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.

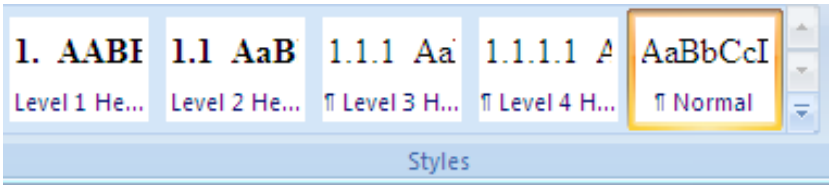
3. All sections in the Protocol Template should be retained to facilitate rapid review. If not appropriate for a given study, please insert "Not Applicable" after the section number and delete unneeded text. Depending on the phase of the study and whether it is a single-agent or combination agent study,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

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).



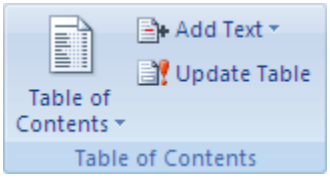
These heading styles will automatically update the Table of Contents (TOC) and convert to Bookmarks in a final PDF protocol document. **Please retain the heading styles.**

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:

   2007 & 2010 MS Word

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



   b. Click **Update entire table**.

   2003 MS Word

   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 2007/10)

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 grant or contract-level organization (Phase 1 Lead Academic Organization [LAO] or Phase 2 Consortium [P2C]) submitting the protocol. Please select from the table of LAOs and P2Cs below.*

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
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).*

The Principal Investigator and all physicians responsible for patient care must have a current FDA Form 1572, Supplemental Investigator Data Form (SIDF), Financial Disclosure Form

(FDF), and CV on file with CTEP. *Failure to register all appropriate individuals could delay protocol approval. If you are unsure of an investigator's status, please contact the Pharmaceutical Management Branch, CTEP at (240) 276-6575 or by e-mail at PMBRegPend@ctep.nci.nih.gov. Please indicate, on the title page, if an Associate Investigator is NOT responsible for patient care and therefore does not require a current 1572, SIDF, FDF, and CV on file.*

The protocol title page of the ***ETCTN*** *Rostered Model template lists all grantees and/or contractors that may potentially participate on an ETCTN protocol.* ***It is the responsibility of the Corresponding Organization to delete the rows of the LAO (UM1) grantees (if phase 2 only) or P2C (N01) contractors (if phase 1 only) that will not be participating on this study from the table below. Individual LAOs or P2Cs (individual rows) should not be deleted without prior approval from CTEP.*** *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, NCIC-CTG, CITN, BMTCTN, ABTC, PBTC, AMC, COGC) should be added under "Participating Organizations" as indicated below.*

Participating Organizations *(For trials involving LAOs,* ***all*** *LAOs must be included; for trials involving P2Cs,* ***all*** *P2Cs must be included.)*

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-IL057 / University of Chicago Comprehensive 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
P2C-11030 / University Health Network Princess Margaret Cancer Center P2C
P2C-CA189 / University of California Davis Comprehensive Cancer Center P2C
P2C-FL065 / H Lee Moffitt Cancer Center P2C
P2C-IL057 / University of Chicago Comprehensive Cancer Center P2C
P2C-MN026 / Mayo Clinic Cancer Center P2C
P2C-OH007 / Ohio State University Comprehensive Cancer Center P2C

P2C-TX035 / University of Texas M D Anderson Cancer Center P2C
Other Participating Rostered Organization #1 (e.g., ALLIANCE, ECOG-ACRIN, NRG, SWOG, COG, NCIC-CTG, 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) *Name* *Address*	*Investigator #1* *Name* *Telephone* *Fax* *E-mail address* *Investigator #2* *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

NCI Protocol #:
Version Date:

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.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

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.

Please insert additional secondary protocol objectives, if pertinent.

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".

3. PATIENT SELECTION

3.1 Eligibility Criteria

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).*

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 11. 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) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 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 Life expectancy of greater than *[#weeks or months]*

3.1.7 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	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.8 *Please insert other appropriate eligibility criteria.*

3.1.9 *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.

3.1.10 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 or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 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.

3.2.4 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.

3.2.5 *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 list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information. 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.]*

3.2.6 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.

3.2.7 *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.

3.2.8 *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.

3.2.9 *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 13.2).

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

*This section applies to **ETCTN** trials only. Non-Network 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 Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to the CTSU Regulatory Office before they can be approved to enroll patients.

The CTSU Regulatory Office tracks receipt of these documents in the CTSU Regulatory Support System (RSS), reviews for compliance, and transmits site approval data to CTEP.

*Keep the following paragraph for protocols reviewed by the **Central IRB (CIRB)-Early Phase Emphasis (EPE)**. Trials not reviewed by CIRB-EPE may delete the below paragraph.*

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing, or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (*i.e.*, laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

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.
- Click on the ETCTN link to expand, then select *[Phase 1 Grants or Phase 2 Consortia depending on which program is leading the trial]*, followed by *[Corresponding Organization]*, and protocol #*[NCI Protocol #]*.
- 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 automatically load to RSS.)

4.2.2 Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval *(and if applicable*, Model Informed Consent) to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.2.3 Checking **Site** Registration Status

Sites can check the status of their registration packets by querying the Site Registration subtab of the members' section of the CTSU Web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

Note: If possible, please allow three working days for site registration approval before attempting to enroll your first patient.

4.3 Patient Registration

The following text is to be used by Non-Network 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.

The following IWRS text is to be used by <u>CTMS-Monitored</u> Non-Network studies only:

<u>IWRS</u>

Patient Enrollment will be facilitated using the Interactive Web Response System (IWRS). IWRS is a web-based registration system available to users on a 24/7 basis. On a successful registration, IWRS will assign a patient number and assign the treatment. Patient enrollment data entered by Registrars in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. IWRS will provide a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- Users must have a valid CTEP-IAM account (*i.e.*, CTEP username and password) to access the IWRS system.
- Users defined with the Registrar role will have the ability to register patient in the study.
- Users defined with the Client Administrator role will have the ability to manage accrual limits, open and close treatment assignments as well as approve slot reservations, if applicable to the study.
- For trials with slot reservation requirements, Registrars will have the ability to request to reserve a slot, which may require approval from users at the lead institution defined as a 'Client Administrator' for the study.

Sections 4.3.1, 4.3.2, and 4.3.3 below are only to be used by ETCTN trials using OPEN/IWRS. Non-Network 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.

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.
- 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. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://theradex.com/CTMS/Downloads.aspx. 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: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

*The following paragraph applies to **ETCTN** trials **only**. Non-Network trials may delete this paragraph.*

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.]*

*The following two paragraphs are for **Non-Network** trials **only**. Trials conducted within the ETCTN may delete the following two paragraphs.*

Eligible patients will be entered on study centrally at the *[Coordinating Center]* by the Study Coordinator. All sites should call the Study Coordinator *[Telephone #]* to verify dose level availabilities. The required forms *[Name of Form(s)]* can be found in Appendix *[Appendix #]*. Following registration, patients should begin protocol treatment within 5 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: This can be edited for leukemia protocols where treatment should be started as rapidly as possible.]*

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP and/or CIP. 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.

5. 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.

