TEMPLATE INSTRUCTIONS

The protocol template is a tool to facilitate rapid protocol development. It is not intended to supersede the role of the Protocol Chair in the authoring and scientific development of the protocol. It contains the "boilerplate" language commonly required in protocols submitted to CTEP. Content may be modified as necessary to meet the scientific aims of the study and development of the protocol. Much of the formatting is needed for electronic submission of the protocol to the FDA and should not be changed unless necessary.

Note: This template contains language specific for Experimental Therapeutics Clinical Trials Network ("**ETCTN**") trials as well as for CTEP-sponsored trials coordinated outside of the ETCTN or other Network/Cooperative Groups ("**Non-Network**," which may include single-center or multi-center trials). Please take note of any instructional text in *italics,* emphasized with red highlighting, which notes where language specifically applies to "**ETCTN**" or "**Non-Network**" trials. Please note that CTEP will designate your trial as either an ETCTN or Non-Network trial when the Letter of Intent (LOI) is approved. If your trial is designated as an ETCTN trial, then all ETCTN specific language must be retained in your protocol. Non-Network trials may delete language specific for ETCTN trials, and vice versa.

1. Each Protocol Template consists of two parts:

   a. Protocol Submission Worksheet: available at http://ctep.cancer.gov/forms/docs/psw.docx. This document contains prompts for required administrative information.

   b. Main Body and Appendices of the protocol: attached below. This document provides standard language plus instructions and prompts for information.

   Please note that the Informed Consent Template is provided as a separate document file.

2. The Protocol Submission Worksheet and Protocol/Informed Consent Template documents should be completed, and all documents (including the Appendices) should be submitted to CTEP for review. For protocol amendments a Summary of Changes should be provided as the first page (page i) of the document, as indicated in the template. The Summary of Changes must provide hyperlinks to the area referenced in the protocol or informed consent document.

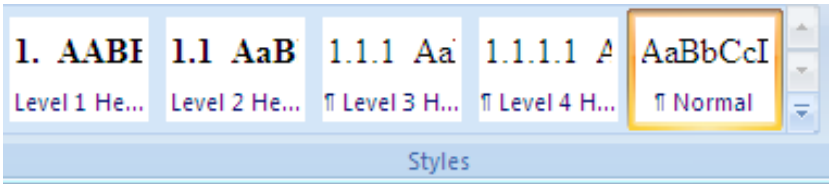
3. All sections in the Protocol Template should be retained to facilitate rapid review. If not appropriate for a given study, please insert "Not Applicable" after the section number and delete unneeded text. Depending on the phase of the study and whether it is a single-agent or combination agent study, include sections as follows:

   - No highlighting – for all protocols
   - Yellow highlighting – for phase 1 protocols
   - Green highlighting – for phase 2 protocols
   - Blue highlighting – for combination agent protocols

- Pink highlighting – for advanced imaging protocols
- Red highlighting – for language that is dependent on whether the trial is coordinated within the ETCTN ("ETCTN") or outside of it ("Non-Network"). **Read this text carefully and decide which language applies to your protocol.**
- Grey highlighting – language for ETCTN protocols that are participating in the ETCTN Biobanking and Molecular Characterization Initiative

4. All Protocol Template instructions and prompts are in *italics*. **As you complete the information requested, please delete the italicized text.**

5. Please note that the Protocol Template has built-in styles for headings levels 1-4 (Level 1 Heading – Level 4 Heading; see image below).



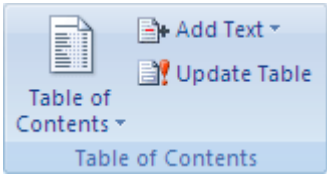
These heading styles will automatically update the Table of Contents (TOC) and convert to Bookmarks in a final PDF protocol document. **Please retain the heading styles.**

6. Before updating the TOC, please ensure that the **Title Page** is page 1 of the protocol. For any pages preceding it (*i.e.*, Summary of Changes) use alternative numbering (i, ii, iii, iv, …). Use Section Breaks as necessary to preserve this numbering scheme.

7. To update the TOC in your protocol document:

   MS Word 2007 or later

   a. Under the **References** tab, in the **Table of Contents** group, click **Update Table**.



   b. Click **Update entire table**.

   MS Word 2003

   a. Click the table of contents.

   b. Press F9.

Please do not edit the TOC manually.

8. Please redline, highlight or underline new or modified text as this will facilitate rapid review.

9. Note that CTEP cannot accept MS Word files that:
   - are read-only
   - are password protected
   - contain macros
   - are saved with a file extension other than .doc (Word 2003) or .docx (Word 2007 onward)

10. For problems or questions encountered when using these documents (Protocol Submission Worksheet or Protocol/Informed Consent Template), please contact the CTEP Protocol and Information Office (PIO) by e-mail (pio@ctep.nci.nih.gov).

SUMMARY OF CHANGES – Protocol

For Protocol Amendment # to:

NCI Protocol #:
Local Protocol #:

NCI Version Date:
Protocol Date:

Please provide a list of changes from the previous CTEP approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the 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'). When appropriate, a brief justification for the change should be included.

#	Section	Page(s)	Change
1.			
2.			
3.			
4.			
5.			

(Please retain the section break below, so that the Title Page is page "1" of the document.)

NCI Protocol #: *Use the number assigned to the LOI by the NCI.*

Local Protocol #: *Please insert your local protocol # for this study.*

ClinicalTrials.gov Identifier: *[Insert ClinicalTrials.gov NCT#, if known, in the format "NCTxxxxxxxx"; otherwise, "TBD"]*

TITLE: A Phase 1 Study of *or* A Phase 2 Study of *[CTEP and/or CIP IND Agent]* in Combination with *[Other Agent*(s)*]* in *[Solid Tumors/Study Disease]*

Use Simplified Disease Classification (SDC) terminology for study disease. Please refer to the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/codes_values.htm) for a complete list of SDC disease terms.

Corresponding Organization: *Use this field for* ***ETCTN*** *trials (Non-Network trials should delete). This is the name of the Lead Academic Organization (LAO) submitting the protocol. Please select from the table of LAOs below and please include the CTEP code.*

Coordinating Center: *Use this field for* ***Non-Network*** *trials (ETCTN trials should delete). Multicenter trials can only list one organization/ institution as the Coordinating Center.*

Principal Investigator:
Name
Institution
Address
Address
City, State/Province, Zip Code/Postal Code, Country
Telephone
Fax (optional)
e-mail address

Non-Network trials *should include all* ***Co-Investigators*** *in the same format as above (including name, institution, address, phone, and e-mail) and must delete the "Participating Organizations" and "Non-Member Collaborators" tables below.*

A study can have only one Principal Investigator. The Principal Investigator must be a physician and is responsible for all study conduct. *Please refer to the Investigator's Handbook on the CTEP Web site for a complete description of the* ***Principal Investigator's*** *responsibilities (http://ctep.cancer.gov/investigatorResources/default.htm#Investigators_handbook).*

All study personnel listed on the title page must have a current registration on file with CTEP. *Refer to section 4.1 for document requirements for each registration type and system access requirements. Failure to register all study personnel on the title page could delay protocol*

approval. If you are unsure of an individual's registration status, please contact the Pharmaceutical Management Branch, CTEP at (240) 276-6575 or by e-mail at RCRHelpDesk@nih.gov.

The protocol title page of the ***ETCTN*** *Rostered Model template lists all grantees that may potentially participate on an ETCTN protocol.* ***It is the responsibility of the Corresponding Organization to list the LAOs that will be participating on this study within the table below. Please contact PIO (PIO@ctep.nci.nih.gov) for further instruction and guidance regarding the listing of participating LAOs.*** *Additional Non-ETCTN single institution participants should be added under "Non-Member Collaborators" according to the formatted example. Additional Non-ETCTN rostered organization participants (e.g., ALLIANCE, ECOG-ACRIN, NRG, SWOG, COG, CCTG, CITN, BMTCTN, ABTC, PBTC, AMC, COGC) should be added under "Participating Organizations" as indicated below.*

Participating Organizations *(Only the participating LAOs should be listed.)*

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
Other Participating Rostered Organization #1 (e.g., ALLIANCE, ECOG-ACRIN, NRG, SWOG, COG, CCTG, CITN, BMTCTN, ABTC, PBTC, AMC, or COGC; list one organization per row; add more rows as necessary)

Non-Member Collaborators *(additional individual participating sites within an* ***ETCTN*** *trial that are not members of a participating rostered organization)*

Institution #1 (non-rostered institution; insert more rows below as necessary for additional institutions; please include the CTEP Institution Code, which can be found at http://ctep.cancer.gov/protocolDevelopment/codes_values.htm)	*Investigator #1* *Name* *Telephone* *Fax* *E-mail address* *Investigator #2*

Name *Address*	*Name* *Telephone* *Fax* *E-mail address* *Investigator #3* *Name* *Telephone* *Fax* *E-mail address*

If this study includes an investigational agent supplied by the NCI Division of Cancer Treatment and Diagnosis and will involve a Canadian institution(s), a Clinical Trials Application (CTA) will need to be submitted to Health Canada for their participation in the study. A Canadian investigator should be designated to be responsible for preparing and submitting the CTA to Health Canada for the Canadian institution(s). Procedures and forms for preparing and submitting a CTA to the Canadian HPFB are available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_application-eng.php. A copy of the "No Objection" letter must be forwarded to the Pharmaceutical Management Branch at PMBAfterHours@mail.nih.gov when available.

Statistician:
(if applicable)
Name
Address
Address
Telephone
Fax
e-mail address

Study Coordinator:
(if applicable)
Name
Address
Address
Telephone
Fax
e-mail address

Responsible Research Nurse:
Name
Address
Address
Telephone
Fax
e-mail address

Responsible Data Manager:
Name
Address
Address
Telephone
Fax
e-mail address

Please list all agents and their suppliers in the fields below, including any imaging agents. "Supplier" is defined as the entity that provides the clinical supply of the agent. If the agent is purchased through commercial sources, then please mark supplier as "commercial".

NCI-Supplied Agent(s): *[Agent Name and NSC #]*
Other Agent(s): *[Agent Name, NSC # (if applicable), and Supplier]*

*Below, please describe the IND Status of this study by choosing IND #/Sponsor **OR** Exemption from IND requirements, making sure to delete the inapplicable field(s).*

IND #: *[Enter the # of the IND under which this study will be performed. Enter "TBD" if an IND # is not yet available.]*
IND Sponsor: *[If this study is being conducted under an IND sponsored by CTEP, then enter "DCTD, NCI". If this is solely an imaging study and is to be conducted under a CIP IND, then enter "Cancer Imaging Program, NCI"]*

OR

Study Exempt from IND Requirements per 21 CFR 312.2(b).

If an IDE is not applicable to this study, then please delete the following fields (IDE #, IDE Sponsor, Device Name):
IDE #: *[Investigational Device Exemption #]*
IDE Sponsor:
Device Name: *[This can include investigational* in vitro *diagnostics, which are regulated as devices]*

Protocol Type / Version # / Version Date: *[Type* / Version # / Version Date]*

**Protocol types: Original, Revision, or Amendment*

SCHEMA

Please provide a schema for the study. If preferred, a summary or synopsis may be provided. Please refer to the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm) for Guidelines for Treatment Regimen Nomenclature and Expression.

