Investigator-Initiated Interventional Study Protocol

Title: *Include phase (e.g., phase I, phase II, etc.), design (e.g., randomized, double blind, placebo controlled, etc.), if the study is multi-center, the investigational drug, target disease(s) and stage (e.g. advanced, relapsed/refractory)] For example: A phase II, randomized, double-blind, placebo-controlled, multi-center study of the effects of XXXX on infarct size in participants with diabetes mellitus presenting with acute myocardial infarction.*

Clinical Study Protocol Number:	*Mount Sinai Study Number*
Principal Investigator (PI):	*Name and contact information of the Principal Investigator*
Coordinating Center:	*List the name of the coordinating site*
Participating Site PIs:	*For multi-site trials, list participating site PIs and their contact information*
Additional Investigators:	*Name and contact information of any other investigators*
Investigational New Drug (IND)/ Investigational Device Exemption (IDE) Number:	*Insert IND or IDE number, if applicable. This number is assigned by the United States Food and Drug Administration (FDA). Please write "pending" if not yet available and "Not Applicable" if not applicable.*
IND/IDE Sponsor:	*Name and contact information of the IND/IDE sponsor*
Statistician:	*Name and contact information of study biostatistician*
Medical Monitor:	*Name and contact information of the study medical monitor*
Study Management Provider(s):	*Name and contact information of the study management provider(s)*
Funding Source(s):	*List the name(s) and contact information of the funding sponsor(s)*
Study Agent(s):	*List the study agent name(s) (generic, followed by marketed name), if applicable*
Study Agent Provider(s):	*Study agent provider and contact information (e.g. NIH, or company)*
National Clinical Trials (NCT)/ ClinicalTrials.gov Number:	*Include the National Clinical Trial (NCT) number assigned once the trial is registered on the ClinicalTrials.gov website*
Initial Version:	*Insert date*
Amended Version:	*Insert date*

Table of Contents

Statement of Compliance

The Statement of Compliance (also known as the Protocol Signature Page or "PSP") must be included in the protocol. Upon finalizing the protocol, the Principal Investigator (PI) will sign the Statement of Compliance. The signed Statement of Compliance will be retained for documentation. For multi-institutional studies, the site PI will also sign the Statement of Compliance. A copy of the signed Statement of Compliance should be sent to the coordinating site, and the original retained for documentation.

This is an investigator-initiated study. The study site principal investigator (PI) is conducting this study, and acting as the study sponsor. By signing this document, the study site PI agrees to:

- Fulfill the legal and ethical obligations of both PI and sponsor
- Carry out the study in accordance with the protocol, all relevant laws, regulations and standards outlined in the clinical study agreement, and all ethical and scientific standards of Good Clinical Practice (GCP), as required by applicable United States (US) laws and applications, including but not limited to, US Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- Ensure that the study protocol and all associated documents, including informed consent form(s), recruitment materials, and all participant materials, will be reviewed and approved by the Institutional Review Board (IRB) before any study participant is enrolled
- Ensure that no deviation from or change to the protocol will occur without documented approval from the IRB, except when necessary to eliminate immediate hazards to study participants
- Comply with and accept the oversight of the study monitors
- Ensure that all personnel involved in the conduct of this study have completed the appropriate human participant protection training and are informed of their obligations in meeting the above commitments.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (printed)

_____

Principal Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

Statement of Confidentiality

The Statement of Confidentiality must be included in the protocol. Upon finalizing the protocol, the Principal Investigator (PI) will sign the Statement of Confidentiality. The signed Statement of Confidentiality will be retained for documentation. For multi-institutional studies, the site PI will also sign the Statement of Confidentiality. A copy of the signed Statement of Confidentiality should be sent to the coordinating site, and the original retained for documentation.

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from Mount Sinai unless disclosure on ClinicalTrials.gov is federally required.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (printed)

_____

Principal Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

1.0 Summary

Please include a summary of the research to be conducted in textual, tabular, and diagrammatic format. Include the study title, phase, design, objectives, endpoints, statistical considerations, participant population/key eligibility criteria, treatment plan, total enrollment, time to completion, and participating sites. Please ensure consistency with other sections of this protocol.

1.1 Synopsis

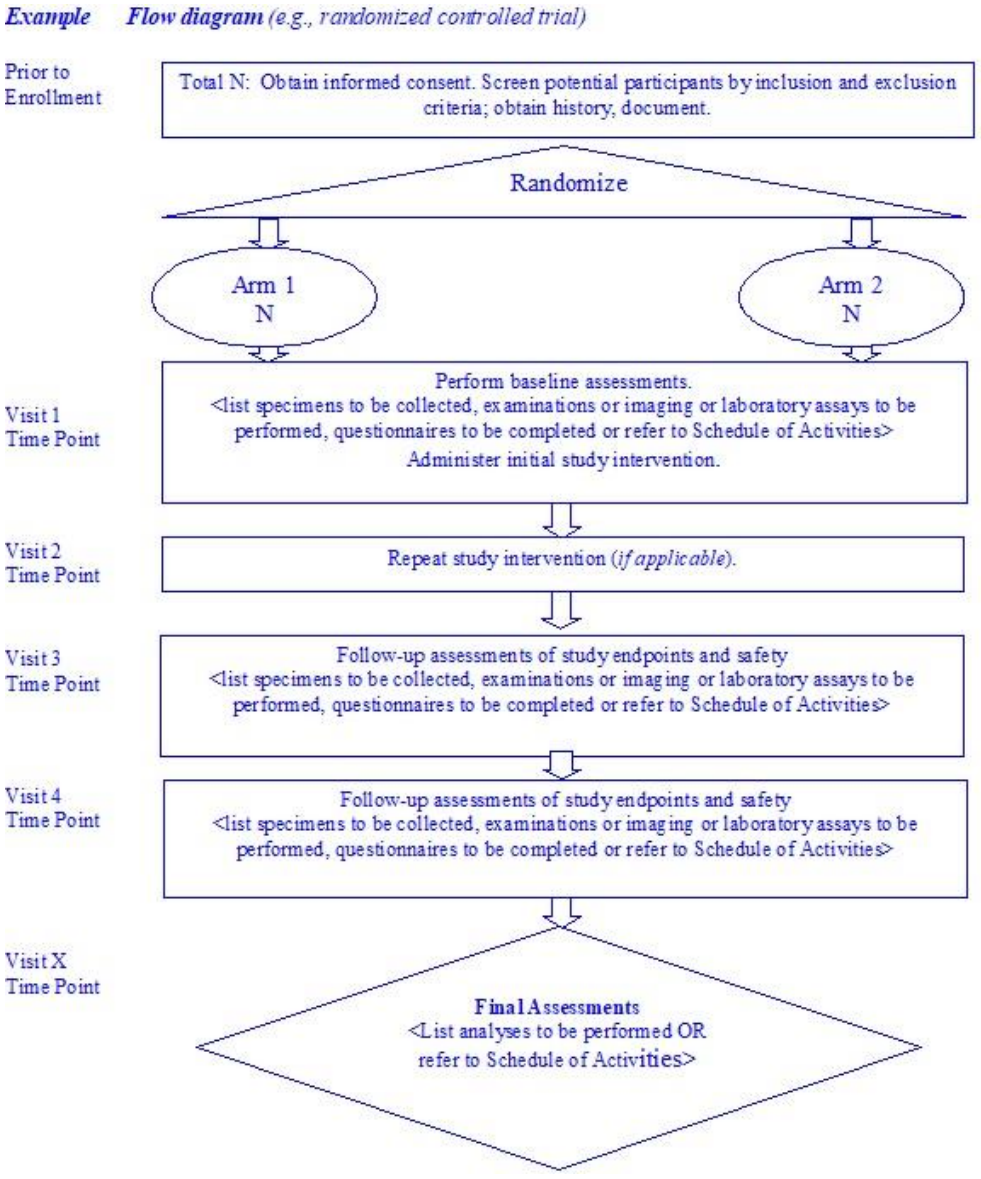
Please include key information from the study summary in the table below.

Title	*Please ensure this is identical to the title on the protocol title page*
Phase	*Select Phase 1, II, or III*
Study Design	*e.g. randomized, adaptive, etc.*
Objectives	*Please list the primary, secondary and tertiary/correlative/exploratory study objectives. Please ensure that the objectives are identical throughout the protocol.*
Endpoints	*Please list each study endpoint. Please ensure that the study endpoints are identical throughout the protocol*
Statistical Considerations	*Please summarize pertinent statistical information. Include the following components as applicable:* • *Statistical design and methodology* • *Sample size* • *Maximum number of subjects that can be enrolled* • *Minimum number needed to answer scientific question*
Study Participant Population/Key Eligibility Criteria	*Please summarize key eligibility criteria. Include the following components as applicable:* • *Gender* • *Age range (e.g. 18-100)* • *Demographic group* • *General health status* • *Geographic location* • *Diagnosis and Diagnostic Parameters* • *Disease stage* • *Prior treatments*
Study Agent(s), Dose, Route, and Regimen	*If none, please state "Not Applicable"* *If applicable, please provide study agent name (generic name, followed by marketed name)*
Duration of Administration	*Please state the duration of study agent administration (e.g. "Until disease progression or unacceptable toxicity")*
Total Number of Participants	*Please list the total number of participants to be enrolled in the study*
Estimated Enrollment Period	*Estimated time (in months) from when the study begins enrollment until completion of enrollment.*
Estimated Study Duration	*Estimated time (in months) from when the study begins enrollment until completion of data analysis.*
Participating Sites	*List of participating sites, with contact information*