5.1 Agent Administration

Treatment will be administered on an *[inpatient/outpatient]* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. 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]	***[Agent Y]***	***[Agent Z]***

	(units)	***(units)***	***(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."

5.1.1 *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.).*

5.1.2 *Other Agent(s)*

*Please describe in detail any prophylactic or supportive care regimens required for administration of each 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.).*

5.1.3 *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".*

5.1.4 *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:

5.2 *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 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. *An accelerated titration design of the investigator's choice may be substituted. An example 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.

5.3 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.

5.4 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, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be followed for *[# of weeks]* 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.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. 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:

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]***

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
*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		
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.		

7. 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 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 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 7.1).*

The Comprehensive Adverse Event 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 of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. 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.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 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.

7.1.1.2 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.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 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.

7.2 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access

to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 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 7.1.1) 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 7.3.4.

- **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.

7.3 Expedited Adverse Event Reporting

7.3.1 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 7.3.3).

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.

7.3.2 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.

7.3.3 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 <u>both</u> 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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria **<u>MUST</u>** 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

<u>Expedited AE reporting timelines are defined as:</u>

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

[1]Serious adverse events that occur **<u>more than</u>** 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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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 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

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

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]

7.4 Routine Adverse Event Reporting

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

*<u>The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete**:**</u>*
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.

7.5 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.

7.6 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.

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 7.1.

*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 12.3).

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 12.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can 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 and a "current" password. 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.

8.1.3.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.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. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Please briefly describe all planned correlative studies in the appropriate subsections 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 **all proposed biomarker studies** 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 13.4, 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 9.1, 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.

9.1 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.

9.1.1 *Title – Integral Laboratory Correlative Study #1*
9.1.1.1 Collection of Specimen(s)
9.1.1.2 Handling of Specimens(s)
9.1.1.3 Shipping of Specimen(s)
9.1.1.4 Site(s) Performing Correlative Study

9.1.2 *Title – Integral Laboratory Correlative Study #2*
9.1.2.1 Collection of Specimen(s)
9.1.2.2 Handling of Specimens(s)
9.1.2.3 Shipping of Specimen(s)
9.1.2.4 Site(s) Performing Correlative Study

9.2 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.

9.3 Integrated Correlative Studies

9.3.1 *Title – Integrated Laboratory Correlative Study #1*
9.3.1.1 Collection of Specimen(s)
9.3.1.2 Handling of Specimens(s)
9.3.1.3 Shipping of Specimen(s)
9.3.1.4 Site(s) Performing Correlative Study

9.3.2 *Title – Integrated Laboratory Correlative Study #2*
9.3.2.1 Collection of Specimen(s)
9.3.2.2 Handling of Specimens(s)
9.3.2.3 Shipping of Specimen(s)
9.3.2.4 Site(s) Performing Correlative Study

9.4 Exploratory/Ancillary Correlative Studies

9.4.1 *Title – Exploratory/Ancillary Laboratory Correlative Study #1*
9.4.1.1 Collection of Specimen(s)
9.4.1.2 Handling of Specimens(s)
9.4.1.3 Shipping of Specimen(s)
9.4.1.4 Site(s) Performing Correlative Study

9.4.2 *Title – Exploratory/Ancillary Laboratory Correlative Study #2*
9.4.2.1 Collection of Specimen(s)
9.4.2.2 Handling of Specimens(s)
9.4.2.3 Shipping of Specimen(s)
9.4.2.4 Site(s) Performing Correlative Study

9.5 Special Studies

9.5.1 *Title – Special Correlative Study #1*
9.5.1.1 Outcome Measure
9.5.1.2 Assessment
9.3.1.2.1 Method of Assessment
9.3.1.2.2 Timing of Assessment
9.5.1.3 Data Recording
9.3.1.3.1 Method of Recording
9.3.1.3.2 Timing of Recording

10. 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.

11. 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.

11.1 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.

11.1.1 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.

11.1.2 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.

11.1.3 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.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 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 beaccepted 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

11.1.5 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.

11.1.6 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.

11.1.7 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.

11.2 Antitumor Effect – Hematologic Tumors

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

11.3 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.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 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 (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

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.

12.1.1 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/CTMS. 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 ctms@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/CTMS. 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 ctms@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, either by FTP burst of data or via the CDS web application. 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.

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.

12.1.2 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 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).

See Section 12.1.1 for details on CDUS reporting. As the data management center for this trial, Theradex is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

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 12.1.1). 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.

12.2 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.

12.3 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. STATISTICAL CONSIDERATIONS

13.1 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). Accelerated escalation designs with intrapatient dose escalation are encouraged. An example 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.

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/

13.2 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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13.3 Stratification Factors

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

13.4 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.

13.5 *For phase 2 protocols only:* **Reporting and Exclusions**

13.5.1 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)]*.

13.5.2 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.

REFERENCES

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

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.*

SUMMARY OF CHANGES -- Consent

NCI Protocol #:
Local Protocol #:
Protocol Version Date:

Protocol Title:

Informed Consent Version Date:

Please provide a list of changes from the previous CTEP-approved version of the Informed Consent Document (ICD). The list shall identify by page and section each change made to the ICD with hyperlinks to the section in the ICD. 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.			*If there are no changes to the ICD, please use the following statement in the change memo of your protocol:* There are no changes to the content of the ICD. The date has been changed to match the most recent version of the protocol.
2.			
3.			
4.			
5.			

NCI Consent Form Template Version Date: May 12, 2013

NCI Consent Form Template for Adult Cancer Trials

NOTES FOR CONSENT FORM AUTHORS* (instructions updated 12/13/13):

- This document provides a Template to follow when writing consent forms for the majority of oncology trials. It recognizes the significant differences between various types of trials and provides phase-specific examples of recommended consent form language. This Template is not meant to be fully comprehensive; however, the lay language used and the format of the information should be followed as closely as possible when applying it to a specific study. In all cases, consent form authors should use simple language and be concise.

- Based upon the consensus of an expert, cross-disciplinary panel, the NCI strongly recommends that consent forms not exceed six to nine pages. Suggestions for making the consent form more concise include:
    1. Focus on what makes the study different from the care a patient would typically receive. Instead of trying to cover everything that might happen during the trial, limit the information to the research issues.
    2. Eliminate repetition of information.
    3. Use lay language and explain concepts simply.
    4. Use Times New Roman size 12 font.

- In the Template, instructions to consent form authors are formatted in a box. Placeholders for protocol-specific details, e.g., drug/intervention names and descriptions, are in italics; however, regular font should be used when inserting the details into the suggested consent form language.

- A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

- The Template date in the header is for reference to this Template only and should not be included in the consent form distributed to investigators.

- A simplified study schema should be included in the consent form if the study includes randomization, otherwise it is optional.

- Recommendations for use of educational attachments to the consent form may be found on the last page of this Template. For example, while a lay-language, easy-to-read study calendar is a useful tool for study participants, it should not be part of the main consent form but could be included as an optional attachment. IRB review of attachments is required. **For CTEP-sponsored trials**, the ICD and all attachments must be submitted as a **single Word** or **PDF** document.

*These notes for authors are instructional and should not be included in the consent form distributed to investigators.

NOTES FOR LOCAL INVESTIGATORS*:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

*These notes for investigators are instructional and should not be included in the consent form sent to IRBs.