If appropriate, a table may be used to describe the regimen; see examples below for phase 1 single-agent and combination dose-escalation protocols. The table should include the route of administration (PO, IV, etc.*) and dosing schedule (QD, BID, Days 1-5,* etc.*).*

For phase 1 single-agent protocols:

Dose Escalation Schedule	
Dose Level	Dose of *[CTEP IND Agent]* *
Level 1	
Level 2	
Level 3	
Level 4	
Level 5	
* *Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*	

For phase 1 combination protocols:

Dose Escalation Schedule			
Dose Level	**Dose***		
	Agent X (units)	***Agent Y (units)***	***Agent Z (units)***
Level 1			
Level 2			
Level 3			
Level 4			
Level 5			
**Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*			

For phase 2 single-agent or combination protocols, provide study-specific schema or synopsis.

Please indicate when advanced imaging will be performed in the study.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 *Please insert primary protocol objectives.*

Please specify advanced imaging Primary Objective if applicable.

1.2 Secondary Objectives

1.2.1 *[All phase 1 studies must include the following text as a secondary objective.]* To observe and record anti-tumor activity. Although the clinical benefit of [this/these] drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 *Please insert additional secondary protocol objectives, if pertinent.*

1.2.3 *[If this is an ETCTN study participating in the Biobanking and Molecular Characterization Initiative, also include as secondary objectives the items highlighted in grey:]* To perform molecular profiling assays on malignant and normal tissues, including, but not limited to, *[add relevant assays as needed, e.g., whole exome sequencing (WES), messenger RNA sequencing (RNAseq), etc.]*, in order to:

1.2.3.1 identify potential predictive and prognostic biomarkers beyond any genomic alteration by which treatment may be assigned, and

1.2.3.2 identify resistance mechanisms using genomic DNA- and RNA-based assessment platforms.

1.2.4 To contribute genetic analysis data from de-identified biospecimens to Genomic Data Commons (GDC), a well annotated cancer molecular and clinical data repository, for current and future research; specimens will be annotated with key clinical data, including presentation, diagnosis, staging, summary treatment, and if possible, outcome.

1.2.5 To bank formalin-fixed, paraffin-embedded (FFPE) tissue, blood (for cell-free DNA analysis), and nucleic acids obtained from patients at the ETCTN Biorepository at Nationwide Children's Hospital.

Please specify advanced imaging Secondary/Exploratory Objective if applicable.

2. BACKGROUND

2.1 Study Disease(s)

For phase 1 or 2 disease-specific studies, please provide background information on the study

disease.

2.2 CTEP and/or CIP IND Agent(s)

*Please provide background information below on the CTEP and/or CIP IND study agent(s), including information to support safety issues and the rationale for the proposed starting dose, dose escalation scheme, and regimen chosen. Please also provide information on the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical pharmacokinetics, and major route of elimination. If available, please include information on the metabolism of the study agent in humans and its potential for drug interactions, if any interactions (*e.g.*, via the P450 enzyme system). If protocol is a single-agent study, please insert background information directly under heading 2.2 and remove subheadings 2.2.1, 2.2.2, etc., for multiple-agent studies.*

Please include information regarding the rationale for advanced imaging as appropriate; include information on the pharmacology, toxicology, and previous human imaging studies from the current Investigator's Brochure as applicable. ***For complete information, please refer to the current Investigator's Brochure:*** *[Insert title, version and date of NCI/CIP IB]. Contact CIP regulatory staff at NCICIPINDAGENTS@mail.nih.gov for the current Investigator's Brochure.*

2.2.1 CTEP and/or CIP IND Agent #1

2.2.2 CTEP and/or CIP IND Agent #2

2.3 Other Agent(s)

Please provide background information on other agent(s) and/or treatments in this study, including information to support safety issues and the rationale for the proposed starting dose and dose escalation scheme, if applicable.

2.4 Rationale

Please provide the background and rationale for this therapy/combination therapy/advanced imaging (in this disease).

2.5 Correlative Studies Background

Please provide background information on each planned correlative study including the biologic rationale and hypothesis as well as the relevant preclinical and clinical (if available) data. Refer to "Guidelines for Correlative Studies in Clinical Trials" (http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm). If this trial includes no correlative studies, this section should be marked "N/A".

Text for studies participating in the ETCTN Biobanking and Molecular Characterization Initiative is provided below.

The molecular landscape of cancer is just beginning to be defined. However, we do not know enough about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, we will attempt to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

3. PATIENT SELECTION

3.1 Eligibility Criteria

Note for all protocols: If study has an integral biomarker to determine eligibility to study or specific treatment arms, then the relevant eligibility criteria must be stated (e.g., Presence of [specific gene mutations and variants]).

3.1.1 *For phase 1 protocols:* Patients must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

OR

Patients must have histologically or cytologically confirmed *[Study Disease] Please specify eligible disease(s)/stage(s) using the CTEP Simplified Disease Classification (http://ctep.cancer.gov/protocolDevelopment/codes_values.htm).*

Note: Radiological evaluation should occur within approximately 30 days prior to enrollment initiation. Studies using progression-free survival (PFS) as an endpoint will require a stricter window for radiological evaluation.

3.1.2 *For phase 2 protocols: Please insert appropriate criteria for the particular patient population. Note: Lesions are either measurable or non-measurable using the criteria provided in Section 12 (Measurement of Effect). The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. Suggested text is provided below.*

Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 12 (Measurement of Effect) for the evaluation of measurable disease.

OR

Please insert appropriate criteria for diseases other than solid tumors. Criteria for selected hematologic malignancies can be found in the following references: J Clin

Oncol 17(4):1244-53, 1999 (non-Hodgkin's lymphoma); J Clin Oncol 8(5):813-19, 1990 (acute myeloid leukemia); and Blood 887(12):4990-97, 1996 (chronic lymphocytic leukemia).

3.1.3 *Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (e.g., no more than 6 cycles of an alkylating agent; no more than 450 mg/m^2 doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (e.g., no more than 3000 cGy to fields including substantial marrow).*

3.1.4 Age ≥18 years. Please state reason for age restriction. If applicable, the following text can be used.

Because no dosing or adverse event data are currently available on the use of *[CTEP and/or CIP IND Agent]* in combination with *[other agents]* in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.6 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN
– creatinine	≤ institutional ULN OR
– glomerular filtration rate (GFR)	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.7 *Please insert other appropriate eligibility criteria.*

3.1.8 *Please use or modify the following paragraph as appropriate.*

The effects of *[CTEP and/or CIP IND Agent]* on the developing human fetus are unknown. For this reason and because *[Agent Class]* agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of

[CTEP and/or CIP IND Agent] administration.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. *[if appropriate*]

3.2.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1). *[if appropriate]*

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 *The investigator(s) must state a medical or scientific reason if patients who have brain metastases will be excluded from the study. Suggested text is provided below:*

Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to *[CTEP and/or CIP IND Agent(s)]* or other agents used in study.

3.2.6 *Please state appropriate exclusion criteria relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent(s). Examples of such agents or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (e.g., P-glycoprotein). Specifically excluded substances may be listed below, stated in Section 8 (Pharmaceutical Information), and presented as an appendix. If appropriate, the following text concerning CYP450 interactions may be used or modified.*

Patients receiving any medications or substances that are inhibitors or inducers of *[specify CYP450 enzyme(s)]* are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. *[Appendix C is a sample patient information sheet that can be tailored to this specific protocol and presented to the patient.]*

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 *The investigator(s) must state a medical or scientific reason if pregnant or nursing patients will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_pregnant.htm). Suggested text is provided below:*

Pregnant women are excluded from this study because *[CTEP and/or CIP IND Agent]* is *[a/an Agent Class]* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with *[CTEP and/or CIP IND Agent]*, breastfeeding should be discontinued if the mother is treated with *[CTEP and/or CIP IND Agent]*. These potential risks may also apply to other agents used in this study.

3.2.9 *The investigator(s) must state a medical or scientific reason if patients who are cancer survivors or those who are HIV positive will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_hiv.htm). Suggested text is provided below:*

HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with *[CTEP and/or CIP IND Agent(s)]*. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.10 *Please insert other appropriate agent-specific exclusion criteria.*

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the Planned Enrollment Report (table provided under Section 9.2).

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This section applies to ***ETCTN and other CTMS-monitored*** *trials (CTMS-Routine and CTMS-Comprehensive). Non-Network/non-CTMS trials may delete all text under 4.2 and replace with "N/A".*

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

[If this is an ETCTN study participating in the Biobanking and Molecular Characterization Initiative, also include:] NOTE: Sites must utilize the Central IRB (CIRB) as their IRB of record to participate in this protocol.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *[NCI protocol #]* protocol page located on the CTSU Web site. Permission to view and download this protocol is

restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol #*[NCI Protocol #]*.

  Example (to be deleted): "Click on the By Lead Organization to expand, and then select LAO-MA036 and protocol #9999."
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For [*NCI protocol #*] Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.)
- For applicable ETCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process. *(Only add if RT modality credentialing is part of the study design.)*
- *If applicable, add to this bulleted list any other protocol-specific documents or requirements (e.g., site or investigator specialized credentialing; evidence of training; study-specific regulatory forms) needed for site registration and approval. Include any processing instructions, or reference the location in the protocol or appendices where further instructions can be found.*

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab

→Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Delegation of Task Log (DTL) ***(for studies with a DTL)***

Each site must complete a protocol-specific DTL. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. The DTL application is located on the CTSU members' website at www.ctsu.org. Any individual at the enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the DTL application.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

The following text is to be used by Non-Network, non-CTMS-Monitored trials. ETCTN trials may delete these paragraphs and use Sections 4.3.1, 4.3.2, and 4.3.3 instead.

To register a patient, the following documents should be completed by the research nurse or data manager and faxed *[Fax #]* or e-mailed *[e-mail address]* to the Study Coordinator:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form
- *Other appropriate forms (*e.g.*, Eligibility Screening Worksheet, Registration Form)*

The research nurse or data manager at the participating site will then call *[Telephone #]* or e-mail *[e-mail address]* the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- register the patient on the study
- assign the patient a dose
- fax or e-mail the patient study number and dose to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration.

Sections 4.3.1, 4.3.2, 4.3.3, and 4.3.4 below are to be used by ETCTN trials using OPEN/IWRS, as well as all other CTMS-monitored studies (Routine and Comprehensive) activated after January 2017. Other trials may delete these sections.

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

Keep the following paragraph only if using slot reservations; otherwise it can be removed (one paragraph):
For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. *If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.*
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.3.3 Patient Enrollment Instructions

Include any special instructions related to slot reservations or patient enrollment. For example, if sites must reserve a slot in IWRS and then submit documentation to the study team before their slot request will be approved and they are able to enroll the patient in OPEN, describe that here, including a listing of all required documents/steps. Otherwise this sub-section can be deleted.