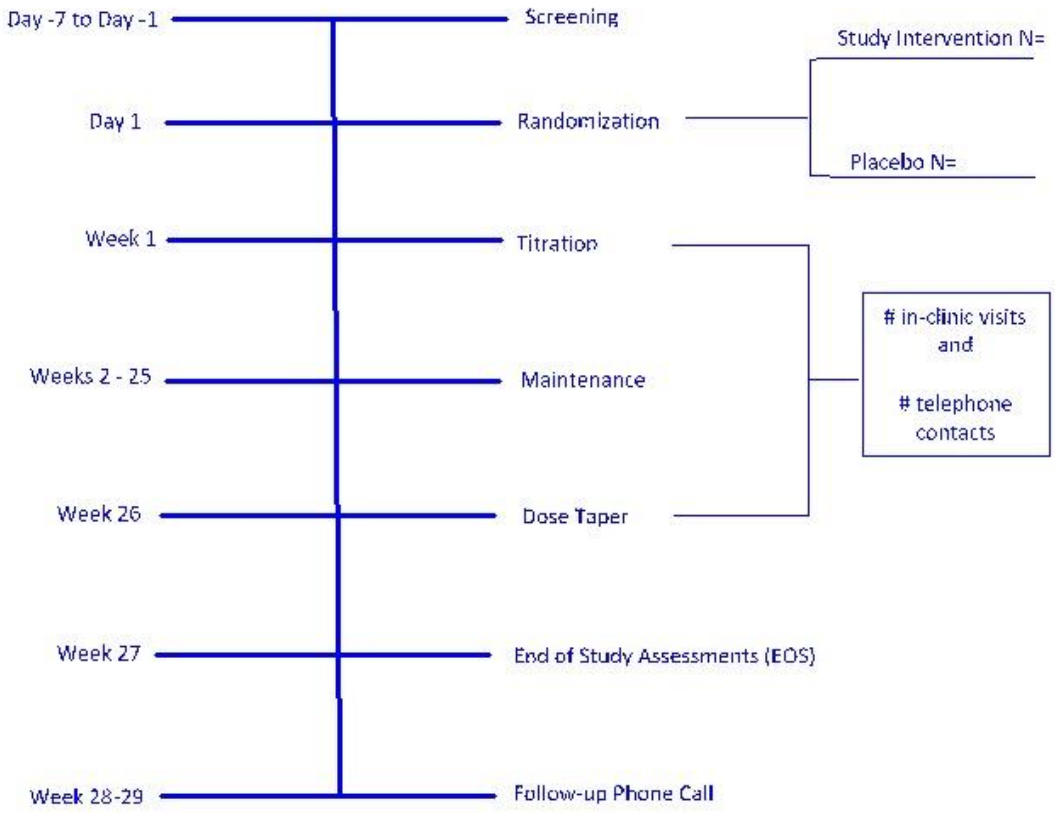
1.2 Study Schema

Please provide a diagrammatic description of the study regimen. This should be a "snapshot" of the overall study design and treatment/intervention. Include the major decision points and all possible research treatments. If applicable, indicate when advanced imaging will be performed in the study. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Depending on the nature of your study, one example may be more appropriate than another. Regardless, the examples included here are intended to guide the development of a schematic that is appropriate to the planned study design and will need to be customized for each protocol. Revise with study-specific information and adapt the diagram to illustrate study design. The time point(s) indicated in the schematic should correspond to the time points in the study Schedule of Activities.

Study Schema Examples:



Example provided as a guide, customize as needed: Timeline diagram *(e.g., randomized controlled trial)*



Example: Randomized trial

Diseases:

STS - Soft Tissues Sarcoma
OGS - Osteogenic Sarcoma
RMS - Rhabdomyosarcoma
ES - Ewings Sarcoma

Drugs:

DOX - Doxorubicin
DTIC - Dacarbazine
IFF – Ifosfamide

Stratify

OGS
RMS
ES
OTHER

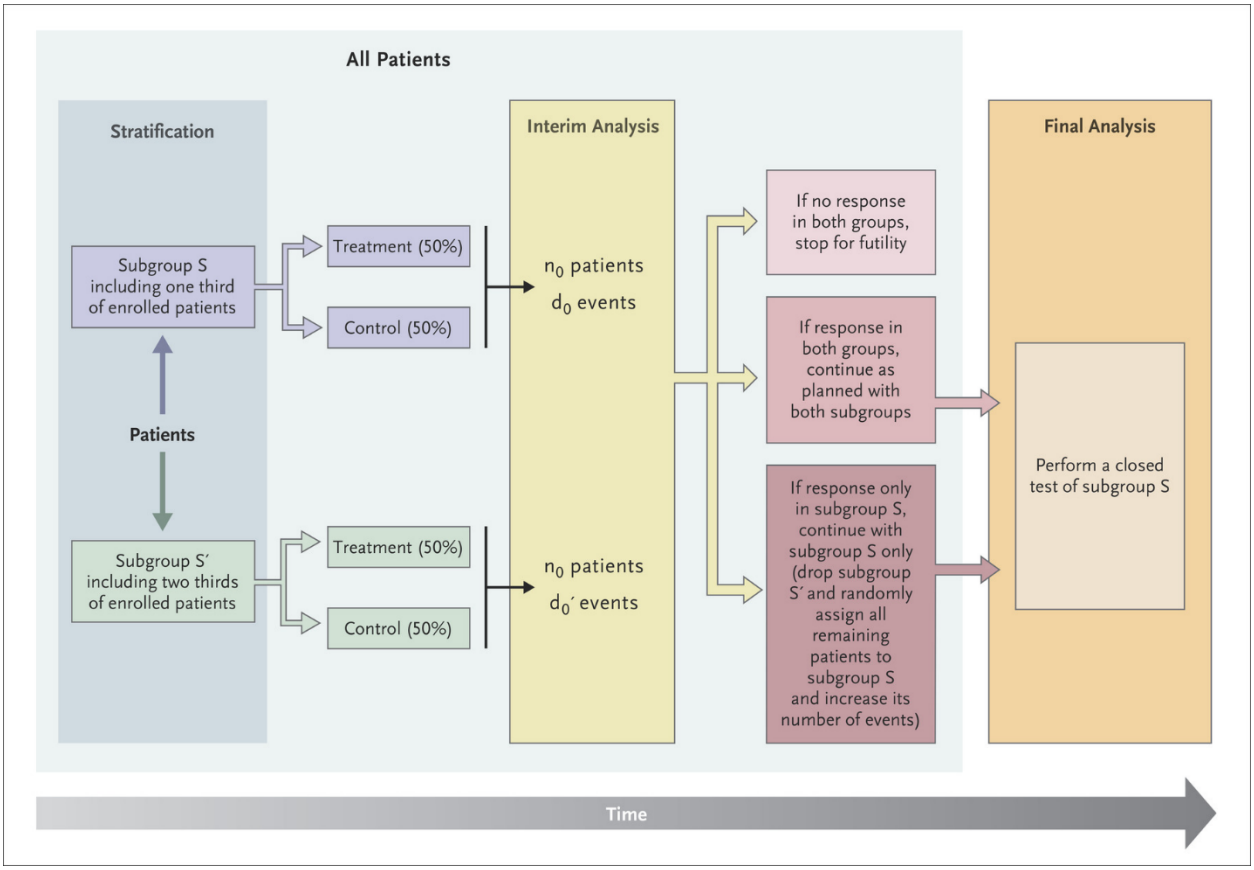
RANDOMIZE

Treatment

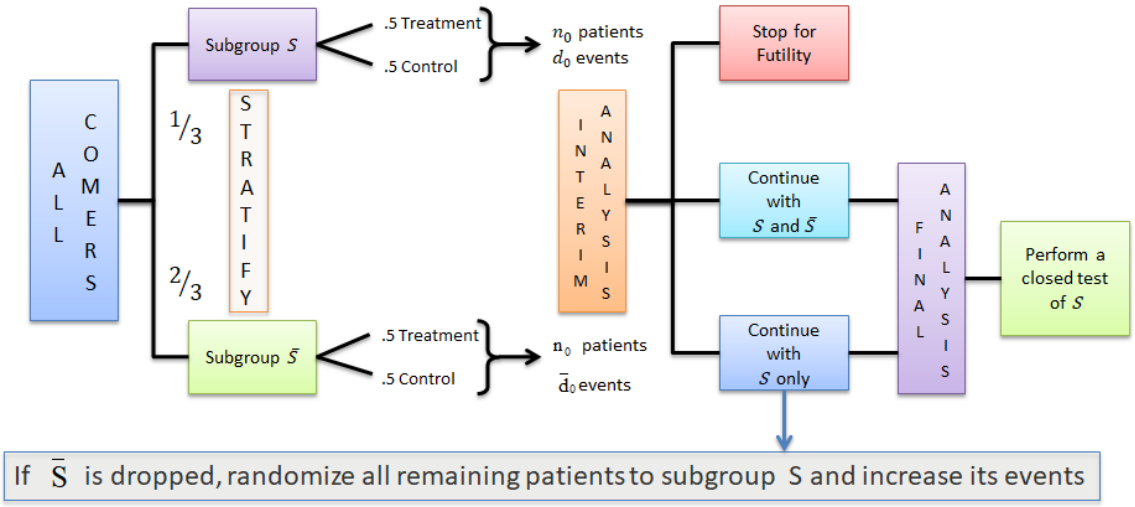
ARM A: DOX/DTIC
q 3 wk x 4

ARM B: DOX/DTIC/IFF
q 3 wk x 4

Adaptive Study Design:

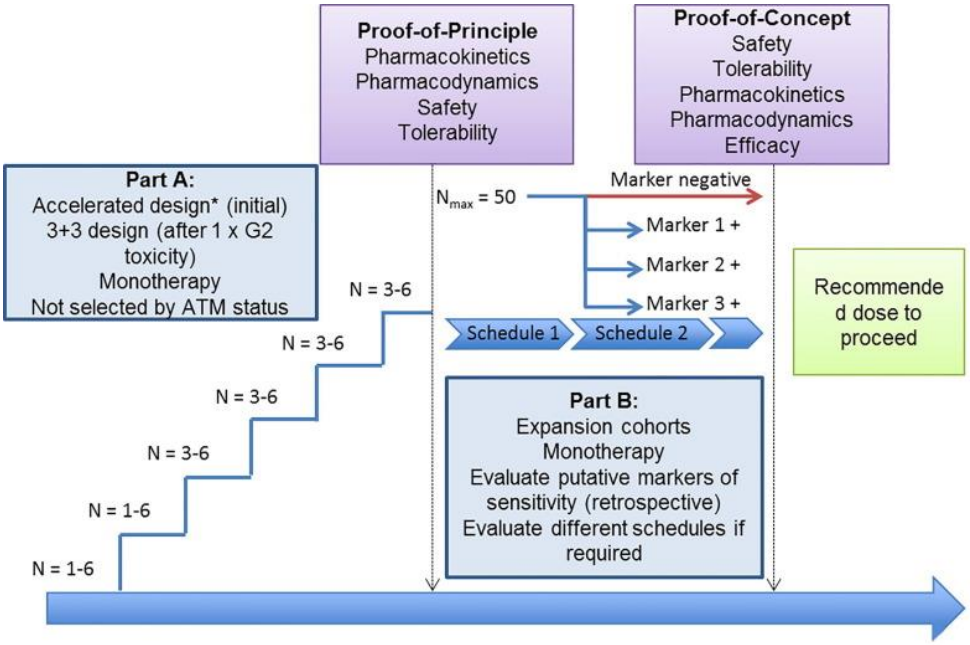


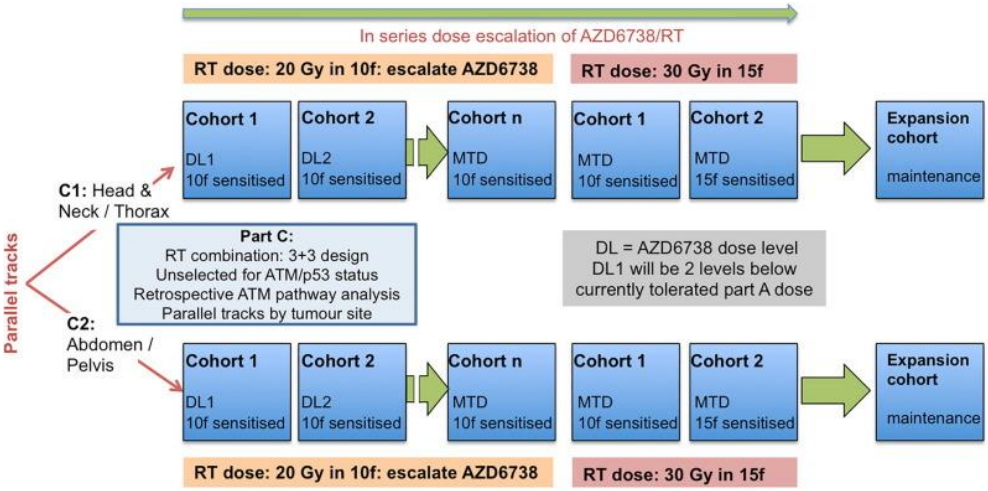
Schematic Representation of Protocol

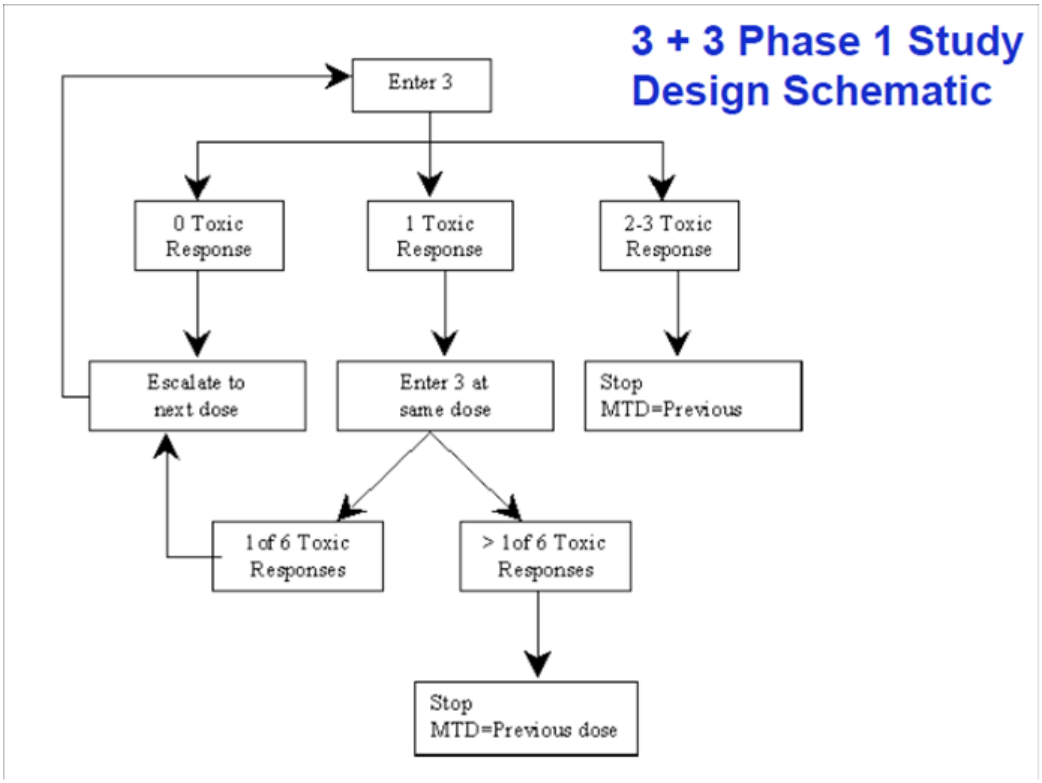


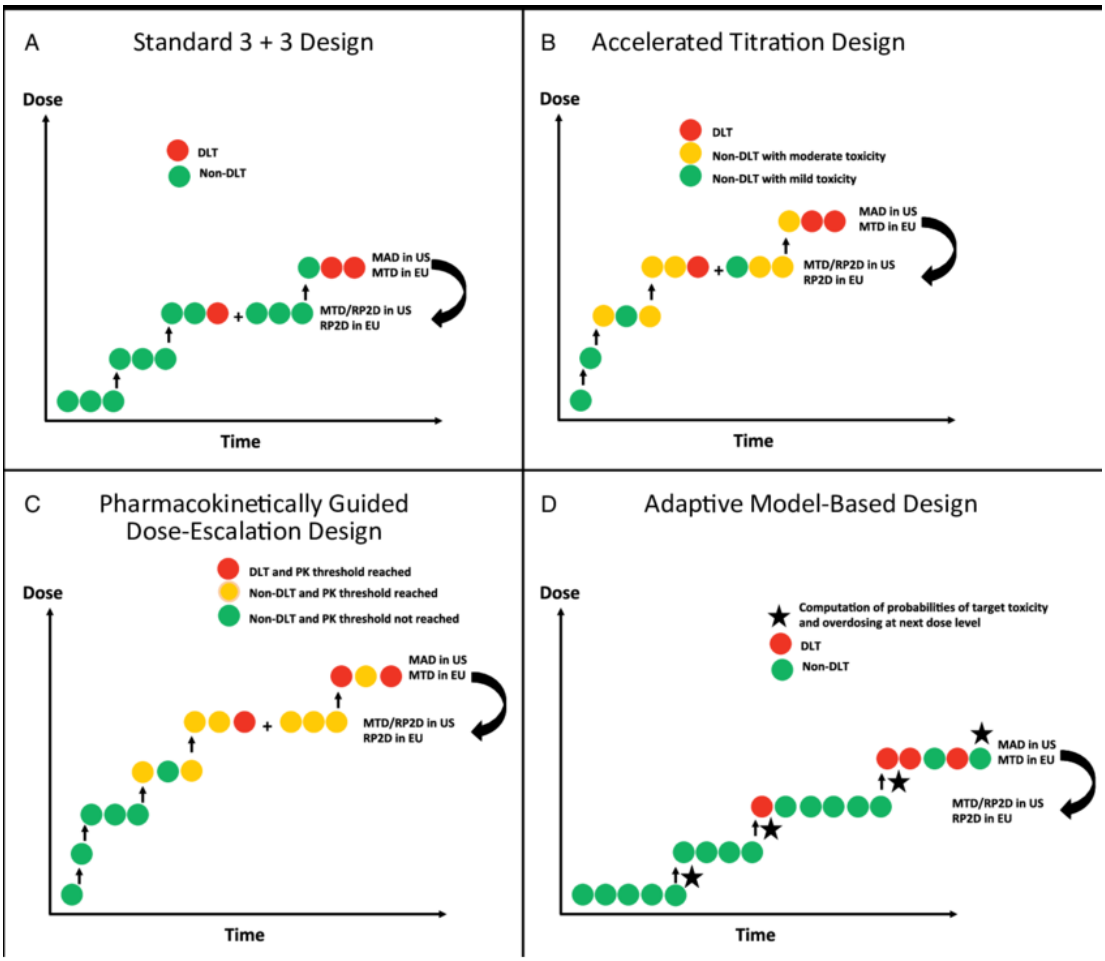
10 Sept 2013 FDA and Industry Workshop. 9-18-2013

Phase I:

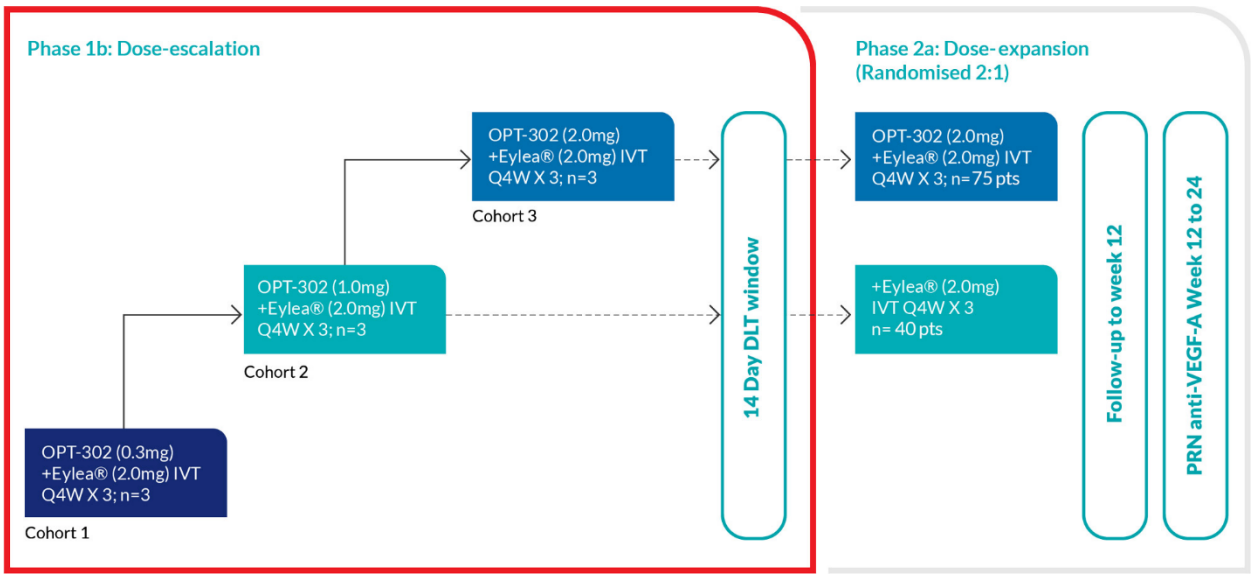

Proof-of-Principle
Pharmacokinetics
Pharmacodynamics
Safety
Tolerability
Proof-of-Concept
Safety
Tolerability
Pharmacokinetics
Pharmacodynamics
Efficacy
Part A:
Accelerated design* (initial)
3+3 design (after 1 x G2 toxicity)
Monotherapy
Not selected by ATM status
N = 3-6
N = 3-6
N = 3-6
N = 3-6
N = 1-6
N = 1-6
Nmax = 50
Marker negative
Marker 1 +
Marker 2 +
Marker 3 +
Schedule 1
Schedule 2
Recommended dose to proceed
Part B:
Expansion cohorts
Monotherapy
Evaluate putative markers of sensitivity (retrospective)
Evaluate different schedules if required


In series dose escalation of AZD6738/RT
RT dose: 20 Gy in 10f: escalate AZD6738
RT dose: 30 Gy in 15f
Cohort 1
DL1
10f sensitised
Cohort 2
DL2
10f sensitised
Cohort n
MTD
10f sensitised
Cohort 1
MTD
10f sensitised
Cohort 2
MTD
15f sensitised
Expansion cohort
maintenance
C1: Head & Neck / Thorax
Parallel tracks
Part C:
RT combination: 3+3 design
Unselected for ATM/p53 status
Retrospective ATM pathway analysis
Parallel tracks by tumour site
C2: Abdomen / Pelvis
DL = AZD6738 dose level
DL1 will be 2 levels below currently tolerated part A dose
RT dose: 20 Gy in 10f: escalate AZD6738
RT dose: 30 Gy in 15f

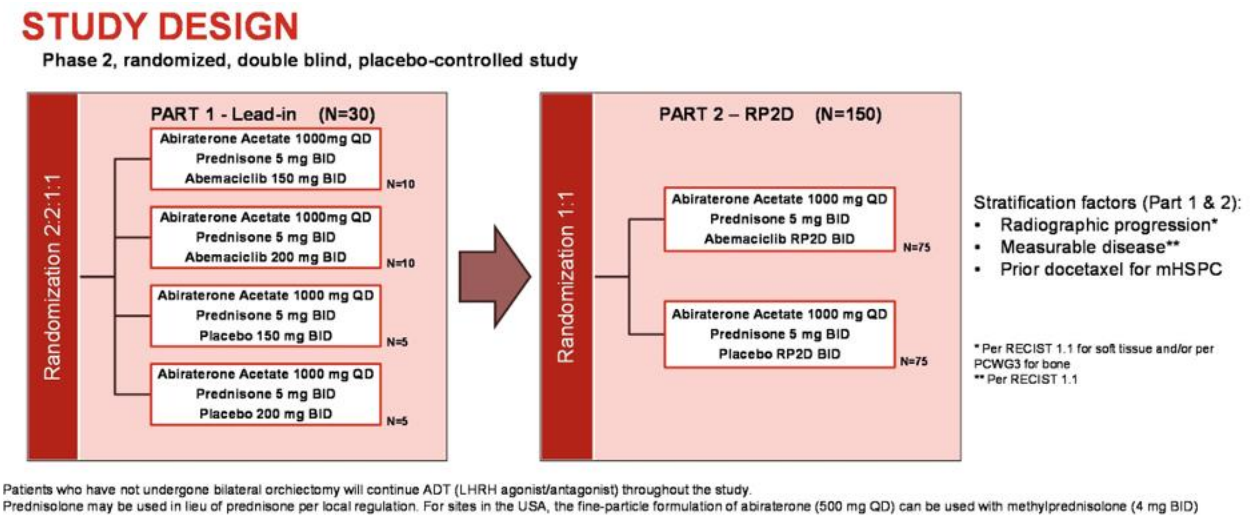

3 + 3 Phase 1 Study
Design Schematic
Enter 3
0 Toxic Response
1 Toxic Response
2-3 Toxic Response
Escalate to next dose
Enter 3 at same dose
Stop MTD=Previous
1 of 6 Toxic Responses
> 1 of 6 Toxic Responses
Stop MTD=Previous dose


A
Standard 3 + 3 Design
Dose
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
B
Accelerated Titration Design
Dose
DLT
Non-DLT with moderate toxicity
Non-DLT with mild toxicity
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
C
Pharmacokinetically Guided
Dose-Escalation Design
Dose
DLT and PK threshold reached
Non-DLT and PK threshold reached
Non-DLT and PK threshold not reached
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
D
Adaptive Model-Based Design
Dose
Computation of probabilities of target toxicity
and overdosing at next dose level
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time

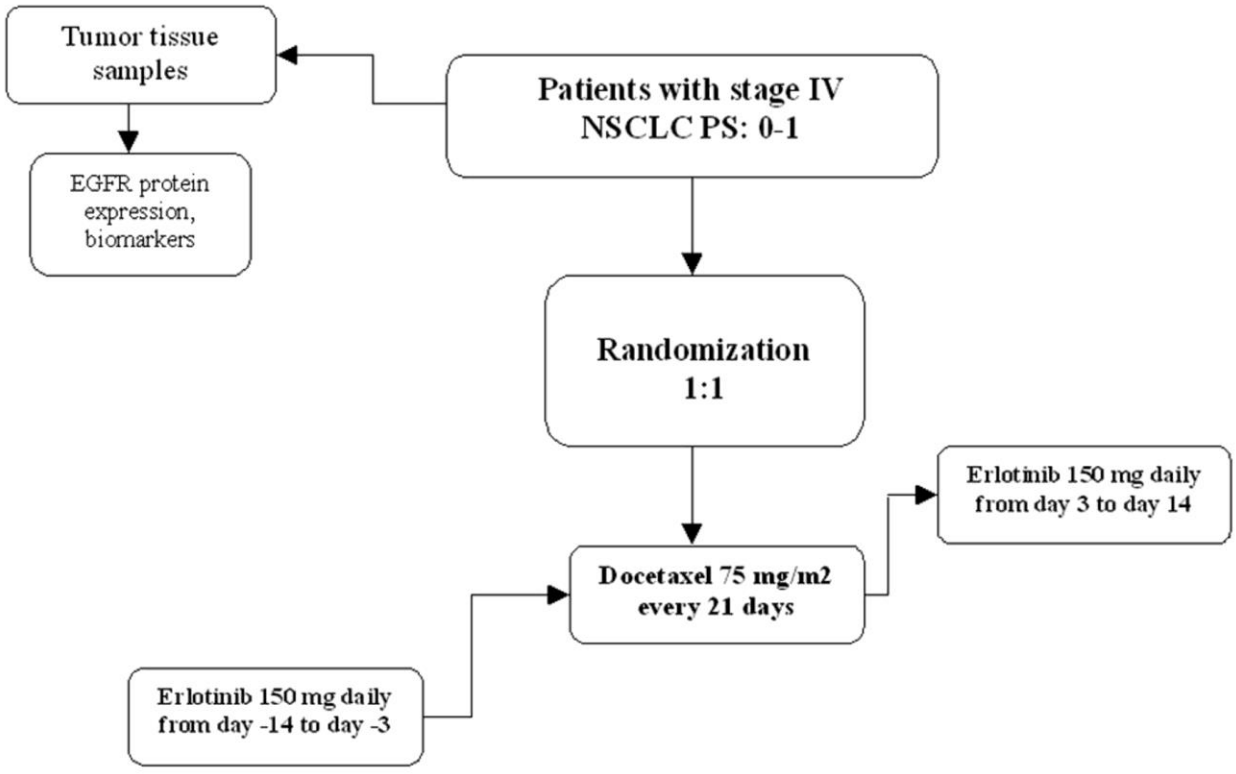
Phase I/II:

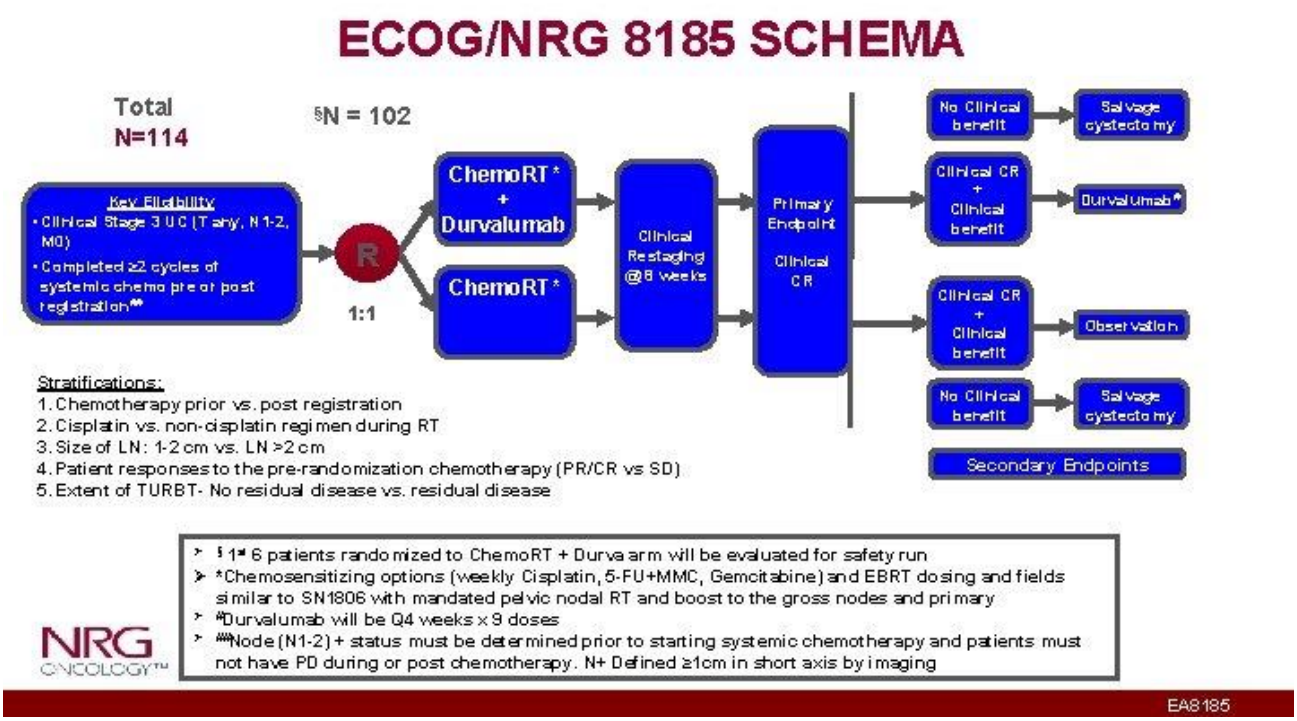

Phase 1b: Dose-escalation
Phase 2a: Dose-expansion
(Randomised 2:1)
OPT-302 (0.3mg)
+Eylea® (2.0mg) IVT
Q4W X 3; n=3
Cohort 1
OPT-302 (1.0mg)
+Eylea® (2.0mg) IVT
Q4W X 3; n=3
Cohort 2
OPT-302 (2.0mg)
+Eylea® (2.0mg) IVT
Q4W X 3; n=3
Cohort 3
14 Day DLT window
OPT-302 (2.0mg)
+Eylea® (2.0mg) IVT
Q4W X 3; n=75 pts
+Eylea® (2.0mg)
IVT Q4W X 3
n= 40 pts
Follow-up to week 12
PRN anti-VEGF-A Week 12 to 24

Phase II:



Patients who have not undergone bilateral orchiectomy will continue ADT (LHRH agonist/antagonist) throughout the study.
Prednisolone may be used in lieu of prednisone per local regulation. For sites in the USA, the fine-particle formulation of abiraterone (500 mg QD) can be used with methylprednisolone (4 mg BID)





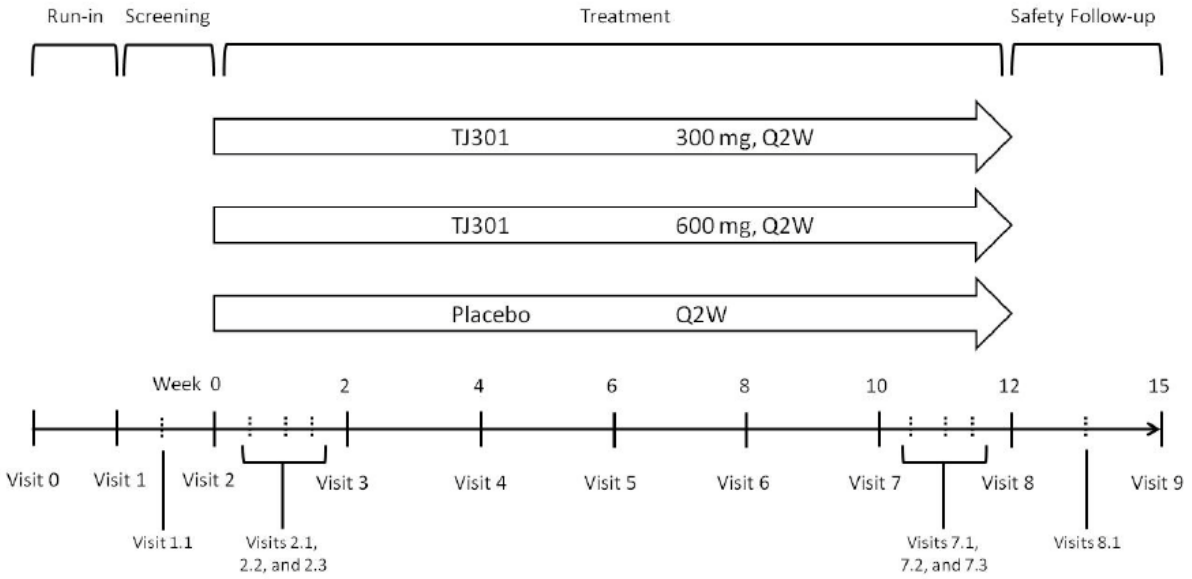
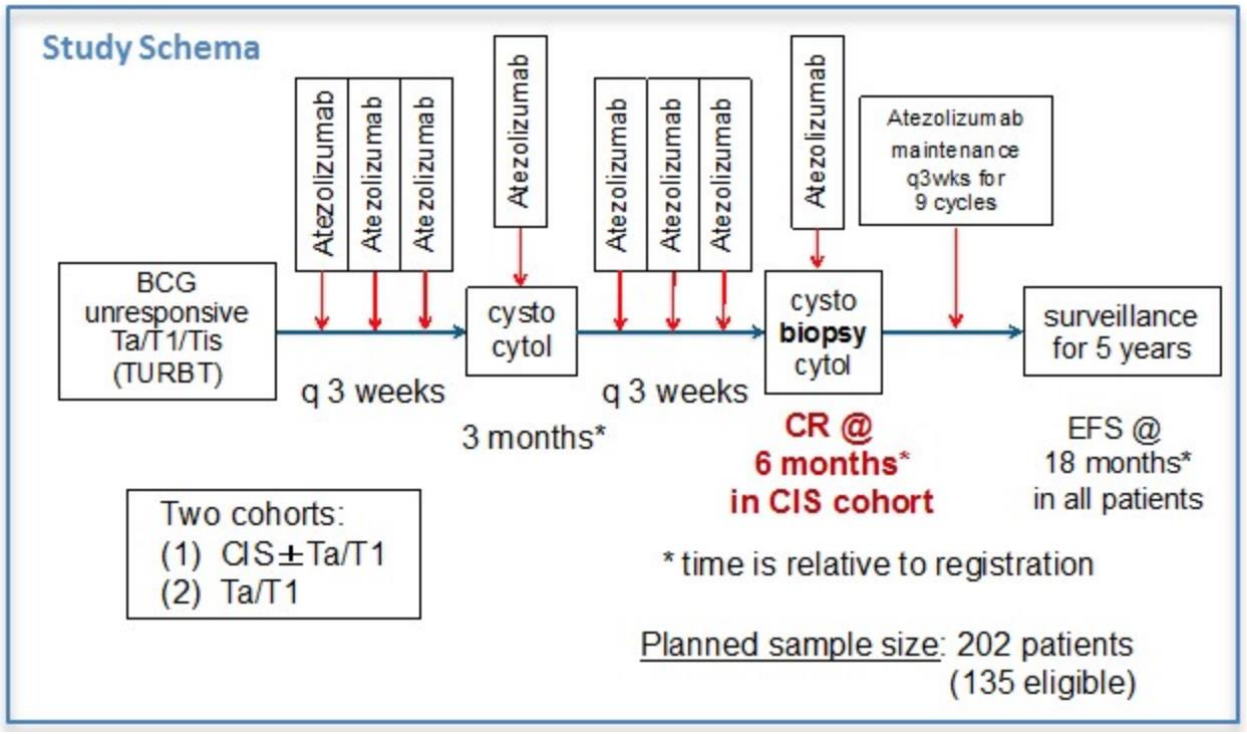
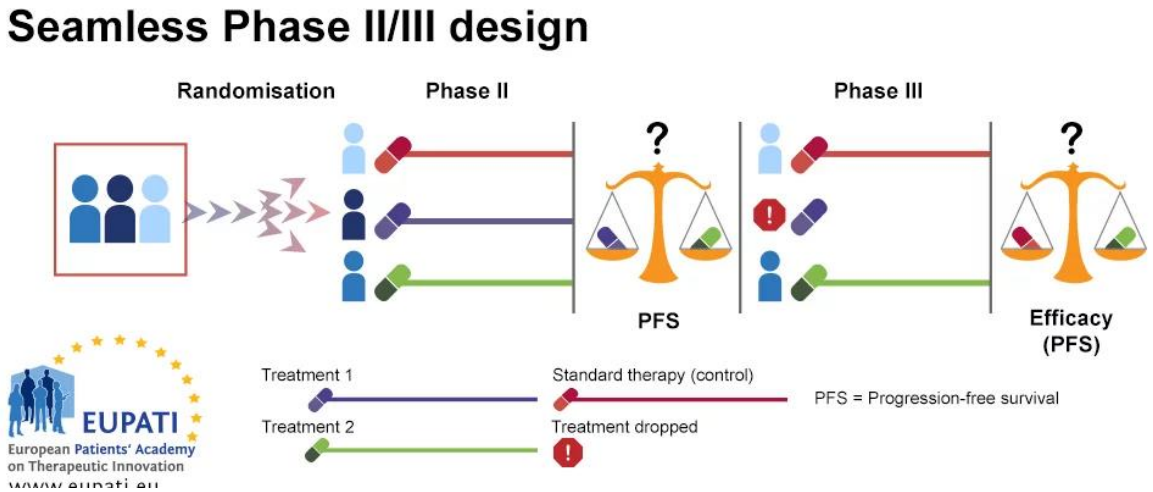