Consent Form

Notes to consent form authors about the Study Title:

1. **Section length limit: Both titles together should take up no more than one-quarter page.**
2. Include two titles:
   a. The reader-friendly lay title, which is called the "Study Title for Study Participants".
   b. The official title, which can be used by potential study participants for Internet searches and aids in tracking by study administrative personnel.
3. For the lay title:
   a. Provide a brief (<20 words) title of the study in lay language.
   b. Use general terms.
   c. To make title concise, list the usual approach generically; e.g., chemotherapy, radiation therapy, surgery; rather than providing specific names, e.g., docetaxel, IMRT, laparoscopy.
   d. The study drug should be named.
   e. Use BOLD font.
4. For the official title:
   a. Insert study ID number, e.g., Protocol 0000, and official study title as provided by the study sponsor.
   b. Do not use BOLD font.

Study Title for Study Participants: (Insert Lay Title here)

Text Examples for Lay Title:

- **Testing the addition of the antibody, cetuximab, to usual chemotherapy in advanced lung cancer**

OR

- **Testing the combination of two approved chemotherapy drugs after surgery for early stage lung cancer**

OR

- **Testing pioglitazone to prevent oral cancer in people with oral leukoplakia**

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: (Insert Official Title here)

What is the usual approach to my *(insert type of cancer, precancerous condition, early detection, prevention of cancer, diagnosis, other)*?

Notes to consent form authors:

1. **Section length limit: This section should be between five and nine sentences and take up no more than one-quarter page.**
2. While there may not be a single, uniformly adopted standard of care in a particular disease, precancerous condition, or high-risk group, clinical trials generally assume a usual approach that the research hopes to improve upon. Providing a brief description of a usual approach, which should not be overly specific or detailed, allows the research to be placed into an appropriate context. Whenever appropriate, include an estimate of the expected outcome if the usual approach is utilized.
3. For chemoprevention trials, state the precancerous condition or high-risk status (e.g., current or former smoker, oral leukoplakia) and the usual intervention received if not participating in a study.
4. Avoid naming specific drugs as these could change with the availability of new treatments, except where a particular agent is so commonly accepted that it provides the easiest explanation.

Text Examples for Chemoprevention/ Supportive Care Studies:

Text Example: Chemoprevention Studies
You are being asked to take part in this study because you are at increased risk for *(insert type of cancer, e.g., lung)* cancer. People who are at increased risk and choose not to participate in a study are usually followed closely by their doctor to watch for the development of cancer or *(as appropriate)* may receive a hormonal agent *(specify)* that has been approved by the FDA.

Text Example: Screening/Supportive Care/Symptom Management Studies
Treatments for cancer can cause side effects such as nausea and vomiting. People who do not take part in this study will receive standard medications that have been approved by the FDA for nausea and vomiting.

Text Example: Behavioral Study
Treatments for cancer can cause side effects such as fatigue. People who do not take part in this study will receive recommendations, such as encouragement to exercise, and/or ways to adjust their daily activities so they are less tired.

Text Examples for Chemotherapy/Radiation Therapy/Surgery/Biologics/Imaging/Other Studies:

Text Example: Phase 1 First in Human/Novel Route/Combination Studies or Non-randomized Phase 2 Studies
You are being asked to take part in this study because you have *(insert type of cancer, e.g., advanced pancreas)* cancer. You have already been treated with *(insert treatment modality, e.g., chemotherapy)* and your disease is now growing. People who are not in a study are usually treated with *(insert usual treatment modality, e.g., more chemotherapy) (indicate if FDA-approved).*

Text Example: Phase 2 Single Arm Study of a New Agent
You are being asked to take part in this study because you have *(insert type of cancer, e.g., advanced brain cancer)* which has grown or has recurred. People who are not in a study are usually treated with either surgery, radiation, or with drugs *(indicate if FDA approved).* Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

Text Example: Randomized Phase 2/3 Studies in Previously Untreated Patients
You are being asked to take part in this study because you have *(insert type of cancer, e.g., advanced prostate cancer that is sensitive to hormones)*. People who are not in a study are usually treated with hormonal drugs *(indicate if FDA approved)*. Chemotherapy drugs are not usually used until the hormonal drug stops working against your type of cancer. For patients who receive the usual approach for this cancer, about *(insert appropriate number)* out of 100 are free of cancer at five years.

Text Example: Phase 3 Randomized Studies with Multiple Randomizations
You are being asked to take part in this study because you have *(insert type of cancer, e.g., advanced non-small cell lung cancer).* People who are not in a study are usually treated with surgery, chemotherapy, and radiation therapy. There are several FDA-approved chemotherapy drugs that are commonly used along with the radiation therapy. *(Modify the following sentence to be consistent with the study)* For patients who receive the usual approach for this cancer, about *(insert appropriate number)* out of 100 are free of cancer at five years.

Text Example: Imaging Studies
You are being asked to take part in this study because you have *(insert type of cancer, e.g., advanced lung)* cancer. People who are not in a study are usually diagnosed or have their treatment monitored with a *(insert type of scan, e.g., CT)* scan. These scans use *(insert type of mechanism, e.g., radiation, magnets)* to take pictures of your cancer.

What are my other choices if I do not take part in this study?

Notes to consent form authors:
1. **Section length limit: This section should be no more than one-quarter page.**
2. Additional bullets should include, when appropriate, alternative procedures or interventions.
3. For comparative effectiveness studies in which two approved commercially-available approaches (tests, drugs, surgery, radiation, diagnostics, etc.) are being compared, the option of receiving one of the approaches outside of the trial should be included.

Use the following text for all studies:
If you decide not to take part in this study, you have other choices. For example:
- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer *(as appropriate, consider adding) but you may want to receive comfort care to relieve symptoms.*

Why is this study being done?

Notes to consent form authors:

1. **Section length limit: This section should be between five and seven sentences and take up no more than one-quarter page.**
2. Provide a brief, phase-specific description of why the study is being done. For single arm phase 2 studies, indicate what is known about the drug/approach and indicate the amount of improvement (e.g., tumor shrinkage by one quarter is expected compared to the tumor's present size). For randomized phase 2 or 3 trials only, indicate the type and amount of improvement (e.g., survival, time to cancer recurrence, decrease in symptoms) that can be observed if the study is positive.
3. Insert the names and types of investigational drugs/agents/interventions where indicated.
4. Insert the number of people taking part in the study.
5. If modifying the Template language is necessary, use simple, concise, lay language.

Text Examples for Chemoprevention/Supportive Care/Other Studies:

Text Example: Phase 1 Dose Escalation Chemoprevention Studies
The purpose of this study is to test the safety of *(insert name of drug or agent)* at different doses to find out what effects, if any, it has on people. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 Non-randomized Chemoprevention Studies
The purpose of this study is to test the safety of *(insert name of drug or agent)* and find out what effects, if any, *(insert name of drug or agent)* has on people and their risk of *(insert type)* cancer. *(Indicate if the drug is FDA-approved or not). (Add the following sentence as appropriate).* The study drug has not been shown to shrink *(specify cancer type)* but it has shrunk several types of cancer in animals. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 or 3 Randomized Chemoprevention Studies
The purpose of this study is to compare the safety and effects of *(insert name of drug or agent)* with *(insert name of currently-used drug or placebo)* on people and their risk of *(insert type)* cancer. In this study, you will get either *(insert name of drug/agent)* or placebo, a *(insert appropriate description for the placebo, e.g., pill/liquid)* that looks like the study drug but contains no medication. To be better, the study drug should increase life by 1 year or more compared to the usual approach. There will be about *(insert number)* people taking part in this study.