If this is an ETCTN study participating in the Biobanking and Molecular Characterization Initiative, also include the following text:

For the ETCTN Biobanking and Molecular Characterization Initiative, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning three separate and unique identification numbers to the patient, a Universal patient ID (UPID), an Intrinsic ID, and a Treatment patient ID. The UPID and Intrinsic ID are both associated with the patient and used each and every time the patient engages with the ETCTN

Biobanking and Molecular Characterization portion of this protocol. Neither of these IDs contain any information or link to this treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data. The Intrinsic ID is needed by the Biorepository to maintain quality control of positively identifying specimens for association with a particular patient.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Keep the following paragraph if using slot reservation; otherwise, it can be removed (one paragraph):
Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *[# of days]* days.* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.
*[*Note: For leukemia protocols, treatment should be started as rapidly as possible.]*

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Biomarker Plan

*Use the table below to provide the study biomarker plan. List the **priority** (1, 2, 3, etc.); **biomarker name** (e.g., specific gene mutations, proteins, cells, etc.); **biomarker assay** (e.g., whole exome sequencing [WES], RNA sequencing [RNA-Seq], immunohistochemistry [IHC],*

flow cytometry, etc.); ***biomarker type*** *(i.e., integral, integrated, or exploratory) and* ***purpose*** *(e.g., for eligibility criterion, to correlate findings with response to agent[s], etc.); whether biomarker is* ***"M" (mandatory) or "O" (optional)****;* ***timing*** *of the assay (e.g., baseline, post-progression, upon meeting a pre-specified efficacy endpoint, etc.);* ***specimen*** *type (e.g., fresh tumor tissue [FFPE], frozen tumor tissue, blood, serum, plasma, etc.);* ***quantity needed*** *(e.g., number of needed cores or slides for tumor tissue or tubes for blood, volume of blood, etc.); and name of* ***laboratory*** *conducting the assay.*

Note that integral biomarkers must be listed as mandatory, whereas integrated and exploratory biomarkers can be either mandatory or optional. Please see the following articles for guidance on determining when mandatory biopsies are appropriate: Ganti, A.K. ("Tissue Specimens in Clinical Trials: A Double-Edged Sword." The Asco Post. *2017.) and Peppercorn* et al. *("Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology*." J Clin Oncol. *2010; 28:2635-40.).*

Please also briefly describe, <u>in text form,</u> the overall rationale for the biomarker plan and all tissue collection and biomarker/correlative assays. If multiple assays will require use of a limited amount of tumor tissue, indicate how the use of tissue will be prioritized.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	*[Add biomarker name]*	*[Add biomarker assay]*	*Integral* *[Add relevant text]*	M	*[Add relevant timepoints]*	*[Add specimen type]*		*[Add laboratory name]*
2	*[Add biomarker name]*	*[Add biomarker assay]*	*Integrated* [*Add relevant text]*	*[Add M or O]*	*[Add relevant timepoints]*	*[Add specimen type]*		*[Add laboratory name]*
3	*[Add biomarker name]*	*[Add biomarker assay]*	*Exploratory* *[Add relevant text]*	*[Add M or O]*	*[Add relevant timepoints]*	*[Add specimen type]*		*[Add laboratory name]*
[Add number]	ETCTN Biobanking and Molecular Characteriza-tion Initiative	N/A	Exploratory H&E slides for scanning (Aperio) and storage for future research		Baseline, *[Add other timepoints as needed]*	Fresh tumor tissue biopsies (FFPE, tumor block, unstained slides)	*[Add # of needed cores/ slides]*	ETCTN Biorepository
[Add number]	ETCTN Biobanking and Molecular Characteriza-tion Initiative	N/A	Exploratory For future cell free DNA (cfDNA) studies		Baseline, *[Add other timepoints as needed]*	Plasma	*[Add # of needed tubes, etc.]*	ETCTN Biorepository
[Add number]	ETCTN Biobanking and Molecular Characteriza-tion Initiative	Whole Exome Sequencing	Exploratory *[Add relevant text, e.g., For somatic DNA and/or cfDNA analysis]*		Baseline, *[Add other timepoints as needed]*	Tumor tissue, blood, *and/or* plasma	*[Add # of needed tubes, etc.]*	NCI MoCha Lab
[Add number]	ETCTN Biobanking and Molecular Characteriza-tion Initiative	RNA sequencing	Exploratory *[Add relevant text, e.g., For RNA analysis]*		Baseline, *[Add other timepoints as needed]*	Tumor Tissue	*[Add # of needed tubes, etc.]*	NCI MoCha Lab

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
[Add number]	ETCTN Biobanking and Molecular Characteriza-tion Initiative	Germline Whole Exome Sequencing	Exploratory For germline DNA analysis		Baseline, *[Add other timepoints as needed]*	Blood	*[Add # of needed tubes, etc.]*	NCI MoCha Lab

Renumber/reprioritize and add/delete rows as needed for planned correlative studies.

Specimen Collection Schedule

Please provide the type of specimen and the timepoint (study cycle/day) of each specimen collection procedure, and mark the appropriate boxes with an "X" to denote collection on that study day.

Specimen Type	**Baseline (Pre-treatment)**	***[Timepoint #2]***	***[Timepoint #3]***	***[Timepoint #4]***	***[Timepoint #5]***	***[Timepoint #6]***	***[Timepoint #7]***
Specimen type #1	*X*						
Specimen type #2	*X*						

Please briefly describe each planned correlative study in the appropriate subsection(s) below. Also please see the "Guidelines for Correlative Studies in Clinical Trials" provided with the LOI response and available on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm).

*The description for **each proposed biomarker study** should include specific information, as outlined below (where applicable).*

1. *Provide a hypothesis and rationale for biomarker utility and a description of the impact on therapeutic agent development based on the following considerations:*
    a. *Biological and/or mechanistic rationale with data to support relationship between biomarker and agent effects*
    b. *Intended use within the proposed study*
    c. *Preclinical* in vitro *and* in vivo*, and clinical results, if applicable*
2. *Describe the assay method's appropriateness for the study*
3. *Describe the investigator's and clinical laboratory's experience and competence with the proposed assays*
4. *Provide the data supporting the degree of biomarker "fit for purpose" and clinical qualification - these data should include reliability of analytical performance*
5. *It is recommended that the templates for IHC, ISH or Somatic Mutations be used for describing the status of assays, especially those that are intended to be for integral or integrated markers; these can be found on the CDP website (http://www.cancerdiagnosis.nci.nih.gov/scientific_programs/pacct/templates.htm)*
    a. *In all cases, the laboratory's Standard Operating Procedures (SOPs) for all integral assays should be submitted to CTEP with the initial protocol submission for review.*
    b. ***ETCTN** trials requiring the use of patient specimens may insert the "Correlative Science Proposal Submission Form" for ETCTN studies into the protocol (this form can be found at http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm).*
6. *Justify the number of patients and specimens:*
    a. *To demonstrate feasibility*
    b. *To demonstrate that studies are likely to produce interpretable and meaningful results*
7. *Give thoughtful consideration to the risk to the patient of obtaining samples, specimens, or data for biomarker studies in the context of data on biomarker validity and degree of clinical qualification*

***Explicit instructions for handling, preserving, and shipping specimens should be provided**. If samples will be shipped to a central laboratory for processing and analysis, responsible parties and contact information should be provided in addition to instructions for handling, preserving, and shipping the specimens.*

A plan for statistical analysis of the results of the correlative study(ies) should be provided in Section 9.4, Analysis of Secondary Endpoints.

A correlative study title using meaningful descriptive text should be provided for each planned correlative study using the Protocol Submission Worksheet found on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/default.htm). These titles will facilitate documentation of contributions to basic science in the context of the clinical trial.

For all biomarker studies, please specify whether the study is "integral," "integrated," or "ancillary/exploratory," as defined by Dancey et al. *("Guidelines for the Development and Incorporation of Biomarker Studies in Early Clinical Trials of Novel Agents*." Clin Cancer Res. *2010; 16:1745-55.). For example, an "integral" bioassay is one that is necessary for the trial to proceed,* i.e., *the outcome determines patient disposition. Note especially that if integral markers are to be used to make individual patient decisions, then CLIA regulations will apply (http://wwwn.cdc.gov/CLIA/Default.aspx).*

If development of diagnostic assays to identify patients who might benefit from a molecularly targeted therapy is planned, validation in a central reference laboratory, tissue banking, and standardization of procedures is of high importance. Information on endpoint validation including additional background (as needed), description of the assay(s) used, materials and methods, and assay validation should be provided in an appendix (see also the instructions under Section 5.2, Integral Laboratory or Imaging Studies).

A format for presentation of the required information is shown below.

If this trial does not include correlative or special studies, this section should be marked "N/A" and all instructions as well as the text below deleted.

5.2 Integral Laboratory or Imaging Studies

If the protocol includes any ***integral*** *biomarker studies using* in situ *hybridization (ISH), immunohistochemistry (IHC), and/or DNA-based mutation assays, you may fill out the appropriate template (found at http://www.cancerdiagnosis.nci.nih.gov/scientific_programs/pacct/templates.htm) and attach to this protocol submission as separate Appendices (see Appendix D).* **ETCTN** *trials requiring the use of patient specimens may insert the "Correlative Science Proposal Submission Form" for ETCTN studies into the protocol (this form can be found at http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm).*

If the laboratory or laboratories performing the studies has an alternatively-formatted document that supplies the same level of information regarding validation, materials and methods, etc., *it may be used instead of the templates.*

In all cases, the laboratory's Standard Operating Procedures (SOPs) for all integral assays should be submitted to CTEP with the initial protocol submission for review.

5.2.1 *Title – Integral Laboratory Correlative Study #1*
5.2.1.1 Collection of Specimen(s)
5.2.1.2 Handling of Specimens(s)
5.2.1.3 Shipping of Specimen(s)
5.2.1.4 Site(s) Performing Correlative Study

5.2.2 *Title – Integral Laboratory Correlative Study #2*
5.2.2.1 Collection of Specimen(s)
5.2.2.2 Handling of Specimens(s)
5.2.2.3 Shipping of Specimen(s)
5.2.2.4 Site(s) Performing Correlative Study

5.3 Investigational Device Information

If an investigational device requiring an IDE is to be used in this trial, please provide the IDE #, IDE title, and the IDE sponsor. This section should be deleted if no investigational devices requiring an IDE are used.

5.4 Integrated Correlative Studies

5.4.1 *Title – Integrated Laboratory Correlative Study #1*
5.4.1.1 Collection of Specimen(s)
5.4.1.2 Handling of Specimens(s)
5.4.1.3 Shipping of Specimen(s)
5.4.1.4 Site(s) Performing Correlative Study

5.4.2 *Title – Integrated Laboratory Correlative Study #2*
5.4.2.1 Collection of Specimen(s)
5.4.2.2 Handling of Specimens(s)
5.4.2.3 Shipping of Specimen(s)
5.4.2.4 *Site(s) Performing Correlative Study*

5.5 Exploratory/Ancillary Correlative Studies

5.5.1 *Title – Exploratory/Ancillary Laboratory Correlative Study #1*
5.5.1.1 Collection of Specimen(s)
5.5.1.2 Handling of Specimens(s)
5.5.1.3 Shipping of Specimen(s)
5.5.1.4 Site(s) Performing Correlative Study

5.5.2 *Title – Exploratory/Ancillary Laboratory Correlative Study #2*
5.5.2.1 Collection of Specimen(s)
5.5.2.2 Handling of Specimens(s)
5.5.2.3 Shipping of Specimen(s)
5.5.2.4 Site(s) Performing Correlative Study

Text for studies participating in the ETCTN Biobanking and Molecular Characterization Initiative is provided below.

