEP or FDA Requests for Amendment

As the IND (or trial sponsor, CTEP *may* on occasion request that a study be modified. The FDA, as a regulatory agency, may also require that a study be modified. CTEP will notify the study Principal Investigator or Study Chair regarding the issues that require amending. The

letter will describe what changes are required, when the Amendment Request Submission is required, and any other details (i.e., temporary study closure, IRB notification, etc.). An Amendment Request in response to a CTEP or FDA request should *not* incorporate other protocol changes. The CTEP or FDA request shall be included by the Principal Investigator or Study Chair as part of the Amendment Request Submission packet, or referenced in the Amendment Request Cover Letter.

15. Emergency Approval of an Amendment Request

An investigator may contact CTEP by telephone to obtain emergency approval of a change in those rare circumstances where an immediate change is necessary to assure patient safety (new toxicity data has become available, correction of a typo in the treatment section, etc.). The point of contact will typically be the CTEP Investigational Drug Branch physician responsible for the investigational agent utilized on the study. If CTEP staff is unavailable (i.e., holiday), the change can be made and implemented without CTEP prior approval. CTEP should be notified by telephone on the next working day, regarding any emergency change. In those rare circumstances where emergency approval is obtained, a follow-up, written Amendment Request describing the change(s) must be submitted to CTEP's PIO within three working days.

16. Central IRB (CIRB) Amendment Review Process

Amendments for all CTEP-sponsored phase 3 trials are reviewed by the NCI Central IRB (CIRB). NOTE: CIRB does not apply to Division of Cancer Prevention (DCP), Cancer Imaging Program (CIP), or Radiation Resources Program (RRP)-sponsored trials. The CIRB review process is separate and distinct from the CTEP review process. With the exception of the editorial and administrative changes (see section 5), all amendments for CTEP-sponsored phase 3 trials require *both* CTEP and CIRB approval prior to implementation. As per CTEP's Amendment Request Submission policy, editorial and administrative updates can be made without prior CTEP or CIRB review and approval (see section 5). The CTEP/CIRB reviews occur in a sequential fashion. The process is as follows.

Amendment Request Submission –

The Amendment Request is submitted to CTEP's PIO as per CTEP and local policies and procedures.

CTEP Review –

CTEP will review the document as per standard operating procedure. If the amendment is acceptable to CTEP, and it meets the above criteria (CTEP-sponsored phase 3), it will be forwarded to the CIRB for review. CTEP will send the investigator a notification that the study is 'approved on-hold pending CIRB review.' NOTE: The amendment *cannot* be implemented until the Principal Investigator or Study Chair receives final confirmation of approval from CTEP.

CIRB Review –

All correspondence during this stage will be between the CIRB and the Lead organization (i.e., NCI Cooperative Group. To avoid a conflict of interest CTEP is not involved in any communication between the CIRB and the site. The CIRB will directly contact the study Principal Investigator or Study Chair to resolve any CIRB questions. The investigator

will provide a cover letter that addresses each of the CIRB comments and recommendations in a point-by-point fashion (similar to the process used to respond to a CTEP protocol consensus review). The protocol document shall be modified in conjunction with the cover letter. The Version Date on the protocol title page shall be modified to reflect the most recent Amendment Submission to CTEP. NOTE: The CIRB has an expedited review process for administrative or editorial changes.

The study Principal Investigator or Chair response shall address only the CIRB comments and questions. The inclusion of additional investigator initiated changes, beyond what the CIRB requested, will result in delays. If the Principal Investigator or their designee identifies that an amendment, that has been submitted to and is currently still being reviewed by CTEP or the CIRB (i.e., CTEP has not approved or disapproved the amendment), requires further changes, the site should either withdraw the current amendment and resubmit a revised document or wait until they have a response (i.e., approval) from CTEP before submitting a second amendment with the additional changes (see section 4).

CIRB Approval –

Once the CIRB is satisfied with the study, the CIRB will notify both CTEP and the study Principal Investigator or Study Chair. NOTE: The amendment *cannot* be implemented until CTEP has sent an amendment approval letter to the study Principal Investigator or Study Chair.

The CIRB will forward their approval letter and if needed the revised protocol document to CTEP. If necessary, the CIRB will include a summary of changes that have been made since CTEP review.

CTEP Final Review and Approval –

CTEP will assess any CIRB initiated changes. If the changes are found to be acceptable then CTEP will send the Principal Investigator or Protocol Chair an 'approval letter' and the changes may be implemented. If there is any issue with the CIRB initiated changes, then CTEP will contact the investigator and the CIRB to resolve any pending issues.

Appendix A: Amendment Request Submission Checklist

Protocol and Information Office
Cancer Therapy Evaluation Program, DCTD, NCI
Executive Plaza North, Rm. 7000
Rockville, MD 20892
pio@ctep.nci.nih.gov

Amendment Request Submission Checklist

NCI Protocol #: Organization (local) Protocol #

DID YOU INCLUDE THE FOLLOWING?