Text Example: Supportive Care Studies
You have cancer and will be receiving chemotherapy that may cause nausea and vomiting. The purpose of this study is to test whether *(insert name of drug/intervention)* can reduce nausea and vomiting. The effects of *(insert name of drug/intervention)* will be compared to *(a placebo or the usual approach). (If applicable, include the following sentence.)* A placebo is a *(insert appropriate description for the placebo, e.g., pill/liquid)* that looks like the study drug but contains no medication. There will be about *(insert number)* people taking part in this study.

Text Example: Behavioral Study
You have *(insert type)* cancer and will be receiving chemotherapy that will cause fatigue. The purpose of this study is to test whether *(insert intervention, e.g., yoga)* can reduce fatigue. The effects of *(insert intervention)*

will be compared to *(describe comparative intervention, e.g., listening to relaxation tapes, or "the usual approach").*

Text Examples for Chemotherapy/Radiation Therapy/Surgery/Biologics/Imaging/Other Studies:

Text Example: Phase 1 Dose Escalation Studies
The purpose of this study is to test the safety of a study drug called *(insert name of research drug, e.g., TST1234)*. This drug has been tested in animals but not yet in people. This study tests different doses of the drug to see which dose is safer in people. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 1 Novel Route/Combination Studies
This study uses a combination of drugs *(insert names of drugs, e.g., carboplatin and paclitaxel)* that have already been FDA-approved to be given by vein. The purpose of this study is to test whether giving one of the drugs *(insert name of drug, e.g., carboplatin)* through the belly along with the other drug *(insert name of drug, e.g., paclitaxel)* by vein is safe. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 Non-randomized Studies
The purpose of this study is to test any good and bad effects of the study drug called *(insert name of drug, e.g., bevacizumab). (Insert name of drug(s)or investigational approach)* could shrink your cancer but it could also cause side effects. Researchers hope to learn if the study drug will shrink the cancer by at least one-quarter compared to its present size. *(The following sentence should be included as appropriate). (Insert name of drug(s))* has already been FDA-approved to treat other cancers. *(The following sentence should be included only if the agent has not shown evidence of activity in humans).* It has not been tested in *(insert type of cancer, e.g., rectal)* cancer, but has shrunk several types of tumors in animals. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 or 3 Randomized Studies
The purpose of this study is to compare any good and bad effects of using a *(specific drug, surgery or radiation approach)* along with the usual chemotherapy, surgery or radiation therapy to using the usual chemotherapy, surgery or radiation approach alone. The addition of *(insert name of drug(s) or investigational approach)* to the usual *(chemotherapy, surgery or radiation)* could shrink your cancer/prevent it from returning *(as appropriate)* but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the study drug(s)/study approach should increase life by six months or more compared to the usual approach *(select other study primary endpoints as appropriate). (The following sentence should be included if appropriate).* This chemotherapy drug, *(insert name of drug, e.g., docetaxel),* is already FDA-approved for use in *(insert type of cancer, e.g., prostate)* cancer but is usually not used until *(e.g., hormone drug)* stops working. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 3 Randomized Studies with Multiple Randomizations
The purpose of this study is to test two things:

(1) Compare any good and bad effects of using *(e.g., a higher dose [74 Gray] of radiation)* to the usual dose of *(e.g., 60 Gray).*
(2) Compare any good and bad effects of adding *(e.g., an extra antibody drug called cetuximab)* to the usual chemotherapy *(e.g., carboplatin and paclitaxel)* to using the usual chemotherapy alone.

Either of these different approaches could shrink your cancer but could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. If better, the new approaches should improve survival by 6 months compared to the usual

approach. *(Include the following sentence, if applicable.)* Both the *(insert description of first research intervention, e.g., higher radiation dose)* and *(insert description of second research intervention, e.g., cetuximab)* have already been tested for safety; however, they are not part of the usual approach.

There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 or 3 Study with Integral Biomarker(s)
Another purpose of this study is for researchers to learn if a biomarker test is helpful to decide … *(insert purpose of biomarker test, e.g., decide who should be enrolled in this study or decide which study group you will be in).* An *(insert how biomarker sample will be obtained, e.g., extra tube of blood will be drawn or tissue from your surgery will be used, etc. …)* for the biomarker test. Researchers do not know if using the biomarker test is better, the same, or worse than if you… *(insert purpose of biomarker test, e.g., enrolled in this study or were put in a study group)* without using the biomarker test.

Text Example: Imaging Studies (Diagnostic, staging, or response to therapy)
The purpose of this study is to test *(insert name of research intervention, e.g., PET)* scans, which are a different way to take pictures of your type of cancer. The researchers want to see if *(insert name of intervention, e.g., PET)* scans are better or the same as what is usually used, *(insert name of usual approach, e.g., CT)* scans, at diagnosing or monitoring your type of cancer. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 0/First-in-human Imaging Study
The purpose of this study is to test if *(insert name of research intervention, e.g., F18-Fluoroglutamine)* can be used to take pictures of your type of cancer. This will be the first time that *(insert name of research intervention, e.g., F18-Fluoroglutamine)* is being tried in people. There will be about *(insert number)* people taking part in this study.

Text Example: Phase 2 Non-randomized Imaging Agent Studies (biomarker example)
The purpose of this study is to test if an imaging drug, not approved by the FDA, called *(insert name of drug/agent, e.g., ^{18}F-fluoride)* is useful for evaluating your type of cancer. This drug is used to perform a *(insert type of scan, e.g., PET)* scan. The researchers want to see if the *(insert type of scan, e.g., PET)* scan, using the study drug, can improve upon the usual scans at diagnosing or monitoring your type of cancer. There will be about *(insert number)* people taking part in this study.

What are the study groups?

Notes to consent form authors:
1. **Section length limit: This section should be between seven to ten sentences and take up no more than three-quarters page.**
2. Provide a brief, phase-specific description of the study groups.
3. Insert the names and types of drugs/agents/interventions as needed.
4. For randomized studies, if the assignment is not 1:1, include a brief description of the assignment.
5. Clearly identify the investigational arm(s).
6. If modifying the Template language is necessary, use simple, concise, lay language.

Text Example: Phase 1 Dose Escalation Studies
Different doses of the study drug *(insert name of research drug)* will be given to several study participants. The first several study participants will receive the lowest dose. If the drug does not cause serious side effects, it will be given to other study participants at a higher dose. The doses will continue to increase for every group of study participants until side effects occur that require the dose to be lowered. Then the study is stopped. You *(insert appropriate information, e.g., will/will not)* be able to receive additional doses of the drug.

Text Example: Phase 2 Non-randomized Studies
All study participants will get the same study intervention. It will include the usual radiation therapy and chemotherapy *(insert usual chemotherapeutics, e.g., 5-fluorouacil or capecitabine).* All study participants will also get the study drug *(insert name of research drug, e.g., bevacizumab).*

Text Example: Randomized Phase 2 Treatment Studies and Chemoprevention Studies
This study has two study groups. Group 1 will receive the study drug *(insert name of research drug)* and Group 2 will receive a placebo, a *(insert appropriate description for the placebo, e.g., pill/liquid)* that looks like the study drug but contains no medication.