5.5.3 ETCTN Biobanking and Molecular Characterization Initiative

Background: A primary goal of this study is to obtain archived and/or fresh tumor and normal tissue and blood specimens from patients enrolled to ETCTN clinical trials for biobanking and *[modify as needed: WES, RNA sequencing (RNA-Seq), isolation of cell-free DNA (cfDNA), etc.]*. Patient specimens will be analyzed to identify tumor mutations, amplifications, or translocations that may inform about the disease or about drug treatment mechanism of action, potential prediction of response, and interrogation of mechanisms of primary or secondary resistance to treatment in the early cancer drug development environment. Such profiling may also have predictive or prognostic import.

A tumor biopsy (or archived tumor specimen) and blood draw will be obtained from patients who sign the informed consent document to enroll in this treatment trial. Additional specimens for this ancillary study may be collected along with treatment trial specimens according to the schedule specified on each individual treatment protocol (*e.g.*, post-progression or upon meeting a pre-specified efficacy endpoint). The total number of biopsies to be collected should be determined by consideration of the overall study design, patient safety, and patient consent, but should not exceed six (6) total biopsy procedures over the course of the study.

5.5.3.1 Collection of Specimen(s)

5.5.3.1.1 Biopsy Procedure and Processing

For the collection of biopsy specimens, fine needle aspiration (FNA) followed by core needle biopsy, with submission of the FNA and the biopsy cores, is the preferred technique. Blood samples from consenting patients will also be collected and submitted with each biopsy. Sites may perform embedding of the biopsy tissue rather than using the ETCTN Biorepository resource. If this option is selected, the site should refer to Appendix 4 of the ETCTN Biobanking and Molecular Characterization Initiative (BMCI) Laboratory Manual. Please refer to Appendix E for additional details.

Formalin-fixed paraffin-embedded (FFPE) blocks will be used, preferably, for dual extraction of DNA and RNA, and the highest yield of nucleic acids will be from FFPE blocks that are ≤6 months-old. A preexisting FFPE tumor tissue block,

preferably of tissue collected within 6 months prior to registration, may be submitted for analysis in addition to, or in lieu of, a new biopsy sample. Older specimens may be submitted, but the yield of nucleic acids may be lower, and characterization and analysis may be compromised. In lieu of the tissue block, the site may also submit 30-50 unstained slides; 4 of these slides (including the top cut) are to be on charged slides, followed by 30-40 on uncharged slides for macrodissection and nucleic acid extraction.

5.5.3.1.2 Blood Collection

At the time of the biopsy, two 10 mL Streck tubes and one 10 mL EDTA tube of blood will be collected for analysis of germline DNA and banking of plasma for future cell free DNA (cfDNA) studies. Blood collections will be performed according to standard procedures and will be shipped to the Biorepository with the tumor specimen.

[Add text related to collection of blood specimens for flow cytometry, serum assays, etc., as needed]

5.5.3.1.3 Preferred Core Biopsy Procedure

It is preferred that at least four core biopsies 16-18 gauge in diameter and at least 1 cm in length after a fine needle aspiration (FNA) specimen are obtained and shipped in formalin to the ETCTN Biorepository.

If fine needle aspiration (FNA) is available, especially for sampling of bone lesions to assure specimen adequacy and to avoid specimen decalcification, use of FNA before core needle biopsy is preferred. For all specimen types, the tumor cellularity yielded by FNA may be superior to core needle biopsy in some patients, particularly when the lesion is comprised predominantly of fibrosis, bone, or other non-tumor tissue. However, it is very unlikely that an FNA will provide enough material to complete WES or RNA seq.

Real-time cytopathologic immediate evaluation of the FNA specimen can confirm that the chosen target area of a lesion is satisfactory for obtaining the core needle biopsy specimens. This preferred procedure with on-site assessment increases the frequency of successful molecular testing for patient eligibility.

If real-time cytopathology assessment of FNA specimens is not available, collection of FNA specimens prior to core needle biopsy procurement is recommended.

Specimens should be placed immediately into buffered formalin (provided at the site) in the provided specimen collection container.

5.5.3.1.4 Collection of Snap-Frozen Biopsy

After sufficient cores have been collected for shipping in formalin, and if the patient has provided consent to collect additional tissue, another 1-2 core biopsies may be collected, snap-frozen and stored under vapor phase liquid nitrogen, and shipped on dry ice for banking at the ETCTN Biorepository.

5.5.3.1.5 Acceptable Biopsy Procedures and Specimen Types

- Core needle biopsy tissue (4 cores if possible) and touch preparation slides. Inclusion of fine needle aspiration (FNA) smears (unstained) and rinses are preferred but not required. Submission of FNA alone is not acceptable.
  - Percutaneous biopsy with local anesthetic.
  - Excisional cutaneous biopsy with local anesthetic.
  - Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications <2%.
  - Biopsy with removal of additional tumor tissue during a **medically necessary** mediastinoscopy, open surgery, laparoscopy, gastrointestinal endoscopy, peritoneal, bronchoscopy, or craniotomy.
  - Removal of additional tumor tissue during a medically necessary surgical procedure.

A preexisting formalin-fixed paraffin-embedded (FFPE) tumor tissue block may be submitted for analysis in addition to, or in lieu of, a new biopsy sample. Tissue must have been collected within 6 months prior to registration.

Brain biopsies will be permitted ONLY if the patient has medical necessity for craniotomy for clinical care, (e.g. candidate for a primary re-resection).

Mediastinal, open surgical or laparoscopic, gastrointestinal, peritoneal or bronchial endoscopic biopsies are permitted ONLY when obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial.

No laparoscopic, or endoscopic or open surgical procedure will be performed solely to obtain a biopsy for this protocol.

Contraindications to percutaneous biopsy:

- Significant coagulopathy or anticoagulation treatment that cannot be adequately corrected.
- Severely compromised cardiopulmonary function or hemodynamic instability.
- Lack of a safe pathway to the lesion.
- Inability of the patient to cooperate with, or to be positioned for, the procedure.

If a site is deemed appropriate for biopsy with minimal risk (no more than 2% risk of serious complication requiring hospitalization) to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made.

[Additional specimen types as needed]

5.5.3.1.6 Imaging Procedures

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be performed only if they are considered to be of low risk (<2% major complication rate) to the participant as determined by the investigators and Interventional Radiologist.

5.5.3.1.7 Oversight of Tumor Specimen Collection

For biospecimen collection, it is suggested, but not required, that a pathologist or qualified designee at the submitting institution assure the presence of tumor in solid tissue specimens and deem the biospecimen suitable for research with minimally 30% non-necrotic tumor content. If a pathologist or designee is not available at the submitting institution, the pathologist at the ETCTN Biorepository will assess tumor quantity and quality.

Alternatively, the pathologist of the submitting institution may confirm histopathology and histological characteristics of the biospecimen.

It is the responsibility of the submitting institution to provide only those biospecimens that are not necessary for diagnostic purposes.

5.5.3.1.8 Procedure to Recall Biospecimens for Diagnostic/Patient Care Purposes

If needed, residual tissue or blood that is currently stored in the biobank can be reclaimed. If DNA or RNA analysis is required, some or all specimens may be retuned for documented diagnostic/patient care or medically necessary events, including a request by or on behalf of the patient for tissue to determine eligibility for enrollment in a research protocol/clinical trial. Accessioned specimens, extracted nucleic acids, or slides sent to a reference laboratory **cannot be reclaimed**.

The ETCTN Biorepository will need to be notified in writing of the specific reason for recalling the specimens as well as of what specimen types (*e.g.*, FFPE blocks) need to be returned. Investigators should use their local records to retrieve and provide the number of the specimen that needs to be returned.

A description of the extenuating circumstance(s) will be required to accommodate the recall request. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness. This does not cover patient issues related to needing or wanting

genetic information or specimens for genetic testing for personal risk from germline or somatic findings.

5.5.3.1.9 Supportive Care

Local anesthesia will be administered as needed. Sedation may be used for comfort if considered safe for the patient.

Brain biopsies will be permitted ONLY if the patient has medical necessity for craniotomy for clinical care, (e.g. candidate for a primary re-resection). Open or laparoscopic surgical biopsies, mediastinal, gastrointestinal, or bronchial endoscopic biopsies can ONLY be obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial.

5.5.3.2 Handling of Specimens(s)

5.5.3.2.1 Processing of Biospecimens

Specimens received at the ETCTN Biorepository for molecular characterization analyses, such as WES and RNA-Seq, will be processed for DNA/RNA extraction as follows:

Tumor tissue received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide, and for nucleic acid extractions, additional RNase-free slides.

Whole blood collected in Streck tubes will be centrifuged to separate PBMCs and plasma, and will be stored in a -80°C freezer.

DNA and RNA will be co-extracted from tumor tissue. DNA will be extracted from the whole blood collected in the EDTA tube. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA and RNA will be shipped to the central sequencing laboratory for analysis.

5.5.3.2.2 Next Generation Sequencing

DNA and RNA libraries for WES and RNA-Seq will be generated at the central sequencing laboratories by standard procedures. Sequencing will be carried out on an Illumina 2500 sequencer, and these results will have variant calling through the procedures associated with the GDC. Results from these assays, annotated with limited clinical data (presentation, diagnosis, staging, summary treatment, outcome, etc.), will be stored in the Database of Genomes and Phenotypes (dbGaP) and in the GDC.

[Add handling details for other bioassays as needed]

5.5.3.2.3 Banking and Use of Specimens in Future Research

Any biospecimens remaining after processing will be retained indefinitely at the ETCTN Biorepository under appropriate storage conditions. Specimen types may include:

- FFPE block
- Snap-frozen tumor biopsy samples
- PBMCs
- Plasma from Streck tubes (for future cfDNA analysis)
- Isolated nucleic acids
- *[Add other specimen types as needed]*

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained at the ETCTN Biorepository. Protocol-specified studies should be clearly described and prioritized in the protocol, and in general, should not require additional review and approval. Investigators are encouraged to consult with the ETCTN Biorepository for the evaluation of residual tissue specimens approaching depletion for protocol-specified studies.

Banked specimens may be distributed to investigators for laboratory research studies as specified in the protocol or after appropriate review of the proposed research studies by CTEP. In cases where additional clarification about laboratory research studies is needed, review and approval of a submitted analysis and data sharing plan by the NCI, ETCTN, CIRB, and if appropriate, the NCI Collaborator, may be needed.

If future use is denied or withdrawn by the patient, the samples will be destroyed and not used in any future study. Biospecimen recalls for patient issues related to needing/wanting genetic testing to determine personal risk from germline/somatic findings is not permitted (see Procedure to Recall Biospecimens).

The ETCTN Biorepository will not deplete a biospecimen unless written permission is received from the ETCTN Program Directors or designee. The investigator must provide a written proposal describing the nature of the research to be performed, the technical and analytical validation of the assays being used, the goals, objectives and statistical analysis plan for the research being performed. The investigators should submit this concept/proposal through the CTEP Protocol and Information Office (PIO). The proposal will be reviewed by the Medical Officer assigned to the protocol and will be reviewed by the CTEP Protocol Review Committee (PRC) for approval or disapproval for use of biospecimens that may be depleted.

Manual checks of minimal biospecimens may occur at the time of distribution to confirm the amount available in relationship to the amount requested by the researcher. Once minimal amounts are reached, the ETCTN Program Directors of the biospecimen resource is notified before specimens are distributed.