Check all that apply:

☐ A detailed cover letter that clearly identifies, by page AND section each change made to a protocol document. All changes will be listed and described in a point-by-point format (i.e., Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate, a brief justification for the change should be included.

☐ A revised un-marked (without handwritten notes or highlights) copy of the protocol document that accurately reflects the Amendment Request Cover Letter. INCLUDING:

- All protocol attachments listed in the table of contents regardless of whether any changes occurred to these sections.
- The Informed Consent regardless of whether any changes occurred to this document.

Note: If Case Report Forms (CRFs) are identified in the Table of Contents and the amendment does not affect the CRF, you do not need to include the CRF in the Amendment Request Submission packet. The Amendment Request Cover Letter should indicate that no changes were made to the CRFs.

☐ The protocol title page shall include a Version Date that reflects the most recent Amendment Submission to CTEP.

☐ If your organization takes advantage of the CTEP's Editorial/Administrative Update policy (see section 5), the protocol title page *must* include an Update Date to reflect the date of the most recent change to the study (see section 9.2 for more information regarding update dates).

☐ If the amendment is in response to a CTEP or FDA request for change, the original change request letter should be attached or referenced.

☐ OPTIONAL – In addition to the above, the site may include a revised copy of the protocol with all changes specified in the Amendment Request Cover Letter highlighted throughout the document.

Amendment Requests that do NOT include ALL the above documentation will be placed on-hold and the site contacted to submit the missing information. The Amendment Request will NOT be processed or reviewed by CTEP until all required documentation is submitted.

Appendix B: Protocol Status Definitions

CDUS Code	Status Term	Status Definition
AP	*Approved*	Trial has official CTEP approval.
AC	*Active*	Trial is open to accrual.
TC	*Temporarily Closed to Accrual*	Trial is temporarily not accruing.
TB	*Temporarily Closed to Accrual and Treatment*	Trial is temporarily not accruing and patients are not receiving therapy.
CL	*Closed to Accrual, Patients still on Treatment*	The protocol has been closed to patient accrual. Patients are still receiving therapy.
CB	*Closed to Accrual, All Patients have Completed Treatment*	The protocol has been closed to patient accrual. All patients have completed therapy, but patients are still being followed according to the primary objectives of the study. No additional investigational agents are needed for this study.
CP	*Completed*	The protocol has been closed to accrual, all patients have completed therapy, and the study has met its primary objectives. A final study report/publication has been submitted to CTEP.
AD	*Administratively Completed*	The protocol has been completed prematurely (e.g., due to poor accrual, insufficient drug supply, IND closure). The trial is closed to further accrual and all patients have completed protocol treatment. A final study report is not anticipated.

Note: The code 'RE' (Reactivated) is no longer a valid option for current protocol status.

Appendix C: Index

1-year turnaround.....6
30-day timeframe.....12
3-day turnaround.....13
7-day turnaround.....1

A

acceptance.... 1, 3, 4, 5, 7, 11, 13, 14
accrual.....7, 12
accrual goal/target.....6, 11
accrual suspension 12
action letter 12
activation notice.....7
active.....7, 11
address 5
administrative change/update 1, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14
Administrative or Editorial Update policy..... 3, 7, 8, 9, 10, 11, 13
Adverse Event (AE).....10, 12
AE action letter.....12
agent 1, 5, 6, 12, 13
Agent Specific Expected Adverse Event List (ASAEL).....12
amendment effective date 10
amendment page numbers.....2
Amendment Request Cover Letter 2, 3, 4, 5, 11, 13
Amendment Request Submission Checklist.....A-1
amendment withdrawal.....4, 5, 14
ancillary supporting documentation 2
animal data.....12
approval 1, 2, 3, 4, 5, 6, 7, 10, 11, 13, 14
approval letter 13, 14
approval packet.....12
approved on-hold.....13
ASAEL 12
ASCII.....11
attachments 2
automatic disapproval.....1

B

batch 6

C

CAEPR 12
Cancer Center 1
Cancer Imaging Program (CIP) ...13
case report forms.....2
CDUS 7
Central Institutional Review Board (CIRB)..... 5, 8, 11, 13, 14
Central Operations Office.....1
CIP.....13
CIRB..... 5, 8, 11, 13, 14
Clinical Data Update System (CDUS)..... 7
Clinical Trial Support Unit (CTSU) 8, 11
co-investigator.....1, 5, 6, 12
comment.....8, 14
Common Terminology Criteria for Adverse Events (CTCAE) v3.0 12
Comprehensive Adverse Events and Potential Risks List (CAEPR) . 12
concept..... 12
consensus review..... 14
consortia..... 1
contact information 5
Cooperative Group.....1, 6, 13
Corel WordPerfect 11
cover letter 2, 3, 4, 5, 11, 13, 14
CTCAE v3.0 12
CTEP..... 13
CTEP contract..... 1
CTEP IND agent.....1, 12
CTEP request 12, 13
CTEP-sponsored 1, 13
CTSU 8, 11