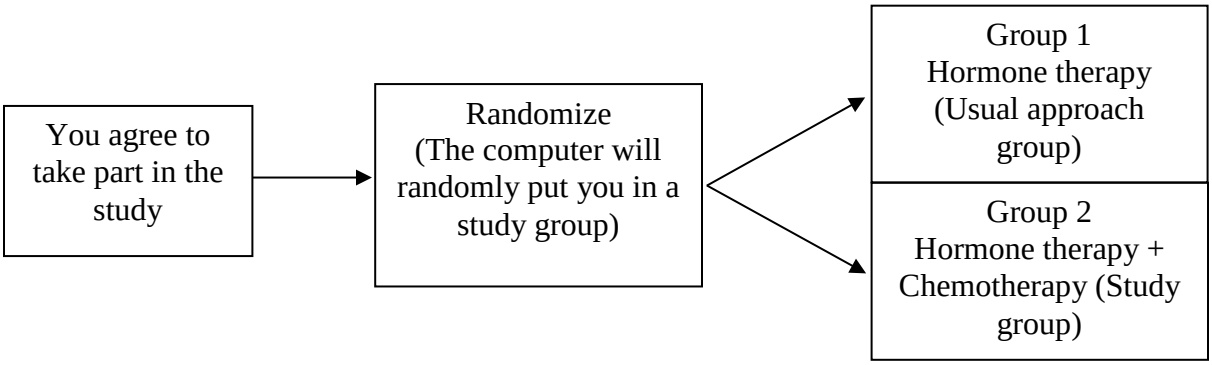
A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

Text Example: Phase 3 Randomized Studies
This study has two study groups.

- Group 1 will get the usual *(insert description of intervention, e.g., hormone or chemotherapy)* drug used for this type of cancer *(insert name of drug[s]).*
- Group 2 will get the usual *(insert description of intervention, e.g., hormone or chemotherapy)* drug used for this type of cancer *(insert name of drug[s])* plus a study drug called *(insert name of research drug, e.g., docetaxel).*

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others.

(Note to informed consent authors: Study chart is optional if there is no randomization.) Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



Text Example: Phase 3 Randomized Studies with Multiple Randomizations
All participants in this study will be given chemotherapy and radiation therapy.

- Group 1 will get the usual chemotherapy *(insert names of drugs, e.g., carboplatin and docetaxel)* and the usual radiation dose *(insert dose, e.g., 60 Gray).*
- Group 2 will get the usual chemotherapy *(insert names of drugs, e.g., carboplatin and docetaxel)* with a higher radiation dose than usual *(insert research dose, e.g., 74 Gray).*
- Group 3 will get the usual chemotherapy *(insert names of drugs, e.g., carboplatin and docetaxel)* and the usual radiation dose *(insert dose, e.g., 60Gray)* and a study drug called *(insert name of research drug, e.g., cetuximab).*
- Group 4 will get the usual chemotherapy plus the higher radiation dose plus the study drug called *(insert name of research drug, e.g., cetuximab).*

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.

(Insert chart with four Groups, similar to the randomized study chart provided in the Phase 3 example above.)

How long will I be in this study?

Note to consent form authors:
1. **Section length limit: This section should be one or two sentences and take up no more than one-eighth page.**

Use the following text for all studies:
You will receive the *(insert description of intervention, e.g., study drugs)* for *(insert intervention length).* After you finish *(insert description of intervention),* your doctor will continue to watch you for side effects and follow your condition for *(insert study follow-up length).*

What extra tests and procedures will I have if I take part in this study?

Notes to consent form authors:
1. **Section length limit: If the study has extra tests and procedures, this section is required but should be as brief as possible and take up no more than one-half page. If the study includes mandatory specimen collection, five to ten more sentences may be added and the length can be expanded to one page.**
2. You **do not** need to list those exams, tests, and procedures that are part of the usual approach. If the only exams, tests, or procedures that are being done are those performed using the usual approach, omit this section.
3. Provide a list of research-related exams, tests, and procedures that are not part of the usual approach or that will be done more frequently than usual. Specify the frequency, if applicable.
4. Please note: Sample text has been provided below for mandatory specimen collection. Sample text for optional specimen collection is provided in the "…Optional studies…" section located prior to the Signature line.

Use the following text for all studies requiring extra exams, tests, and/or procedures:
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra (*insert appropriate word, e.g., exams, tests, and/or procedures)* that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra *(insert appropriate word, e.g., exams, tests, and/or procedures)* to find out if you can be in the study:

List exams, tests, and procedures that either would not be done for the usual approach or are performed more frequently than usual. Use bulleted format. Examples of extra exams, tests and procedures:

- MUGA scan
- Blood tests for studies of drug levels
- CT scan of abdomen
- Bone scan

The following text example is provided for studies which include <u>mandatory</u> specimen collection:
[Insert specimen type: Small pieces of cancer tissue removed by surgery, biopsies; A blood sample; A urine sample] will be taken for the study *[state when the sample will be taken, for example, before you begin study drug; after the third dose; etc.]* This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. *[Include brief description of how the specimen will be collected, e.g., "The research biopsy is done in a similar way to biopsies done for diagnosis." Include a brief description of how the specimen will be used.]*

[If applicable, include risks of biopsy or other specimen collection, e.g., "Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur."] [If applicable, include, "You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place."]

[If applicable, include whether any of the specimen left over will be stored for biobanking. If so, indicate that this will be discussed in the section on optional studies.]

[If applicable, describe how the test results will be stored to protect privacy, e.g., "Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information." Also include whether or not the results will be available to the study participant or study doctor.]

Neither you nor your health care plan/insurance carrier will be billed for the collection of the *[insert sample type]* that will be used for this study.

Use the following text for all studies requiring extra exams, tests, and/or procedures:
If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra *(insert appropriate words, e.g., exams, tests, and/or procedures)*. They are not part of the usual approach for your type of cancer. *(If chemoprevention trial, state, "These are not part of the usual approach for your precancerous condition.")*

During the study:

Examples of exams, tests, and procedures:

- Blood tests every month for 1 year
- CT scan of abdomen every 3 months for 2 years
- Bone scan every 3 months for 2 years
- Bone marrow biopsy immediately after study treatment is completed and 1 year later
- Echocardiogram or MUGA scan to see how your heart is working every 3 months

If study calendar is attached, this statement may be included instead of the bullets: **A study calendar that shows how often these *(insert appropriate words, e.g., exams, tests, and/or procedures)* will be done is attached.**

What possible risks can I expect from taking part in this study?

Notes to consent form authors:
1. **Section length limit: Limit this section to two to four pages maximum.**

If you choose to take part in this study, there is a risk that:

Note to consent form authors: Select reasonably foreseeable risks and discomforts that are not physical side effects from the bullets below and/or include others, as relevant. Keep bulleted lists to no more than four items, if possible.

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- *(For randomized studies only) The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.*
- *(For studies requiring genetic testing) There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. (For non-U.S. participants, please verify the existence of such laws before including the following sentence.) There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.*
- *There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.*

The *(specify type of study intervention, such as surgery, radiation therapy, drugs, etc.)* used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.

- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Notes to consent form authors on how to present possible side effects:

1. Side effects of study group(s):
   a. For single-arm studies, list all possible side effects of the study drugs according to the recommendations given in 2-6 below.
   b. For multiple-arm studies with a control, the Table(s) of Possible Side Effects for the control arm should appear first and be followed by the Tables of Possible Side Effects for the drugs/agents used in the experimental arm(s).
   c. If the experimental arm consists of the usual treatment drugs/regimens (the control arm) plus experimental agent(s)/drug(s), the Table of Possible Side Effects for the usual treatment should not be repeated. The following statement should appear before the Table of Possible Side Effects for the investigational drugs/agents: "In addition to side effects outlined above for Group 1 and Group 2, people in this study who are in Group 2 may also experience the possible side effects of (insert name of research drug) listed below."
2. Side effects of procedures:
   a. When describing risks for procedures, describe risks only for procedures that are beyond what would be considered as occurring during the usual treatment approach. The determination of deeming a procedure as part or not part of the usual treatment approach is left to the discretion of the investigator.
   b. Examples of procedures that are not part of the usual treatment approach could include an unusually large amount of blood to be drawn for PK, central line placement to administer the investigational agent, research biopsy, etc.
3. Side effects of supportive drugs named in the consent form:
   a. Non-experimental supportive drugs need not have their side effects listed unless the treatment they support is the research question tested in the study. For example, side effects of Bactrim need not be listed when transplant is part of a study unless transplant is the actual study question in the trial.
4. Side effects of classes of medications:
   a. If general classes of approved medications, such as a hormonal therapy or anti-emetics – where no specific drug is named – are required by the protocol, these do not need to be listed, nor their possible side effects included, in the consent form.
5. Extremely specific possible side effects which are not perceived by the study participant, such as minor changes in lab values, should not be included in the consent form. Lab value changes that could be perceived by the study participant, or could be indicative of harm, should be listed, for example, the phrase "you could have liver damage," would be much more understandable to the study participant than "you could have elevated liver enzymes" or "you could have an elevation in (such-and-such lab value)."

6. Definitions of frequency categories:
   a. "Common, some may be serious" - There is no standard definition of the frequency of risks included in this category however, as a guideline, "Common, some may be serious" can be viewed as occurring in greater than 20% and up to 100% of patients receiving the drug/agent.
   b. "Occasional, some may be serious"- There is no standard definition of the frequency of risks included in this category however, as a guideline, "Occasional, some may be serious" can be viewed as occurring between 4 and 20% of patients.
   c. "Rare, and serious" - Side effects that occur in less than 3% of patients do not have to be listed unless they are serious, in which case they should appear in the "Rare, and serious" category. This categorization will need to be modified for prevention studies.
   d. "Serious" is defined as side effects that may require hospitalization or may be irreversible, long-term, or life-threatening.
   e. "Possible, some may be serious" – This is a unique frequency category and may be used, when appropriate, for informing study participants of possible side effects related to IND agents for which the frequency of individual side effects has not yet been determined.

Notes to consent form authors on how to present possible side effects (continued):

7. Note on stating possible side effects for imaging agents: Certain FDA regulations will need to be considered when imaging agents are used depending on the imaging agent (IND vs. commercial) and the protocol. As examples of such guidances, please refer to: FDA's draft guidance for industry standards for clinical trial imaging endpoints, found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM268555.pdf, and FDA's final guidance: "Developing Medical Imaging Drug and Biological Products" found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm092895.htm. Radiation Safety Committees may also require the mention of certain radiation-related information in the informed consent form.

The following bullets are required for NCI's Cancer Therapy Evaluation Program (CTEP)-sponsored studies. Consent form authors for studies from other sponsors have the option of using them:

1. CTEP is in the process of developing tables of possible side effects for its IND agents as well as for many other drugs commonly used in cancer treatment trials. These Tables should be inserted as illustrated below for the agents/drugs used in the cancer treatment trial. A list of agents/drugs for which tables of possible side effects have been developed, as well as the tables themselves, are available on CTEP's website at the following URL: http://ctep.cancer.gov/protocolDevelopment/#informed_consent
2. If a study uses a drug for which CTEP has not built a table of possible side effects, the same URL can be accessed for the tools and instructions to custom-build a table.
3. For custom-built tables of possible side effects, the same format and frequency categories should be used.

Note to consent form authors:

The following tables of possible side effects for selected drugs and agents have been supplied as examples of what should be included for the regimens or drugs used in the study. Text and tables are examples for a randomized, phase 3 trial in colorectal cancer with Group 1 consisting of FOLFOX or FOLFIRI and Group 2 consisting of FOLFOX or FOLFIRI plus bevacizumab.

Study Group 1 and Group 2 - Possible side effects of FOLFOX or FOLFIRI, either of which is the usual approach for this type of cancer:

Possible Side Effects of FOLFOX

COMMON, SOME MAY BE SERIOUS In 100 people receiving FOLFOX, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Difficulty swallowing • Tiredness • Bruising, bleeding • Numbness and tingling of the arms and legs • Increased risk of sunburn

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving FOLFOX, from 4 to 20 may have:
• Heart attack • Chest pain • Abnormal heartbeat which may cause fainting • Hearing loss • Swelling and redness of the eye • Dry eye, mouth, skin • Problem with eyelid • Blurred vision with chance of blindness • Discomfort from light, watering eyes • Sores in internal organs • Fluid in the belly • Internal bleeding which may cause black tarry stool, coughing up blood, or blood in vomit or urine • Constipation, heartburn, passing gas • Sores in the throat or mouth • A tear or hole in internal organs that may require surgery • Chills, fever • Difficulty walking, opening mouth, with balance and hearing, smelling, eating, sleeping, talking or emptying the bladder • Swelling and redness at the site of the medication injection • Liver damage which may cause yellowing of eyes and skin • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Weight gain, weight loss, loss of appetite • Infection, especially when white blood cell count is low • Dehydration • Pain • Inability to move shoulder or turn head • Dizziness, headache • Changes in taste

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving FOLFOX, from 4 to 20 may have:
• Abnormal body movement including the eye and eyelid • Bleeding from multiple sites including the vagina, testis, or brain • Stroke which may cause paralysis, weakness • Muscle weakness • Seizure • Worry, confusion, depression • Increased urination • Stuffy nose • Cough, hiccups, sinus problems • Swelling of the body which may cause shortness of breath • Scarring of the lungs • Changes in voice • Increased sweating • Hives, hair loss, itching, rash • Flushing, hot flashes • High blood pressure • Low blood pressure which may cause feeling faint • Blood clot which may cause swelling, pain, shortness of breath • Damage to organs which may cause shortness of breath

RARE, AND SERIOUS In 100 people receiving FOLFOX, 3 or fewer may have:
• Kidney damage which may require dialysis • Redness, pain or peeling of palms and soles

Possible Side Effects of FOLFIRI

COMMON, SOME MAY BE SERIOUS In 100 people receiving FOLFIRI, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may require blood transfusion • Constipation, vomiting, nausea, diarrhea • Sores in mouth • Difficulty swallowing • Fever • Pain • Weight loss, loss of appetite • Bruising, bleeding • Tiredness, dizziness • Cough • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving FOLFIRI, from 4 to 20 may have:
• Abnormal heartbeat • Watering eyes, discomfort from light, blurred vision • A tear or hole in the stomach which may require surgery • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Headache • Abnormal eye movement • Difficulty walking • Shortness of breath • Rash, itching • Increased risk of sunburn • Redness, pain or peeling of palms and soles • Scarring of the lungs • Blood clot

RARE, AND SERIOUS In 100 people receiving FOLFIRI, 3 or fewer may have:
• Damage to the heart which may cause swelling • Chest pain • Heart attack which may cause chest pain, shortness of breath

Study Group 2 - In addition to side effects outlined above, people who are in Group 2 may also experience the possible side effects of bevacizumab listed below.