5.5.3.3 Shipping of Specimen(s)

5.5.3.3.1 Specimen Kits and Shipping to the NCI Molecular Characterization Laboratory

Additional information about specimen procurement kits and specimen collection, labeling, processing and shipment to the NCI Molecular Characterization Laboratory are provided in the ETCTN BMCI Laboratory Manual. Please refer to the manual for details.

Shipping Address

Ship the specimen collection to the address below using overnight courier (FedEx), early morning delivery option.

ETCTN Biorepository
Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the ETCTN Biorepository, utilizing the site screening and base intervention payments.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

[Add shipping details for specimens that will be analyzed by reference labs other than the NCI Molecular Characterization Laboratory as needed.]

5.6 Special Studies

5.6.1 *Title – Special Correlative Study #1*
5.6.1.1 Outcome Measure
5.6.1.2 Assessment
5.6.1.2.1 Method of Assessment
5.6.1.2.2 Timing of Assessment
5.6.1.3 Data Recording
5.6.1.3.1 Method of Recording
5.6.1.3.2 Timing of Recording

6. TREATMENT AND/OR IMAGING PLAN

Renumber sections as necessary depending on which sections are included for phase 1 or 2, single-agent or combination, or imaging protocols.

6.1 Agent Administration

Treatment will be administered on an *[inpatient/outpatient]* basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

For phase 1 dose-escalation protocols: State the starting dose of each agent and describe the dose escalation scheme and treatment regimen. ***Use exact doses rather than percentages****. If appropriate, a table may be used to describe the regimen; see examples below for phase 1 single-agent and combination protocols. Please refer to the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm) for Guidelines for Treatment Regimen Nomenclature and Expression.*

The table may include the route of administration (PO, IV, etc.*) and dosing schedule (QD, BID, Days 1-5,* etc.*). Alternatively, this information may be presented in a separate "Regimen Description" table (see below for an example).*

Example for phase 1 single-agent protocols:

Dose Escalation Schedule	
Dose Level	Dose of *[CTEP IND Agent]* *
Level 1	
Level 2	
Level 3	
Level 4	
Level 5	
* *Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*	

Examples for phase 1 combination protocols:

Dose Escalation Schedule			
Dose Level	**Dose***		
	***[Agent X]* (units)**	***[Agent Y]* (units)**	***[Agent Z]* (units)**
Level 1			
Level 2			
Level 3			
Level 4			
Level 5			
**Doses are stated as exact dose in units (*e.g., *mg/m^2, mcg/kg, etc.) rather than as a percentage.*			

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
[Agent X]	*Premedicate with dexamethasone for 3 days prior to [Agent X]*	*** in 500 cc NS*	*IV over 2 hours **before** [Agent Y]*	*Days 1-3, week 1*	*28 days (4 weeks)*
[Agent Y]	*Avoid exposure to cold (food, liquids, air) for 24 hr after each dose.*	*** in 250 cc D5W*	*IV 1 hr after completion of Agent A through separate IV line*	*Days 1-3, week 1*	
[Agent Z]	*Take with food.*	*** tablet*	*PO in the a.m.*	*Daily, weeks 1 and 2*	
***Doses as appropriate for assigned dose level.*					

*For phase 2 protocols: Please describe the regimen (agent, dose, route, and schedule; the sample "Regimen Description" table above may be used, or another table format) and state any special precautions or warnings relevant for investigational study agent administration (*e.g., *incompatibility of the agent with commonly used intravenous solutions, necessity of administering agent with food, how to round a dose of oral agent to available tablet/capsule strengths, premedications etc.). Please refer to the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm) for Guidelines for Treatment Regimen Expression and Nomenclature.*

NOTE: For orally administered agents, a method for assessing compliance with treatment should be included, i.e., "The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course."

6.1.1 CTEP and/or CIP IND Agent(s)

*Please describe in detail any prophylactic or supportive care regimens required for investigational study agent(s) administration and state any special precautions or relevant warnings (*e.g.*, incompatibility of agent with commonly used intravenous solutions, necessity of administering agent(s) with food, premedications, etc.).*

6.1.2 Other Agent(s)

*Please describe in detail any prophylactic or supportive care regimens required for administration of <u>each</u> other agent in the treatment and state any special precautions or relevant warnings (*e.g.*, incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.).*

6.1.3 Other Modality(ies) or Procedures

*Please provide a detailed description of any other modalities (*e.g.*, surgery, radiotherapy) or procedures (*e.g.*, hematopoietic stem cell transplantation) used in the protocol treatment. If this study involves no other modalities or procedures, this section should be marked "N/A".*

6.1.4 Investigational Imaging Agent Administration

*Please describe the imaging agent regimen (agent, dose, route, schedule, timing relative to imaging, special precautions or procedures, required pre-administration lab parameters [*e.g.*, blood glucose]) for imaging agent administration.*

Please provide the following sections:

Image Acquisition Details:

Image Analysis Details:

Image Interpretation Details (including whether there will be local and/or central review, *etc.*):

Imaging Related Procedures:

6.2 *For phase 1 protocols only:* Definition of Dose-Limiting Toxicity

Please provide explicit definitions of the type(s), grade(s), and duration(s) of adverse events that will be considered dose-limiting toxicity(ies), or provide definitions of other endpoints that will be used to determine dose escalations.

Management and dose modifications associated with the above adverse events are outlined in Section 7.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. *An alternative dose-escalation design of the investigator's choice may be substituted, but should be fully detailed here, and a supporting rationale should be provided in this protocol (e.g. in the introduction/background). An example (accelerated titration) can be found on the following Web site (http://linus.nci.nih.gov/~brb/Methodologic.htm).*

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

6.3 Dose Expansion Cohorts:

Once the RP2D is reached, an additional *[insert #; suggest 6]* will be treated at this dose. For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the Principal Investigator will discuss with all

study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. *[Trials using Medidata Rave must keep the following sentence; other protocols may adapt the language in accordance with the monitoring method being used:]* Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.4 General Concomitant Medication and Supportive Care Guidelines

Please state guidelines for use of concomitant medications or any additional appropriate supportive care medications or treatments. The potential for interaction with the cytochrome P450 system should be addressed if applicable. Please use or modify the following paragraph as appropriate.

Because there is a potential for interaction of *[CTEP and/or CIP IND Agent(s)]* with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. *[For example, the potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors. Check the study agent Investigator's Brochure for potential sources of drug interactions]*. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *[# cycles]* or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy

- All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor

- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.6 Duration of Follow Up

Patients will be followed for *[# of weeks/days; <u>minimum</u> of 30 days, or longer depending on the specific agent and protocol]* after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

Treatment plans should explicitly identify when treatment (typically dose) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema.

The following format for an orally available agent is provided as an example and should be modified as appropriate for this protocol.

*<u>If there is an **agent-specific protocol template** available from CTEP, please refer to it for the most current dose modification guidelines for that agent.</u>*

Dose Level	***[Agent Name]* Dose**
-2	*XX mg, schedule*
-1	*XX mg, schedule*
0	*XX mg, schedule*
+1	*XX mg, schedule*
+2	*XX mg, schedule*
+3	*XX mg, schedule*

Note: *All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.*

For combination studies, dose modifications/treatment delays for [CTEP and/or CIP IND Agent(s)] and [Other Agent(s)] may be presented separately or together, as appropriate. Use of a table format is recommended if applicable.

Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use as appropriate. In addition, for your convenience, a blank dose modification table has been provided. Note in the text that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Nausea	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy

Diarrhea	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Neutropenia	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Insert any recommended management guidelines, if appropriate.		

Thrombocytopenia	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Insert any recommended management guidelines, if appropriate.		

Example of Dose Modification Table:

Event	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	*Insert appropriate management guidelines in this column.*	*Insert appropriate management guidelines in this column.*
Grade 2		
Grade 3		

Event	**Management/Next Dose for *[Agent Name]***	**Management/Next Dose for *[Agent Name]***
Grade 4		
**Footnote any relevant guidelines regarding how long a delay in therapy is allowed before patients should go off protocol therapy* ***Footnote any relevant guidelines regarding how many dose reductions are allowed before patients should go off protocol therapy.*		
Insert any recommended management guidelines, if appropriate.		

8. PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

*Sections provided below should be used or deleted as necessary. Adjust the heading levels as appropriate (*e.g.*, if only one agent is included in the protocol template, the subsections below can be deleted, and the pharmaceutical information for that agent inserted directly under heading 8.1). Include a subsection regarding* ***Availability, Ordering,*** *and* ***Accountability*** *for each agent included in the protocol.*

8.1 CTEP and/or CIP IND Agent(s)

Confidential *pharmaceutical information for investigational study agents supplied by CTEP and/or CIP will be provided as attachments to the approved Letter of Intent (LOI) response and should be inserted below as indicated.*

8.1.1 CTEP and/or CIP IND Agent #1 (NSC #)

Insert pharmaceutical and/or imaging information for CTEP and/or CIP IND Agent #1 here.

For CIP agents, include reference to the current Investigator's Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator's Brochure and/or supplier.

Availability

[CTEP and/or CIP IND Agent #1] is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

[CTEP and/or CIP IND Agent #1] is provided to the NCI under a Collaborative

Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.2 CTEP and/or CIP IND Agent #2 (NSC #)

Insert pharmaceutical information for CTEP and/or CIP IND Agent #2 here. If only a single CTEP and/or CIP IND Agent will be used in the trial, this section and the text below should be deleted.

Availability

[CTEP and/or CIP IND Agent #2] is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

[CTEP and/or CIP IND Agent #2] is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

[PMB will provide direction as to when sites can order PMB-supplied agents.]

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Other Investigational Agent(s)

If there are no other investigational agent(s) in this study, this section and the instructions below should be deleted.

A separate pharmaceutical section is needed for each investigational agent containing at least the following information, available from the appropriate Investigator's Brochure:

***Product description**: Include the available dosage forms, ingredients, and packaging, as appropriate. Also state the agent's supplier.*

***Solution preparation** (how the dose is to be prepared): Include reconstitution directions and directions for further dilution, if appropriate.*

***Storage requirements:** Include the requirements for the original dosage form, reconstituted solution, and final diluted product, as applicable.*

Stability: *Include the stability of the original dosage form, reconstituted solution, and final diluted product, as applicable.*

Route of administration: *Include a description of the method to be used and the rate of administration, if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30-60 minutes, intravenous bolus, etc. Describe any precautions required for safe administration.*

Agent Ordering: *Include instructions for agent procurement processes.*

For imaging agents, include reference to the current Investigator's Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator's Brochure and/or supplier.

8.3 Commercial Agent(s)

If there are no commercial agent(s) in this study, this section and the instructions below should be deleted.