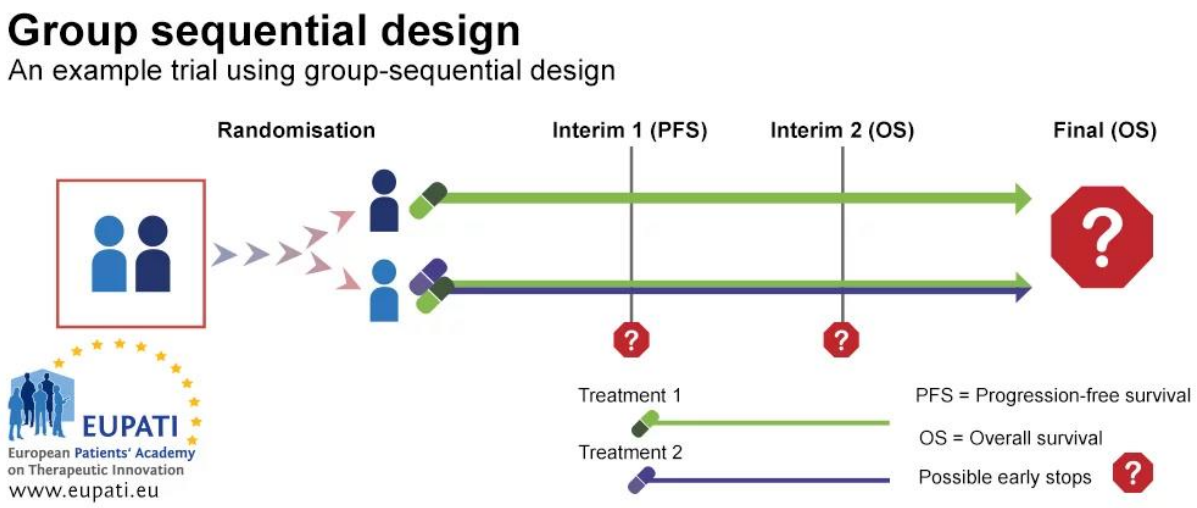
Figure 2 Overview of Trial Design


Study Schema
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
Atezolizumab
maintenance
q3wks for
9 cycles
BCG
unresponsive
Ta/T1/Tis
(TURBT)
cysto
cytol
cysto
biopsy
cytol
surveillance
for 5 years
q 3 weeks
3 months*
q 3 weeks
CR @
6 months*
in CIS cohort
EFS @
18 months*
in all patients
Two cohorts:
(1) CIS±Ta/T1
(2) Ta/T1
* time is relative to registration
Planned sample size: 202 patients
(135 eligible)

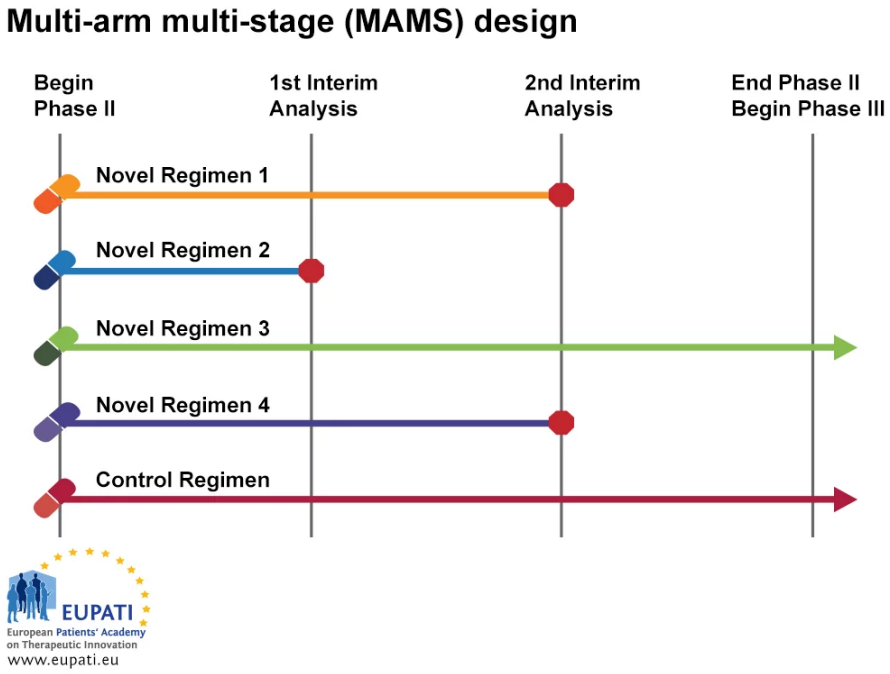
Phase II/III:


Seamless Phase II/III design
Randomisation
Phase II
Phase III
?
?
PFS
Efficacy
(PFS)
EUPATI
European Patients' Academy
on Therapeutic Innovation
Treatment 1
Treatment 2
Standard therapy (control)
Treatment dropped
PFS = Progression-free survival

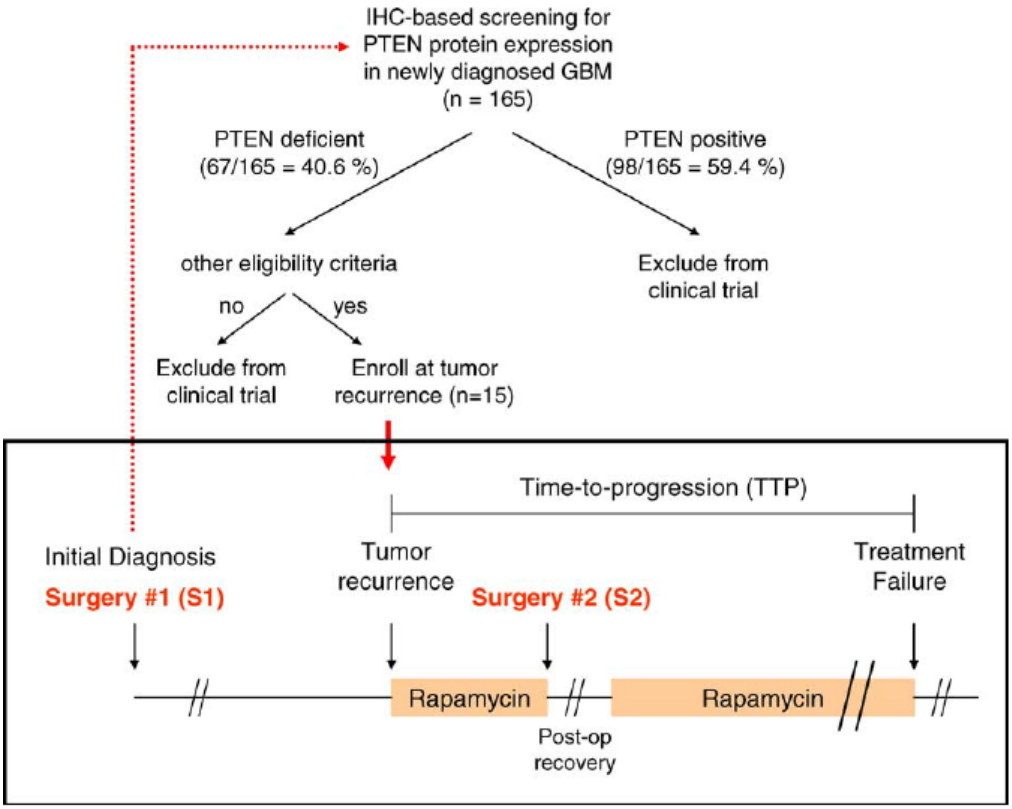
Phase III:



Multi-Arm Multi-Stage (MAMS) Design:



Surgical:



Vaccine:

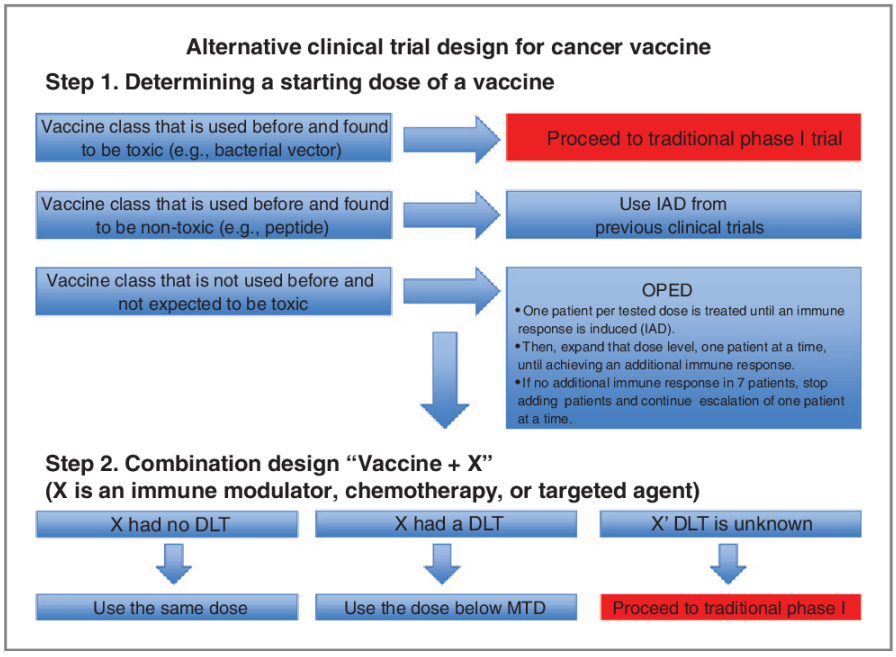
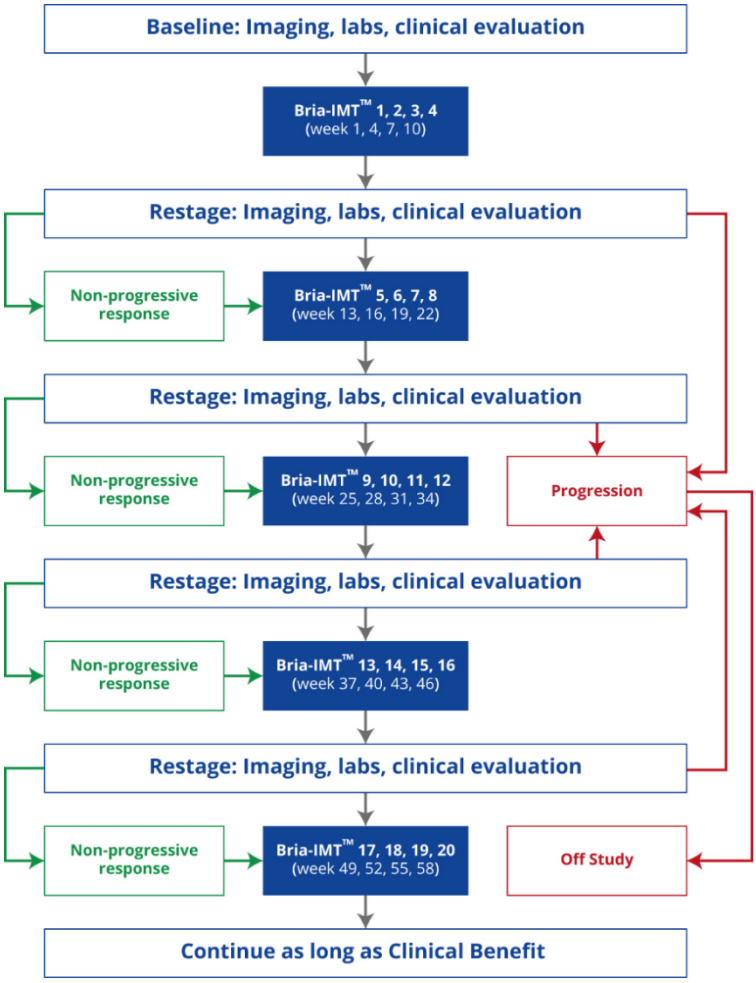


Figure 2. The suggested alternative design for early cancer vaccine development. IAD, Immune Active Dose; OPED, One Patient Escalation Design.

Imaging:



If appropriate, a table may be used to describe the treatment regimen. The diagram and/or table should include the route of administration (PO, IV, etc.) and dosing schedule (QD, BID, Days 1-5, etc.). Please refer to the examples below.

For phase 1 single-agent protocols:

Dose Escalation Schedule	
Dose Level	*Dose of {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.*			

2.0 Study Objectives and Endpoints

State all relevant study objectives and endpoints (primary, secondary, tertiary). When writing this section, please ensure alignment with the language in the statistics section.

2.1 Objectives

This section should provide a detailed description of the study objectives. Objectives are the reason for performing the study and outline the scientific questions to be answered.

The primary objective is the main hypothesis to be tested, or question to be answered, through the conduct of the study. It drives any statistical planning for the study (e.g., calculation of the sample size) to provide the appropriate power for statistical testing.

The secondary objectives are goals that will provide further information on the use of the study intervention.

Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.

Please express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate), and include the general purpose (e.g., feasibility, acceptability, efficacy, effectiveness, safety) and/or specific purpose (e.g., dose response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behavior). Please state the primary objective or hypothesis in quantifiable terms. The primary objective must match the one used in the statistical design of the study.

The study design should describe an adequate plan for answering the primary study question. The objective should correspond to the phase of the study (see below). Quality of Life objectives should be included when applicable.

NA- No Phase: Trials without a Drug or Biologic (for example, studies involving devices or behavioral interventions). Describe the hypothesis being tested.

For drug or biologic interventions, please designate a numerical phase I-IV per 21 CFR 312.21 or 21 CFR 312.85.

Early Phase I: Exploratory

Exploratory studies involve very limited human exposure, with no therapeutic or diagnostic intent (e.g., screening studies, microdose studies). These trials are not designed to establish efficacy or toxicity, but to obtain preliminary data to support the rationale for a subsequent clinical trial. These studies are typically designed to assess feasibility, to define and/or refine the target population, to develop and test the feasibility of obtaining surrogate endpoints, to quickly test the safety of a drug for which there is single agent safety data but which is being used for the first time in combination with a drug that should have no synergistic effects with the agent, to establish measures of safety and efficacy, to establish preliminary estimates of variances, correlations, and/or differences, to evaluate total costs or timelines of doing an experiment, to determine sample recruitment strategies, and to address design and methodological issues for clinical trials. The expected results are intended to translate clinical questions into statistical hypotheses and ultimately to optimize the design of the eventual full-scale clinical trial. The sample size may not be adequate to even detect large differences; however, the data should provide a basis for providing sample size estimation for future clinical trials. Usually exploratory studies are no larger than 10 participants and almost never larger than 20 participants. To determine the sample size, consult a statistician. For more information, please see: FDA guidance on Exploratory IND Studies

Phase I: Evaluation of Toxicity

The primary objective of a Phase I study is to identify a maximum tolerated dose (MTD) for a given dose/schedule and to explore the quantitative (frequency, duration) and qualitative (organ specific) nature of acceptable and unacceptable toxicities. Preliminary information on efficacy may also be obtained.

These studies are concerned with evaluating toxicity and are often the first test of a drug or drug combination in humans. A few participants are entered at a pre-planned dose and accrual is suspended for a review of toxicity. The dose is escalated for the next group of participants if an unacceptable rate of dose limiting toxicity (DLT) is not seen. The dose below that which produced an unacceptable rate of DLT is designated as the MTD, and this dose is used for further testing in Phase II studies. Since a small number of participants (typically 3-6) are treated at each dose level during the dose escalation, the design of a Phase I study will often specify that an additional group of participants (usually fewer than 15) be treated at the MTD once it has been determined. Usually, Phase I studies require a total accrual of approximately 15-30 participants. A statistician should be consulted regarding the study design.

Phase II: Treatment Efficacy

The objective of a Phase II clinical trial in oncology is to assess whether there is adequate anti-tumor activity of a new treatment regimen to pursue further testing, and to describe any associated adverse reactions (toxicities) with a larger sample size than in Phase I trials. The primary endpoint in a Phase II trial is typically response, e.g. shrinkage of the tumor or change in biochemical marker(s), but other endpoints (imaging, biological, and disease progression) are possible as primary or secondary endpoints.

These studies are designed to evaluate the safety and efficacy of a drug that has passed through Phase I testing with acceptable levels of toxicity. Careful monitoring of participants is required since both response and toxicity assessments are necessary. Usually Phase II studies require an accrual of 20-50 participants. A statistician should determine the appropriate number of participants.

Phase III: Comparative Study

The most important objective of Phase III clinical trials in oncology is the randomized comparison of treatments or interventions. Typically, one or more new treatments that have been shown to have anti-tumor activity in Phase II trials are compared to the standard treatment, which could include no treatment or a placebo, depending on the disease. The main endpoint of Phase III trials is usually overall survival and/or disease-free or progression-free survival (DFS or PFS). Different disease programs have different standard endpoints. For most solid tumors, response in advanced stage disease is commonly defined using the RECIST criteria (http://ctep.cancer.gov/guidelines/recist/html). These studies usually require greater than 100 participants. A statistician should determine the final accrual figure.

2.1.1 *Primary Objective*

The primary objective is the main question to be answered. The primary objective drives any statistical planning for the study, e.g., calculation of the sample size to provide the appropriate power for statistical testing.

Please insert the primary study objective(s). Whenever possible, a single primary objective is preferable. Please specify advanced imaging Primary Objective if applicable.

Each objective should include the specific measurement and a description of the metric that will be used. For example, safety, tolerability, and feasibility measures must include the specific metric that will be used to make the assessment (e.g., number of participants experiencing adverse events). What the outcome is and how it will be measured must be clearly stated.

Careful wording of objectives is recommended to facilitate ClinicalTrials.gov registration and reporting requirements. For more information, see Outcome Measures: https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf

2.1.2 *Secondary Objectives*

Secondary objectives are goals that will provide further information on the use of the intervention. Secondary objectives may or may not be hypothesis-driven, may include secondary outcomes, and may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data).