Possible Side Effects of Bevacizumab

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Headache • High blood pressure which may cause blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat which may cause fainting • Dizziness, fainting • Pain • Constipation, heartburn • Bleeding from multiple sites including the vagina or nose, or bleeding in the brain which may cause confusion • Internal bleeding which may cause black, tarry stool, blood in vomit or urine, or coughing up blood • Sores in mouth which may cause difficulty swallowing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Infection, especially when white blood cell count is low • Non-healing surgical site • Weight loss • Loss of appetite • In children or adolescents: may interfere with growth • Kidney damage which may require dialysis • Cough, hoarseness, stuffy nose, shortness of breath • Itching, rash, hives • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving bevacizumab, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, or tiredness • A tear or hole in internal organs that may require surgery • Sores in the throat • Stroke which may cause paralysis, weakness • Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

Examples of research imaging studies:

Text Example: Radiation Risk for Research Imaging Studies
(Each site may need to modify this section to quote correct dosimetry for the type of study being performed and dosimetry for its own scanners and imaging protocols in accordance with its own institutional policies and procedures. The following text and risk estimate is an example only.)

The *(insert type of scan, e.g., PET, CT)* that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation". No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.

The *(insert type of scan, e.g., PET, CT)* that you will receive in this study will expose you to extra radiation that is equal to about *(insert estimate, e.g., 2 year's worth)* of background radiation. Most of the time, this low amount of extra radiation is not harmful to you. However, scientists believe that if you get extra radiation that is more than about 30 year's worth of background radiation, there is a chance of having a harmful side effect, including causing a new cancer. It is estimated that this could occur in about 1 out of every 1000 people who get a very large amount of extra radiation.

Table example of risk presentation for Radiation Therapy Studies.
Examples should be modified to add possible side effects related to treatment location.

Possible Side Effects of Research Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• Reddening, tanning, or peeling of the skin • Mild pain • Hair loss • Tiredness • Diarrhea, nausea • Anemia, which may require transfusion • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Thickening and numbness of the skin • Sores or ulcers on the skin or near the cancer location • Permanent hair loss • Bleeding from the skin • Sores in mouth which may cause difficulty swallowing

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Damage to internal organs • Abnormal opening in internal organs which may cause pain and bleeding

Use the following text for all studies:
Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The *(specify intervention)* used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

Notes to consent form authors:
1. **Section length limit: This section should be between two and three sentences and take up no more than one-eighth page.**
2. The statements below are generic and consent form authors should try to make their language specific to the study question when describing the potential research benefit.

Text Example: Phase 1 Studies
This study is unlikely to help you. This study may help us learn things that may help people in the future.

Text Example: Phase 2 Non-randomized Studies
This study has only a small chance of helping you because we do not know if the study drug/study approach is effective. This study may help researchers learn things that may help other people in the future.

Text Example: Phase 2 and 3 Randomized Studies
It is not possible to know at this time if the study drug(s)/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Notes to consent form authors:
1. **Section length limit: This section should be between five and eight sentences and take up no more than three-eighths page.**

Use the following text for all studies:
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:
- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Notes to consent form authors:
1. **Section length limit: This section should be about four sentences and take up no more than one-eighth page.**

Use the following text for all studies:
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

Notes to consent form authors:
1. **Section length limit: This section should be between four and eight sentences and take up no more than one-quarter page.**
2. If appropriate, state which study agent(s) or procedures are provided free of charge.
3. Indicate if the study participant and/or health plan is likely to be billed for any charges associated with these "free" tests or procedures.
4. Outline any other pertinent financial support.

Use the following text for all studies:
The *(study agent)* will be supplied at no charge while you take part in this study. The cost of getting the *(study agent)* ready and giving it to you *(As appropriate, add: "…is also provided at no charge." Or "…is not paid by the study sponsor so you or your insurance company may have to pay for this.")* It is possible that the *(study agent)* may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of *(As appropriate, add: "caring for" Or "preventing" Or "treating")* your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

(Note to consent form authors and investigators: Insert a description of any compensation for participation or reimbursement for expenses.)

What happens if I am injured or hurt because I took part in this study?

Notes to consent form authors:
1. **Section length limit: This section should be between four and six sentences and take up no more than one-quarter page.**

Use the following text for all studies:
If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors *(will/will not)* offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Notes to consent form authors:
1. **Section length limit: This section should be between four to seven sentences and take up no more than one-quarter page.**
2. The NCI has recommended that HIPAA regulations be addressed by the local institution. Language pertaining to HIPAA compliance may or may not be included in the local consent form, depending on local institutional policy.

Use the following text for all studies:
Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study *(Note to consent form authors: Delete drug company reference if not applicable.)*
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

Notes to consent form authors:
1. **Section length limit: This section should be between six and eight sentences and take up no more than one-quarter page.**
2. The second paragraph below complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all consent forms for any applicable trial under the regulation. The text in this paragraph cannot be revised.

Use the following text for all studies:
You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

Notes to consent form authors:
1. **Section length limit: This section should be between four and six sentences and take up no more than one-eighth page.**

Use the following text for all studies:
You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION: *(Indicate clearly to participants that this is a separate section)*

This section is about optional studies you can choose to take part in

Notes to consent form authors:
1. **Section length limit: If the study mandates some of these optional studies be included, the text should be as brief as possible and take up no more than three pages.**
2. All of the regulatory elements of consent included in the primary consent form must pertain to the embedded optional study. If any do not apply, they must be addressed in the discussion of the optional study.
3. Provide yes/no options at each decision point and do not require initials.
4. After choosing which optional studies included below pertain to your specific research, delete the studies that do not pertain.
5. If modifying the Template language to include other studies is necessary, use simple, concise, lay language.