A separate pharmaceutical section is needed for <u>each</u> agent containing at least the following information, available in the manufacturer's current package insert:

Product description*: Include any dosage form(s), ingredients, and packaging applicable to the protocol. Also, state the agent's supplier or state that it is commercially available.*

Solution preparation *(how the dose is to be prepared): Investigators may refer the reader to the package insert for 'standard' preparation instructions. If the agent is to be prepared in a 'non-standard' or protocol-specific fashion, the reconstitution directions and instructions for further dilution must be included. Appropriate storage and stability information should be included to support the method of preparation.*

Route of administration: *Include a description of the method to be used and the rate of administration, if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30-60 minutes, intravenous bolus, etc. Describe any precautions required for safe administration.*

Agent Ordering: *Include instructions for agent procurement processes. If agent is being purchased, state that the agent is commercially available. Or, if commercial agent is being provided for the study, the supplier should be identified.*

For imaging agents, include reference to the current Investigator's Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator's Brochure and/or supplier.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

Please specify the study design and primary endpoints. Include information on how toxicity will be graded and reported, and state that all patients who receive any amount of the study drug will be evaluable for toxicity. Precisely define the dose escalation scheme and MTD definition (or refer to the section where they are defined). Alternative dose escalation designs may be used (e.g., accelerated titration), but should be fully described in the protocol. An example of an alternative dose escalation schedule can be found on the following Web site (http://linus.nci.nih.gov/~brb/Methodologic.htm). If an optimal biologic dose will be determined in place of or in addition to the MTD, precisely define how this will be done.

Any phase 1, phase 1 combination, or phase 2 study that proposes the use of an expansion cohort, regardless of size or phase, must include a statistical plan for analysis and a stopping rule for futility where appropriate as part of the statistical analysis plan. Types of expansion cohorts include cohorts for dose/schedule refinement, a variety of tumor types, a variety of molecularly-defined subsets, or other drug combinations. Where appropriate, eligibility criteria should be provided and addressed in the informed consent document. A rationale for the inclusion of specific tumor types should be provided. A sample size justification is needed. Defined endpoints for efficacy and futility should be part of the statistical analysis plan.

For recommendations regarding Phase 1 studies, please see the following reference:
Ivy SP, L Siu, E Garrett-Mayer, and L Rubinstein. (2010). Approaches to phase I clinical trial design focused on safety, efficiency, and selected patient populations: A report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res. 16(6):1726.
URL: http://clincancerres.aacrjournals.org/content/16/6/1726.abstract

For recommendations regarding Phase 2 studies, please see the following reference:
Seymour L, SP Ivy, D Sargent, et al. (2010). The design of phase II clinical trials testing cancer therapeutics: Consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res. 16(6):1764.
URL: http://clincancerres.aacrjournals.org/content/16/6/1764.abstract

Additional recommendations for phase 1 and 2 trials can be found on the CTEP website:
http://ctep.cancer.gov/

9.2 Sample Size/Accrual Rate

*Please specify the planned sample size and accrual rate (*e.g.*, patients/month). Add information regarding advanced imaging sample size as appropriate.*

In accordance with NIH policy, the inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the

scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender, race, and ethnicity, and provide a rationale for selection of subjects. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

The NCI suggests that the accrual targets be based on data from similar trials completed by your organization during the previous 5 years. It is hoped that the accrual targets will resemble the gender, ethnic, and racial composition of the U.S. population as closely as possible. Please see the Protocol Submission Worksheet (http://ctep.cancer.gov/forms/docs/psw.docx) for a complete description of ethnic and racial categories and a sample table (which is also provided below).

Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable). Note in some cases, an acceptable response is "Do Not Wish to Provide."

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American					
White					
More Than One Race					
Total					

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9.3 Stratification Factors

Please specify any planned patient stratification factors. Indicate whether dose escalation and MTD determination will be done for each stratum individually.

9.4 Analysis of Secondary Endpoints

If secondary endpoints are included in this study, please specify how they will be analyzed. In particular, brief descriptions should be given of analyses of pharmacokinetic, biologic, and correlative laboratory endpoints.

If responses are reported as a secondary endpoint, the following criteria should be used. Every report should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. It is preferred that 95% confidence limits are given.

9.5 For phase 2 protocols only: Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with *[CTEP and/or CIP IND Agent(s)]*.

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

*The Comprehensive Adverse Event and Potential Risks (CAEPR) list for CTEP-supplied agent(s) will be provided with the LOI approval letter. Sections provided below should be used or deleted as necessary. Adjust the heading levels as appropriate (*e.g.*, if this template is being used for a single-agent protocol, the subsections below can be deleted, and the CAEPR for that agent inserted directly under heading 10.1).*

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.
NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

10.1.1 CAEPRs for CTEP IND Agent(s)

10.1.1.1 CAEPR for [CTEP IND Agent #1]

The Comprehensive Adverse Events and Potential Risks (CAEPR) list will be provided with the LOI approval letter. Please insert the CAEPR here.

10.1.1.2 CAEPR for [CTEP IND Agent #2]

The Comprehensive Adverse Events and Potential Risks (CAEPR) list will be provided with the LOI approval letter. Please insert the CAEPR here.

10.1.1.3 Adverse Event List(s) for [Other Investigational Agent(s)]

Agent not supplied by CTEP: Please include a comprehensive list of all reported adverse events and any potential risks (such as the toxicities seen with another agent of the same class or risks seen in animals administered this agent) as provided by the manufacturer.

10.1.2 Adverse Event List(s) for Commercial Agent(s)

For each commercial agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the package insert(s) for the comprehensive list of adverse events.

10.1.3 CAEPR for [CIP IND Agent #1]

The Comprehensive Adverse Events and Potential Risks (CAEPR) list will be provided with the LOI approval letter. Please insert the CAEPR here.

For each CIP and/or commercial image agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the Investigator's Brochure and/or package insert(s) for the comprehensive list of adverse events.

10.1.4 Adverse Event List(s) for CIP (e.g. Study-Specific) Commercial Imaging Agents

For each CIP study-specific commercial imaging agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the Investigator's Brochure and/or package insert(s) for the comprehensive list of adverse events.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) **NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not

they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Grade 1 and 2 Timeframes	Grade 3-5 Timeframes
10 Calendar Days	24-Hour 5 Calendar Days

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for **ALL** Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution.

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1	Grade 2	Grade 3 Timeframes	Grade 4 & 5

	Timeframes	Timeframes		Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

FOR USE IN CIP STUDIES INVOLVING COMMERCIAL (NON-IND/IDE) AGENTS ONLY

CIP Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a CIP Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes

<table>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td>Not required</td><td>10 Calendar Days</td></tr>
<tr><td colspan="4">NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

<u>Expedited AE reporting timelines are defined as:</u>
○ “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
○ “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.</td></tr>
<tr><td colspan="4">[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
• All Grade 4, and Grade 5 AEs
Expedited 10 calendar day reports for:
• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization Grade 3 adverse events

[2] For studies using PET or SPECT agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011</td></tr>
</table>

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

<u>For this protocol only</u>, the AEs/grades listed below <u>do not require expedited reporting via CTEP-AERS</u>. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]

[a] Indicates that an adverse event required <u>hospitalization</u> for ≥24 hours or <u>prolongation of hospitalization by</u> ≥24 hours of a patient.

- *Use CTCAEv5.0 terminology to specify a System Organ Class (SOC) and a pertaining Adverse Event (AE) to be excluded from expedited reporting (“protocol-specific exclusion,” or PSE) via CTEP-AERS. Examples:*
  - *For example, instead of “Neuropathy” or “Peripheral neuropathy,” which are not CTCAEv5.0 terms, list <u>each</u> specific CTCAEv5.0 term that applies*

("Peripheral motor neuropathy," "Peripheral sensory neuropathy," etc.) and the pertaining SOC "Nervous system disorders".
    - *Instead of "Myelosuppression", which is not a CTCAEv5.0 term, list the AE "Anemia" from the SOC "Blood and lymphatic system disorders" and the AEs "Lymphocyte count decreased" and "Neutrophil count decreased", Platelet count decreased", and "White blood cell decreased" from the SOC "Investigations".*
- *Enter grades for all AEs listed in the table.*
    - *Note: If a specific grade X is listed **without** **a prefix symbol of "≤"**, it is assumed that 1) this specific grade plus all lower grades of that AE are excluded from expedited reporting, and 2) all criteria defining that PSE (e.g., "≥24 h hospitalization") will apply for ≤ grade X.*
    - *If different exclusion criteria should apply to different grades of the same AE, enter pertaining PSEs in separate rows. For example, if grade 4 diarrhea is a PSE **unless** it results in "≥24 h hospitalization", but grades 1-3 are PSEs **regardless** of whether they result in "≥24 h hospitalization", grade 4 must be entered in a separate row from grades 1-3.*
- *For the "≥24 h hospitalization" column, enter "Regardless" or "No" depending on which of the following applies:*
    - *If an AE of a grade X **is excluded** from expedited reporting **regardless of whether** it results in ≥24 h hospitalization or ≥24 h prolongation of hospitalization of a patient, enter "**Regardless**".*
    - *"If an adverse event of a grade X is **excluded** from expedited reporting via CTEP-AERS only when **it DOES NOT** result in ≥24 h hospitalization or ≥24 h prolongation of hospitalization, enter "**No**".*
- *If AEs from the same SOC share the same criteria for exclusion from expedited reporting (Grade and Hospitalization), they may be listed in the same row. However, list all applicable individual CTCAEv5.0 terms.*

For protocols including advanced imaging, please insert information as to the window of time and all other parameters that will determine eligibility of events for AE reporting. For example, for studies using PET and SPECT, or MR, the AE reporting period is limited to:

- [PET & SPECT = 10 radioactive half lives rounded UP to the nearest whole day]
- [MR = 30 days]

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

*The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete:*
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in

future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be

modified as appropriate.

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[c]
[CTEP and/or CIP IND Agent]		A			A			A			A			
[Other Agent(s)]		B	B		B	B		B	B		B	B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every *[# weeks]* weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every *[# weeks]* weeks.												X
B-HCG	X[b]													
Advanced imaging events, as appropriate														
Other tests, as appropriate														
Other correlative studies														

A: *[CTEP and/or CIP IND Agent]*: Dose as assigned; *administration schedule*
B: *[Other Agent(s)]*: Dose as assigned*; administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.

12. MEASUREMENT OF EFFECT

*Please provide response criteria. If the criteria for solid tumors below are not applicable, the investigator(s) should provide agent- or disease-appropriate criteria (*e.g.*, for specific hematologic malignancies, supportive care agents, etc.) with references, and all solid tumor criteria should be deleted.*

For phase 1 protocols only: Although the clinical benefit of [this/these] drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *[# of weeks]* weeks. In addition to a baseline scan, confirmatory scans will also be obtained *[# of weeks]* weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *[# of weeks]* weeks. In addition to a baseline scan, confirmatory scans should also be obtained *[# of weeks]* (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *[CTEP and/or CIP IND Agent(s)]*.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable

dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans

should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

Include this section if time to progression or progression-free survival (PFS) is to be used. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.1.7 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

12.2 Antitumor Effect – Hematologic Tumors

Please provide appropriate criteria for evaluation of response and methods of measurement.

12.3 Other Response Parameters

Other endpoints and the criteria for their measurement should be entered below or reference should be made to the protocol section where these criteria may be found.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

The following language applies to ETCTN trials and other trials using the Central IRB (CIRB):

The language below must be included for any trial that will be reviewed by the Central Institutional Review Board (CIRB)

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a

minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

For non-Network trials and other trials not using the Central IRB:

The language below is intended for trials that are reviewed by an IRB other than the CIRB.

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

*The following three paragraphs may be deleted if Medidata Rave is **not** being used.*

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

The monitoring method will be determined by CTEP and communicated to you. Please use the appropriate text relating to your assigned monitoring method, and delete any text relating to the unused monitoring methods.