D

date of amendment approval 8
date of change/update.....3, 9, 10
date of IRB approval 10
date of line item update.....2, 11
dates included on title page 10
day.....8, 13
DCP..... 13
delay.....7, 11
deny..... 1
designee 3, 4, 14
disapproval letter..... 4
disapprove.....3, 4, 14
distribute 3
Division of Cancer Prevention (DCP)..... 13
document page numbers..... 2
draft amendment 3, 7
duplicate reviews..... 4

E

editorial change/update .1, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14
e-mail 5, 7, 11
emergency approval 13
ethnicity accrual goal/target 11
examples 2, 5, 6, 9, 10, 11
exception..... 2, 7
express courier 11

F

FDA 3, 5, 12, 13
FDA form 1572 5
FDA request 13
final approval..... 5
Food and Drug Administration (FDA)..... 3, 5, 12, 13
format 1, 5, 6
future changes 3

G

guidelines 7

H

handwritten notes 2
highlight 2, 3
human data 12
human subject protection..... 5, 6

I

IDB..... 13
incomplete request..... 1
inconsistencies..... 6
IND..... 1, 12
IND AE action letter..... 12
IND Safety Report..... 12
informed consent 2, 5, 12
institution..... 2, 6
Institutional Review Board (IRB). 2, 3, 5, 8, 10, 12, 13
intergroup study..... 6
Internet 7
Investigational Drug Branch (IDB) 13
Investigational New Drug (IND) .. 1, 12
Investigational New Drug IND) .. 12
investigator..... 1, 3, 4, 5, 7, 12, 13
IRB.....2, 3, 5, 8, 10, 12, 13
IRB approval 2, 10
IRB policy 5, 12

J

justification..... 2, 4

L

lead organization 13
letter 2, 3, 12, 13, 14
Letter of Intent (LOI) 12
line item..... 2, 4
local IRB 5, 12
local policy/procedure .. 1, 2, 3, 8, 9, 10, 13
LOI..... 12

M

merit....3
Microsoft Word....11
milestones....10
month....8

N

non-Cooperative Group study....2
non-physician co-investigators....5
notification....5, 7

O

on-hold....1
Operations Office....1
optional....3
options when amendment is in review....4
organization....8, 10
organization requirement....1, 2, 3
organization-wide....7

P

page numbers....2
participants....6, 7
patient population....12
patient risk....5, 6
patient safety....5, 6, 12, 13
Pharmaceutical Management Branch (PMB)....5, 6
phase 1/2 trials....12
phase 3 trials....13
phone number....9
physician co-investigators....5, 6
PI 1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
PI signature....1
PI/Study Chair approval....8
PIO....4, 7, 11, 12, 13
PIO Status Update Form....7
PMB....5, 6
PMB-supplied agent....5, 6
point of contact....13
point-by-point fashion....2, 9, 14
Portable Document Format (PDF)11
post (Internet)....7
potential risk....12
previously approved amendment... 5
previously enrolled patients.... 12
Principal Investigator.... 3
Principal Investigator (PI).1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
Protocol and Information Office (PIO)....4, 7, 11, 12, 13
Protocol Chair.*See* Study Chair, *See* Study Chair, *See* Study Chair, *See* Study Chair
protocol language.... 6
protocol page numbers.... 2
protocol status change/update.... 7
protocol status definitions....B-1
Protocol Submission Worksheet (PSW).... 11
protocol title page2, 3, 4, 5, 8, 9, 10, 11, 14
PSW.... 11

R

race accrual goal/target.... 11
Radiation Resources Program (RRP).... 13
recommendation....3, 4, 7, 11, 14
reconsenting.... 12
reduced workload.... 6
regimen.... 10
regulatory agency.... 12
report.... 12
request for withdrawal.... 4
request letter.... 13
required documentation.... 1
required format.... 1
resubmit.... 3
resubmit revised amendment.... 14
reverse amendment.... 5
review....1, 3, 4, 5, 7, 8, 11, 13, 14
revise approved amendments.... 4
risk.... 6
RRP.... 13

S

safety change/update.... 9
safety data.... 12
safety report.... 12
scientific amendment.... 6
scientific change/update.... 9
scientific intent.... 5, 6
signature.... 1
standardization of protocol language.... 6
statistical section.... 11
statistician.... 9
status change/update.... 7
status definitions.... B-1
Study Chair.... 3, 12, 13, 14
Study Chair/PI approval.... 8
study design.... 5, 6
study design amendment.... 6
submitter.... 1
suspend accrual.... 12

T

table of contents.... 2
telephone.... 5, 13
title page....2, 3, 4, 5, 6, 8, 9, 10, 11, 14
treatment regimen.... 10
trial sponsor.... 12
typographical correction.... 5, 6, 13

U

U.S. mail.... 11
U10 study.... 6
unmarked copy of document.... 2
update date.... 3, 4, 5, 8, 9, 10, 11

V

version control.... 11
version date..2, 4, 5, 8, 9, 10, 11, 14

W

withdraw amendment.... 4, 5, 14
word-processing program.... 3

Y

year.... 6, 8