Use the following text if optional studies are included:
This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results *(specify: will/ will not)* be added to your medical records and you or your study doctor *(specify: will/will not)* know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Optional imaging study – extra scan *(Note to consent form authors: This example pertains to an extra scan for research purposes)*

If you choose to take part in this study, you will have an extra (*insert name of standard clinical imaging procedure, e.g., PET scan).* This scan is already used in medical care but it would be taken at a time point in

your treatment that is not usual. Researchers would use this scan to (*briefly describe purpose, e.g., try to learn more about how treatment works on cancer).*

If you agree to have this extra scan, it would involve (*briefly describe procedures, e.g., blood draw, contrast agent, time).* The risks would be (*briefly describe, focusing on risks of extra scan, e.g., additional radiation risk, risk of contrast). (As applicable, insert:* The scan *[*may *or* would*]* be used to guide your medical care. *or* The scan would only be used for research and not to guide your medical care.*) If applicable, include the following statement:* There are educational materials available about this type of scan. Ask your study doctor about them, if you would like more information.*)*

Please circle your answer: I choose to take part in the imaging study and will have the extra *(insert name of procedure, e.g., PET scan):*

YES NO

2. <u>Optional imaging study – research scan or procedure</u> *(<u>Note to consent form authors</u>: This example pertains to an investigational scan or procedure.)*

If you choose to take part in this study, you will have an experimental *(insert descriptor - scan or procedure)* called *(insert name of investigational imaging scan/procedure).* Researchers hope this kind of *(insert descriptor - scan or procedure)* might one day be used to (*briefly describe purpose, e.g., learn more about cancer and how treatment works on cancer).* This *(insert descriptor - scan or procedure)* is still being tested and researchers do not know how accurate or useful it is.

If you agree to have this *(insert descriptor - scan or procedure),* it would involve (*briefly describe procedures).* The risks would be (*briefly describe, e.g., risks of investigational contrast agent).* The *(insert descriptor - scan or procedure)* would only be used for research and not to guide your medical care.

Please circle your answer: I choose to take part in the imaging study and will have the experimental *(insert name of scan or procedure):*

YES NO

3. <u>Optional Quality of Life Study</u>

If you choose to take part in this study, you will be asked to fill out a form with questions about *(briefly state topic, e.g., your physical and emotional well-being).* Researchers will use this information to *(briefly describe purpose, e.g., learn more about how cancer and cancer treatment affects people).*

You will be asked to fill out this form at *(insert number)* times: *(insert bulleted list of time indicators, e.g., before surgery, after surgery before chemotherapy, and mode, e.g., inpatient, mail, or phone).* Each form will take about *(insert number)* minutes to complete. The forms will ask about things like (*briefly describe, e.g., fatigue, diarrhea).* You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer.

Please circle your answer: I choose to take part in the Quality of Life study and will fill out these forms:

YES NO

4. Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Note to consent form authors:
1. Section title and content should be modified as applicable based on whether study has optional collections and/or biobanking.
2. Some content for the biobanking consent has been used with the consent of the author, L. M. Beskow. The citation is as follows: Beskow LM, Friedman JY, Hardy NC, Lin L, Weinfurt KP (2010) Developing a Simplified Consent Form for Biobanking. PloS ONE 5(10):e13302. doi:10.1371/journal/.pone.0013302

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

Note to consent form authors: The following is a text example for when a defined/known lab study can be described.)
If you choose to take part in this study, the study doctor for the main study would like to collect *(insert specimen to be collected, e.g., blood)* for research on *(briefly describe purpose).*
(Note to consent form authors: The following is a text example for when a specimen is being collected for future unspecified research.)
If you choose to take part, *(insert specimen to be collected, e.g., a sample of tissue from your previous biopsy)* will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by *(insert name of clinical trials organization)* and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) *Choose applicable sentence for the trial:* About *(insert number)* tablespoons of blood will be collected from a vein in your arm. *OR* A sample from the tissue that was collected at the time of your surgery will be sent to the Biobank. *OR* A sample of tissue will be collected from the optional extra biopsy. *[Revise as necessary to describe sample and collection. Should be noted if sample is drawn at same time as other draws, is residual material from embedded correlative, or already exists (archived tissue).]*
2) *Choose 'a' or 'b' as applicable for the trial:*
   a) Your sample and some related health information will be sent to a researcher for use in the study described above. *(Include the following sentences, if applicable.)* Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
   OR
   b) *For future unspecified research:* Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The

samples will be kept until they are used up. Information from your medical record will be updated from time to time.

3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you. *(Note to informed consent authors: In specific instances, if this statement is not accurate and information may be given to researchers, please include appropriate notification information.)*
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples. *(Note to informed consent authors: In specific instances, if this statement is not accurate and information may be given to study doctors, please include appropriate notification information.)*
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise. *(Revise as necessary to describe risks from the sample collection.)*
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. *(For non-US participants, please verify existence of such laws before including the following text.)* There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only. *(Note to consent form authors: If investigators are receiving samples directly from sites without being coded, modify accordingly.)*
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and *(insert name of clinical trials organization)* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom *(insert name of clinical trials organization)* sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. *(Note to informed consent authors: In specific studies, if this statement is not accurate and information may be given to the study participant's physician for use in their care, please include appropriate notification information.)*

(Use the following sentence as applicable, e.g., when diagnosis has not been established: Your samples may be helpful to research whether you do or do not have cancer.*)* The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial),* at _____ *(insert telephone number of study doctor for main trial).*

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR THE LABORATORY STUDIES:

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to learn about results from this(ese) study(ies).

YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

Use the following text if optional studies have been included:
This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

Notes to consent form authors:
1. **Section length limit: This section should be four to five sentences and take up no more than one-quarter page.**

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'. (Note to protocol authors – remove italicized text if not applicable. Remove italics, if the text does apply.)*

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

Note to Consent Form Authors and Investigators:

Recommendations about Attachments to the Consent Form (CF)

1. Attachments should contain information for the study participant that is considered optional, and is not required for their understanding of the proposed research. Attachments may provide clarification, additional education, or provide information about other facets of overall cancer care.

2. All required information should be contained within the CF itself. If the information is considered mandatory for the participants' understanding of the proposed research, then it should be in the CF.
   a) If a therapy or procedure is truly part of the research design – whether it is drug therapy, surgery, minimally invasive therapy, imaging, etc. – then information describing this therapy/procedure should be part of the CF.
   b) There is a difference between interventions that are part of standard care vs. a new indication of an already marketed intervention when research is being done. Marketed or available interventions (including scans) that are being used for a new indication should be treated as an experimental intervention and their side effects should be in the CF.

3. A study calendar is useful to include as an optional attachment.
   a) Patient advocates have recommended attaching a calendar that is easy for study participants to understand, conveying what has to be done, when, and for how long. It should help the study participant plan his/her life during the study. It should not be formidable-looking or too complicated in format, especially as dates and timing often change during the course of treatment due to unforeseen events.

4. Patient advocates have recommended the use of supportive educational materials that could help study participants better understand research-related information, such as biospecimen banking and treatment-related information for radiation therapy, surgery, chemotherapy, and imaging.
   a) NCI offers educational materials that cover many aspects of cancer, its treatment, and research, for example, the pamphlet, Taking Part in Cancer Treatment Research Studies. This pamphlet, and other materials, may be ordered on the NCI Web site at https://pubs.cancer.gov/ncipl/home.aspx or call 1-800-4- CANCER (1-800-422-6237) to request free copies.
   b) The FAQs about the NIH Certificate of Confidentiality may be found at http://grants.nih.gov/grants/policy/coc/faqs.htm#187. If a study has a Certificate of Confidentiality, the FAQs can be printed and used as an attachment.

5. Since many people do not have access to the Internet, including only web links in an attachment is not considered to be useful.

6. Friendly reminder – attached consent materials to the CF must be reviewed and approved by the IRB.

7. **For CTEP-sponsored trials:** The ICD and all attachments must be submitted to the PIO as a **single Word** or **PDF** document.