*For studies assigned for **CTMS Comprehensive** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

*For studies assigned for **CTMS Routine** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

*For studies assigned for **CDUS** monitoring (2 paragraphs):*
This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

For protocols including advanced imaging, please specify ALL requirements, timing, mechanisms, systems, and backups to be used for recording data to CRFs and reporting data to NCI. Include description of local or centralized image review.

13.2.2 Responsibility for Data Submission

ETCTN trials only:
Suggested text is provided below which can be modified as necessary. Non-Network trials should delete this language and use the "Non-Network" language on the next page.

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the

IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

Non-Network trials:
Suggested text is provided below which can be modified as necessary. If this study is being performed within a single institution, this section should be marked "N/A" and the text below deleted. ETCTN trials should also delete the text below.

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 13.2.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

13.3 CTEP Multicenter Guidelines

Non-Network multicenter studies:
The guidelines below and in Appendix B must be followed for multicenter ***Non-Network*** *studies. Suggested text is provided below which can be modified as necessary. If this study is being performed within a single institution, or if this is an ETCTN trial, this section should be marked "N/A" and the text below deleted.*

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

13.4 Collaborative Agreements Language

If a study agent is provided by CTEP under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA), Clinical Trials Agreement (CTA), Agent-CRADA or Clinical Supply Agreement (CSA)] with the Pharmaceutical Company, this section must be included in the protocol. Information on the study agent's Agreement status will be provided in the approved LOI response. If no Collaborative Agreement applies to the investigational study agent, this section should be marked "N/A" and the text below deleted.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the

Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.5 Genomic Data Sharing Plan

*If genomic data will be studied, analyzed, collected, and stored in an NIH/NCI Genomic Data Biorepository (*e.g.*, dbGaP, Cancer Genomic Database, other), please describe the genomic data sharing plan for this trial. Please refer to the NCI Genomic Data Sharing Policy at http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data for considerations regarding the sharing of data, protection of patient confidential information, and the provision of adequate information in the patient informed consent.*

For ETCTN studies participating in the Biobanking and Molecular Characterization Initiative, include the following text:
The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.6 Incidental/Secondary Findings Disclosure Procedure

For ETCTN studies participating in the Biobanking and Molecular Characterization Initiative, include the following text:
Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following

disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

14. REFERENCES

Please provide the citations for all publications referenced in the text.

The references below are applicable to text used by ETCTN studies participating in the Biobanking and Molecular Characterization Initative:

Green, R.C., J.S. Berg, W.W. Grody, *et al*. (American College of Medical Genetics and Genomics). (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 15(7):565-574.

Kalia, S.S., K. Adelman, S.J. Bale, *et al*. (2016). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 19(2):249-255.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

This appendix is for ***Non-Network*** *trials only. ETCTN trials may delete this appendix.*

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all

IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***[****insert study drug name****]***. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

[Use or delete sections below as appropriate.]

[Insert study drug name] interacts with *[(a) certain specific enzyme(s) in your liver*, certain transport proteins that help move drugs in and out of cells**, the heart's electrical activity (QTc prolongation)****] .

- *The enzyme(s) in question is/are ***[name(s) of CYP isoenzyme(s)]***, and *[insert brief, easy explanation of the nature of the interaction,* i.e., *for substrates: "[insert study drug name] is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme."]*
- **The protein(s) in question is/are ***[name of transporter(s)]*** and *[insert brief, easy explanation of the nature of the interaction,* i.e., *for substrates: "[insert study drug name] is moved in and out of cells/organs by this transport protein."]*
- ***The heart's electrical activity may be affected by *[insert study drug name]*. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

[Insert study drug name] may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is

helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

[Insert study drug name] must be used very carefully with other medicines that use certain ***[liver enzymes or transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity]***. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***["strong inducers/inhibitors or substrates]*** of ***[name(s) of CYP isoenzyme(s)], [transport protein(s), or any medicine associated with greater risk for having QTc prolongation."]***

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- *[Add other specific medications here, if necessary. Examples include acid suppressing drugs, anticoagulants, NSAIDS, digoxin.]*
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **_____.** This clinical trial is sponsored by the NCI. **_____** may interact with drugs that are ***[processed by your liver, or use certain transport proteins in your body or affects the electrical activity of your heart]***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a ***[specific liver enzyme called CYP_____, transport protein, heart's electrical activity (QTc prolongation)]***, and must be used very carefully with other medicines that interact with ***[this enzyme, transporter, or agent]***.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"[strong inducers/inhibitors or substrates of CYP_____, or transporter; or affect the heart's electrical activity.]***"
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is **_____**

  and can be contacted at **_____.**

APPENDIX D BIOASSAY TEMPLATES

If the protocol includes any ***integral*** *biomarker studies using* in situ *hybridization (ISH), immunohistochemistry (IHC), and/or DNA-based mutation assays, you may fill out the appropriate template (found at http://www.cancerdiagnosis.nci.nih.gov/diagnostics/templates.htm) and attach to this protocol submission as separate Appendices.*

If the laboratory or laboratories performing the studies has an alternatively-formatted document that supplies the same level of information regarding validation, materials and methods, etc*., it may be used instead of the templates.*

APPENDIX E COLLECTION OF SPECIMENS

*Collection procedures described in this Appendix E apply to the **ETCTN Biobanking and Molecular Characterization Initiative**.*

Specimen Procurement Kits and Scheduling Sample Collections

- **Specimen shipping kit:** Kits for the collection and shipment of specimens to the ETCTN Biorepository can be ordered online via the **Kit Management** system (https://ricapps.nationwidechildrens.org/KitManagement). Sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Each site may order two kit types per week (weekly max= 2 kits). If more kits are needed than the weekly allowance, contact the distribution center to discuss possible arrangements. Kits are shipped ground, so allow 5-7 days for receipt. Properly plan for additional kits as needed: Immediate ordering of new kits for future use is strongly recommended after existing kits are used. A complete list of kit contents for each kit type is located on the Kit Management system website and in the instructions included with the kits.

- **Scheduling of Specimen Collections:**

    - Tumor tissue cores collected during biopsy procedures that are fixed in the formalin (provided by sites) must be shipped on the same day as collection.

    - *[If the trial site does not perform paraffin embedding:]* Tissue can be collected **Monday through Wednesday** and shipped immediately overnight (FedEx Priority Overnight strongly preferred to avoid potential delays in specimen receipt and processing) for arrival on Tuesday through Thursday at the ETCTN Biorepository at Nationwide Children's Hospital.

    OR

    - *[If the trial site performs paraffin embedding:]* Tissue may be shipped in batches Monday through Wednesday since the Biorepository does not need to perform additional time-sensitive pre-analytic processing on them.

    - Snap-frozen cores may be shipped Monday through Thursday, since the Biorepository does not need to perform additional time-sensitive pre-analytic processing on them.

    - Blood specimens should be collected at the same time as tumor tissue collections and shipped in the same package. If, for any reason, blood specimens are collected alone, fresh blood specimens may be collected and shipped Monday through Friday. Saturday delivery is only available for shipments of fresh blood.

- Do not ship specimens the day before a US federal holiday. If you are unsure whether the ETCTN Biorepository will be able to receive specimens, then please contact the Biorepository.

Biopsy Collection Procedure: Sample collection at clinical sites

Core needle biopsy (CNB) tumor tissues will be collected for molecular profiling. Core biopsies at least 1 cm in length will be obtained through Interventional Radiology by a percutaneous approach using a 16-18-gauge needle. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy or endoscopic biopsy is allowed if medically indicated and can be used for analysis. Biopsies will be sent for analyses as defined in the protocol. Two to five core biopsies will be used for FFPE, and (optionally, and contingent on sufficient material and patient consent) 1-2 additional cores will be immediately snap-frozen in vapor phase of Liquid Nitrogen (LN2) as snap-frozen tissue for biobanking.

Fine-Needle Aspirate (FNA)

If fine needle aspiration (FNA) is available, especially for sampling of bone lesions in order to assure specimen adequacy and to avoid specimen decalcification, use of FNA before core needle biopsy is preferred. Real-time cytopathologic immediate evaluation of the FNA specimen can confirm that the chosen target area of a lesion is satisfactory for obtaining the core needle biopsy specimens. This preferred procedure with on-site assessment increases the frequency of successful molecular testing for patient eligibility.

If real-time cytopathology assessment of FNA specimens is not available, collection of FNA specimens prior to core needle biopsy procurement is recommended.

Please refer to the ETCTN BMCI Laboratory Manual for the FNA collection procedure and for coverslipping instructions.

Collection of Biopsy Specimen using Kits

Specimen jars for collecting tissue in formalin should be labeled with the participant ID, biopsy date and time of collection, protocol number, and type of material. The date and time of collection and shipping date must be entered into the Sample Tracking System (STS) for all submitted specimens.

Specimen size requirement is as follows:

•Surface area of 25mm^2 is optimal. Minimum is 5mm^2.
•Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3.

Excisional Cutaneous Biopsy Specimen Collection and Processing (ALTERNATE PROCEDURE)

These instructions also apply to additional specimens from medically necessary

endoscopic, laparoscopic, or surgical procedures performed for clinical care.

1. Verify patient identification, enrollment in OPEN, and signed consent.
2. Complete Sample Submission Form and label blood collection tubes, cassettes and all specimen collection containers.
3. Obtain four 16-gauge or 18-gauge core needle biopsy specimens from the region of the lesion in which the FNA (IF USED) yielded tumor, place two cores between sponges in each of the two cassettes (total of four cores), snap the cassette lids in place, place the two cassettes into the formalin-filled container as soon as possible after collection to prevent air drying, secure the container lid, and place the container into the shipping kit. If touch preparation slides of cores are made, allow to dry, and then place them in the slide cartridge. Secure the slide container lid and place it in the shipping kit.
4. For pathologic examination of removed tissue, place a portion of the biopsy specimen in a labeled specimen container with fixative for transport to your Pathology Department. (This specimen container is not provided in the shipping kit.) The pathology report must be uploaded to Medidata Rave as soon as available.
5. Log the samples in the in the ETCTN Rave Specimen Tracking System, print the STS-generated shipping manifest and corresponding pathology report and place into the shipping kit.

Collection of Snap-Frozen Specimen (OPTIONAL)

1. Pre-label the cryovial with the protocol, patient ID, patient initials, study visit, as well as the date of collection and snap-freeze the biopsy as specified in the ETCTN BMCI Laboratory Manual.
2. Ship frozen on dry ice (Monday to Wednesday) to the Biorepository (Nationwide Children's Hospital).

Formalin Fixed Paraffin-Embedded (FFPE) Tumor Sample for Research

Even when patients are able to provide a biopsy specimen, prior (archived) representative tumor tissue block may be requested from patients who consent "Yes" to "I agree to allow my tissue to be submitted for research." Tissue may be submitted with the initial biopsy material or separately.

If previously-collected FFPE will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- Formalin-fixed paraffin-embedded tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide,
- Twenty (20) 4 µm unstained air-dried plus slides,
- One (1) or more core punches (minimum of 4 mm diameter) from tumor block.

Blood Sample Collection

Whole blood (WB) samples will also be collected into 1 EDTA (purple-top) tube (10 mL) and 2 cell-free DNA (cfDNA) Streck tubes (2 × 10 mL) to obtain plasma/peripheral blood mononuclear cells (PBMCs).

Collection in EDTA (purple top) Tubes

Collect blood in EDTA tube, and gently invert 5-10 times to mix. Maintain specimens at ambient temeperature (room temperature) during collection and transport. Blood (10mL) collected in an EDTA (purple top) tube will be processed for plasma and DNA per the standard operating procedure (SOP) (see the ETCTN BMCI Laboratory Manual, Appendix: Processing Plasma from Whole Blood).

Collection in Streck Tubes

Collect blood in two cfDNA Streck tubes (10 mL), Cat No. 218992, and invert to mix. **Note: blood must be thoroughly mixed to ensure preservation of specimen.** After collection, blood in cfDNA Streck tubes **should never be refrigerated**, as this will compromise the specimen. Blood in cfDNA Streck tubes is stable at room temperature. These tubes will be shipped to the ETCTN Biorepository for further processing. Upon receipt at the ETCTN Biorepository, blood in cfDNA Streck tubes will be processed for plasma and DNA per the SOP (see the ETCTN BMCI Laboratory Manual, Appendix: Processing Plasma from Whole Blood).

APPENDIX F TRACKING OF SPECIMENS

*Tracking procedures described in this Appendix F apply to the **ETCTN Biobanking and Molecular Characterization Initiative**.*

Tracking of Specimens

It is required that all samples submitted under the ETCTN Biobanking and Molecular Characterization Initiative be entered and tracked using the ETCTN Rave Sample Tracking System (STS). To facilitate tracking of AEs related to the ETCTN Biobanking and Molecular Characterization Initiative, such as complications associated with any biopsy or biopsy-related anesthesia or imaging procedures, specimens submitted to the ETCTN Biorepository should be labelled TAC-BIOSPECIMEN COLLECTION.

Theradex-monitored trials that are shipping to reference laboratories other than the ETCTN Biorepository at Nationwide Children's Hospital are strongly encouraged to use the STS for tracking of their specimens, and should identify the laboratory where specimens are being shipped. Detailed instructions for use of the STS can be found in the ETCTN BMCI Laboratory Manual.

The date and time of collection and shipping date must be entered into the STS for all submitted specimens. Failure to update STS appropriately may result in delays in the central assessments and reporting the presence of deleterious mutations to the patient's treating physician. STS shipment manifest must be included in the package.

NOTE: The corresponding anatomical clinical pathology report (see the Patient Enrollment Instructions section of this protocol) MUST be submitted with the specimen for central confirmation of histology, or the sample will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist. If a new anatomical pathology report cannot be obtained, then the most recent available pathology report (identifying the malignancy) may be provided instead.

In the ETCTN BMCI Laboratory Manual, see the **Tracking of Specimens** section and the **Sample Tracking System Instructions** appendix.

APPENDIX G SHIPPING OF SPECIMENS TO THE ETCTN BIOREPOSITORY

*Shipping procedures described in this Appendix G apply to the **ETCTN Biobanking and Molecular Characterization Initiative**.*

Shipping to the Biobank

[If the trial site does not perform paraffin embedding:] Ship the core biopsies, EDTA tube, and Streck tubes as one shipment at ambient temperature **Monday through Wednesday** for overnight delivery to the Biorepository on Tuesday through Thursday. Note: if not collected the same day, blood can be shipped Monday through Friday for receipt Tuesday through Saturday. Do not delay shipment of tissue in formalin. Please use the same box to ship that was used to receive the kit contents.

OR

[If the trial site performs paraffin embedding:] Tissue may be shipped in batches Monday through Wednesday, since the Biorepository does not need to perform additional time-sensitive pre-analytic processing on them.

Labeling of Specimens

Tissue samples are to be labeled with:

- the Rave generated specimen ID (which includes the protocol number and universal patient ID)
- an Intrinsic ID,
- specimen type (P for primary or M for metastatic),
- collection date,
- surgical pathology ID (SPID) number, and
- block number from the corresponding pathology report.

Blood samples are to be labeled with:

- the Rave generated specimen ID (which includes the protocol number and Universal Patient ID),
- an Intrinsic ID,
- specimen type (blood),
- and collection date.

Packing Instructions

The shipment of all human tissue samples must comply with appropriate regulations as specified by the carrier. Frozen samples should be sent on dry ice. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

1. Before packaging specimens verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed and wrapped in parafilm.
2. Place samples into a biohazard envelope with absorbent material and seal the envelope securely.
3. Place the biohazard envelope into a Tyvek envelope and seal securely.
4. Place the sample(s) and a copy of the shipping manifest and corresponding pathology report (when applicable) and other forms listed in section 3.4.3 of the ETCTN BMCI Laboratory Manual into the insulated shipping container.
5. Place the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Place an Exempt Human Specimen sticker to the side of the container.
8. Ship samples via overnight courier (FedEx preferred) to the address listed below.

Additional notes for specimen shipping

Include a cold (not frozen) pack when shipping specimens during hot weather. In winter months, please include extra insulation, such as bubble wrap inside the shipping container, to prevent specimens from freezing.

When shipping slides, first place them in a plastic slide holder and stabilize by placing cotton or soft paper under the lid. Tape the lid so that is does not pop open during shipment (one piece of tape is sufficient).

Forms to be Included in specimen shipping

Copies of the following forms and reports are required to be included with all submissions of pathology materials:

- The pathology report(s) on tumor from the most recent pre-diagnostic biopsy or surgery specimen(s).

IMPORTANT NOTE: Corresponding anatomical clinical pathology report **MUST** be submitted with the specimen for central confirmation of histology, or the sample will not be processed. This can be a prior pathology report on the same malignancy.

- Reports on immunologic, immunohistochemical, or molecular studies, if performed on the pre-trial materials
- A completed Sample Submission Form. This form is to be submitted with tissue collected for research only
- The Sample Tracking System (STS) generated shipping manifest

NOTE: The pathology report for the submitted biopsy material, if pathology review was performed locally, is required to be uploaded into Rave as soon as it is available.

Shipping Address

Ship the specimen collection to the address below using overnight courier (FedEx), early

morning delivery option.

ETCTN Biorepository
Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the ETCTN Biorepository, utilizing the site screening and base intervention payments.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

APPENDIX H PROCESSING AND STORAGE OF BIOSPECIMENS AT ETCTN BIOREPOSITORY

*Procedures described in this Appendix H apply to the **ETCTN Biobanking and Molecular Characterization Initiative**.*

Core biopsies collected in kits (for FFPE) will be processed by the Biorepository using a Leica ASP6025 processor and paraffin embedded. Biopsies will be sectioned and H&E stained for Aperio scanning and storage of the image, as well as histopathologic analysis. Unstained sections will also be used to isolate DNA/RNA at the Biorepository. DNA/RNA will then be shipped to the NCI Molecular Characterization Laboratory lab for sequencing applications. Any unused FFPE blocks will be stored at the Biorepository.

Snap-frozen biopsies received by the biobank will shipped to the ETCTN Biorepository for biobanking.

Whole blood from both EDTA (purple top) and Streck tubes will be processed. Germline DNA will be isolated from blood; Streck tube samples will be used to isolate cell-free DNA (cfDNA) from plasma. DNA will be shipped to the NCI Molecular Characterization Laboratory for analysis.

Processing and Paraffin Embedding of Formalin Fixed Tissue

Biopsies will be processed for FFPE blocks by the sites or ETCTN Biorepository per the ETCTN BMCI Laboratory Manual (Appendix: Processing of Biopsies for FFPE blocks). Cell block for scanty specimens or smears will be performed by the sites or ETCTN Biorepository as per the ETCTN BMCI Laboratory Manual. (Appendix: Procedure for Cell Block Technique).

Following processing, the tissue will be paraffin embedded using a Thermo Histocenter.

Slides will be stained with H&E for image scanning and histopathological examination by a designated pathologist as per the ETCTN BMCI Laboratory Manual (Appendix: H & E Staining). The H&E section will serve to confirm original diagnosis and also estimate percent tumor content. An adequate biopsy sample will contain at least 50% tumor cells with minimal necrosis and stromal tissue.

RNase-free slides: Slides free of RNase will be created as per the ETCTN BMCI Laboratory Manual (Appendix: Procedure for Preparing RNase Free Slides or Scrolls [for both DNA and RNA Applications]).

Macrodissection: All specimens will undergo tumor enrichment using a standard macrodissection protocol as per the ETCTN BMCI Laboratory Manual (Appendix: Macrodissection) to ensure at least 50% tumor whenever possible.

Blood processing for Plasma/ PBMCs

PBMC processing

PBMCs will be isolated from both EDTA (purple top) and Streck tubes (see the ETCTN BMCI Laboratory Manual).

Plasma processing

Blood samples from Streck tubes will be processed to isolate cfDNA-containing plasma as per the ETCTN BMCI Laboratory Manual (Appendix: Processing Plasma from Whole Blood).

Storage of Specimens at ETCTN Biorepository

- Plasma samples will be stored in a -80°C freezer.
- PBMCs will be stored in a vapor phase of liquid nitrogen (LN_2) freezer.
- FFPE tissue blocks will be stored at ambient temperature.
- Snap-frozen tissue biopsies will be stored in a LN_2 vapor phase freezer.

Isolation of DNA/RNA for Whole Exome Sequencing/Targeted Exome Sequencing (WES/TES) from FFPE specimens and Blood/PBMCs

Biopsy will be extracted for nucleic acids using the Qiagen FFPE All-Prep procedure. 10-uM sections will be obtained for extraction of DNA/RNA. Please refer to the ETCTN BMCI Laboratory Manual (Appendix: DNA/RNA Isolation from FFPE Tissues using Qiagen AllPrep FFPE [DNA] and Roche Highpure miRNA [RNA] Kits).

DNA will also be extracted from PBMCs as detailed in the ETCTN BMCI Laboratory Manual (Appendix: DNA Isolation from Blood using Qiagen QIAamp Kit).

DNA quantitation will be performed using PicoGreen as per the ETCTN BMCI Laboratory Manual (Appendix: Picogreen DNA Quantification**)**.

RNA quality evaluation will be performed using Bioanalyzer (Agilent) as per the ETCTN BMCI Laboratory Manual (Appendix: RNA Nanoassay).

Shipping of Specimen to Central NCI Molecular Characterization Laboratory

All specimens that meet necessary quantity and quality will be sent for sequencing to the central NCI Molecular Characterization Laboratory (ETCTN BMCI Laboratory Manual [Appendix:

Shipping Procedures to NCI Molecular Characterization Laboratory]).

APPENDIX I ASSAY INFORMATION

*Assays described in this Appendix I apply to the **ETCTN Biobanking and Molecular Characterization Initiative**.*

Next-generation sequencing assays (WES and RNA-Seq) will be performed at the Molecular Characterization Laboratory on the purified DNA and RNA aliquots provided by the Biorepository.

Whole-Exome Sequencing/Targeted-Exome Sequencing (WES/TES)

DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated via digital droplet PCR (ddPCR). Library samples are denatured, diluted and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.

RNA-Seq

RNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated via ddPCR. Library samples are denatured, diluted, and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.

Refer to the ETCTN BMCI Laboratory Manual for additional details, including pipeline and data analysis specifications.

Add other applicable assays as needed.