Please insert any secondary objective(s). Each objective should include the specific measurement and a description of the metric that will be used. For example, safety, tolerability, and feasibility measures must include the specific metric that will be used to make the assessment (e.g., number of participants experiencing adverse events). What the outcome is and how it will be measured must be clearly stated.

Careful wording of objectives is recommended to facilitate ClinicalTrials.gov registration and reporting requirements. For more information, see Outcome Measures: https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf

2.1.3 *Tertiary/Exploratory Objectives*

Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.

Please insert any tertiary/exploratory objective(s). Whenever possible, a single objective is preferable. Please specify advanced imaging Primary Objective if applicable.

Each objective should include the specific measurement and a description of the metric that will be used. For example, safety, tolerability, and feasibility measures must include the specific metric that will be used to make the assessment (e.g., number of participants experiencing adverse events). What the outcome is and how it will be measured must be clearly stated.

Careful wording of objectives is recommended to facilitate ClinicalTrials.gov registration and reporting requirements. For more information, see Outcome Measures: https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf

2.2 Endpoints

A study endpoint is a specific measurement or observation used to assess the effect of the study intervention. Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. The primary endpoint is the basis for concluding that the study met its objective. Please give succinct but precise definitions of the study endpoints used to address the study's primary objective (e.g. specific laboratory tests that define safety or efficacy, clinical assessments of disease status, assessments of psychological characteristics, patient reported outcomes, behaviors, or health outcomes). Include the study visits or time points at which data will be recorded or samples will be obtained. Describe how endpoint(s) will be adjudicated, if applicable. Endpoints should conform to ClinicalTrials.gov QC Review Criteria concerning Outcome Measures https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf

Generally, there should only be one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold.

2.2.1 *Primary Endpoint*

Please clearly specify the primary endpoint used to determine primary efficacy, and clearly articulate how the selected primary endpoint is linked to achieving the primary objective. Explain why the primary endpoint was chosen, its importance, and its role in the analysis and interpretation of the study results.

In general, there should be only one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold.

2.2.2 *Secondary Endpoints*

Please clearly specify the secondary endpoints. These may include endpoints related to efficacy and/or safety. Explain how the secondary endpoints are linked to adding more information about the primary

objective, how they are linked to addressing secondary objectives, why the they were chosen, and their importance, and their role in analysis and interpretation of study results.

2.2.3 *Tertiary/Exploratory Endpoints*

Please clearly specify any tertiary/exploratory endpoints.

Tertiary/exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.

2.3 Tabular Summary of Objectives, Endpoints, and Justifications

For purposes of registration and reporting to ClinicalTrials.gov, the terms "Objectives" and "Endpoints" as used in this template align with the terms "Primary Purpose" and "Outcome Measures" in ClinicalTrials.gov, respectively. Provide a description of the study objectives and endpoints, as well as a justification for the selection of each endpoint, in the table format included below. This will provide clear articulation of how the selected endpoints are linked to achieving the study objectives. Data points collected in the study should support an objective or have a regulatory purpose. Careful consideration should be given to the amount of prospectively collected data needed to support study objectives.

An objective is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behavior).

A study endpoint is a specific measurement or observation to assess the effect of the study variable (study intervention). Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct, but precise definitions of the study endpoints used to address the study objectives (e.g., specific laboratory tests that define safety or efficacy, clinical assessments of disease status, assessments of psychological characteristics, patient reported outcomes, behaviors or health outcomes). Include the study visits or time points at which data will be recorded or samples will be obtained. Describe how endpoint(s) will be adjudicated, if applicable.

Primary and secondary endpoints should be adjusted for multiplicity. If a claim is sought for the secondary endpoints, the statistical plan for adjustment for multiplicity should be aligned with those objectives.

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Primary		

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).	*The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is/are the basis for concluding that the study met its objective. Often Phase 2 and 3 trials include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold. However, this is not always the case. For example, in many trials of medical devices there are primary endpoints for both safety and effectiveness.* *In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit.*	*Briefly explain why the endpoint(s) were chosen.*
Secondary		
The secondary objective(s) are goals that will provide further information on the use of the intervention.	*Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention's effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases.*	*Briefly explain why the endpoint(s) were chosen.*
Tertiary/Exploratory		

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.	*Exploratory endpoints should be specified. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.*	*Briefly explain why the endpoint(s) were chosen.*

3.0 Background Information

This section should include:

- *The name and description of the study agent(s)/intervention(s)/investigational product(s).*
- *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance. Include a discussion of any data that does not support the study hypothesis.*
- *A summary of relevant clinical research. A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies.*
- *The importance of the study and any relevant treatment issues or controversies. If similar studies have already been conducted, clearly explain why this one is necessary. It should be clear to a reviewer why this study is unique and important, and how its results will add to the current understanding of the area.*
- *Focused discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in the References section of the protocol). Highlight what is already known about the research question and what remains unclear.*
- *Applicable clinical, epidemiological, or public health background or context of the study. If the proposed study involves treatment, include a clear description of the current standard of care.*

3.1 Study Disease(s)

Please provide background information on the study disease(s). Please include a description of the epidemiology of the disease, including known demographic characteristics of the target population, or subpopulations, who are likely to have access to the product or treatment regimen under an IND or with FDA approval.

Describe the need, relevance and priority for the study. For example, "osteoarthritis in post-menopausal women affects N women over the age of 50. Patient symptoms are characterized by…."

3.2 Therapeutic Intervention(s)

Please provide background information on any IND agents, including information on the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical pharmacokinetics, major route of elimination and safety profile. If available, please include information on the metabolism of the study agent in humans and its potential for drug interactions. Please include information regarding

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 IB].

3.2.1 *IND Agent #1*

3.2.2 *IND Agent # 2*

3.3 Other Agents

Please provide background information on any other agents, treatments, or therapeutic interventions in this study, including information to support safety issues and the rationale for the proposed starting dose and dose escalation scheme, if applicable.

NOTE: If the specific doses and schedule of other agent(s) given as part of a standard treatment for the disease are not important in determining the objectives of the study, this should be clearly stated (e.g. CHOP as per institutional standards). However, this should only be done when the dose and schedule, including modifications, are not important in determining one or more objectives.

4.0 Scientific Rationale and Justification for Study Design

Please provide the rationale for evaluating the study intervention in this disease.

State the problem or question under study (e.g., describe the disease and current limitations of knowledge or therapy).

Clearly state the hypothesis. Include specific aims or major goals of the project.

Describe the scientific and medical data (e.g., results of observational studies and early clinical trials) that justify the study, its design, and the intervention groups. Include any data from animal and human studies relevant to mechanism of action, effect size, and possible effects of the intervention on selected outcomes.

Name and describe the intervention regimen(s) and justify why the intervention(s) have been chosen.

Describe and justify the:

- *Route of administration*
- *Dosage of the study agent*
- *Dosing regimen of the study agent*
- *Intervention period, frequency and intensity*
- *Selection of study population*
- *Rationale for the type and selection of control (e.g., placebo, no treatment, active drug, dose-response, historical), if applicable. Discuss known or potential problems associated with the control group chosen in light of the specific disease and therapies being studied, if applicable.*

Please include information to support safety issues, the rationale for the proposed starting dose, dose escalation scheme, and regimen chosen. Please also provide the rationale for the type and frequency of any advanced imaging.

5.0 Potential Risks and Benefits

5.1 Known Potential Risks

Include a discussion of known potential risks from either clinical or nonclinical studies.

- *If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of risk information.*
- *If the product is investigational, the Investigator's Brochure (IB) should be the primary source of the risk information. In addition, relevant published literature can also provide relevant risk information.*
- *If the risk profile cannot be described from the package insert, device labeling, or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately.*

Potential risks and discomforts must be minimized to the greatest extent possible by using procedures such as appropriate training of personnel, monitoring, withdrawal of the subject upon evidence of difficulty or adverse event; and referral for treatment, counseling or other necessary follow-up.

Consider not only immediate risks, but also delayed or long-term risks

Consider physical, reproductive, psychological, social, legal, and economic risks as well as community or group harms (e.g., breach of confidentiality is a common risk in social and behavioral research). If applicable, describe risks to others who are not subjects (e.g., group harms, harms to society).

If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered, and explain why alternative procedures are not included.

Provide a description of alternative courses of action which are available should the participant elect not to participate in the study. If there are no alternatives available to the subject, this should be stated.

Summarize the known and potential risks and benefits of the interventions. Justify why the study should move forward. Why does the value of the information to be gained through the study outweigh the risks involved?

5.2 Known Potential Benefits

Include a discussion of known potential benefits from either clinical or nonclinical studies.

- *If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of potential benefit information.*
- *If the product is investigational, the IB should be the primary source of the potential benefit information. In addition, relevant published literature can also provide potential relevant benefit information.*
- *If the potential benefit cannot be described from the package insert, device labeling, or the IB, the potential benefit information discussion will result from published literature and should be included and referenced appropriately.*

Describe any physical, psychological, social, legal, economic, or any other potential benefits to individual participants, or society in general, as a result of participating in the study, addressing each of the following:

- *Immediate potential benefits*
- *Long-range potential benefits*

Note that payment to participants, whether as an inducement to participate or as compensation for time and inconvenience, is not considered a "benefit." Provision of incidental care is also not to be considered a benefit.

5.3 Assessment of Potential Risks and Benefits

Include an assessment of known potential risks and benefits, addressing each of the following:

- *Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design*
- *Justification as to why the value of the information to be gained outweighs the risks of participation in the study*

Sample Text:

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study.

6.0 Overview of Study Design and Intervention

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the Study design. A description of the study design should be consistent with the Protocol Summary and should include:

- *The type/design of trial (e.g., placebo-controlled, double-masked, parallel design, open-label, dose escalation, dose-ranging, group- or cluster randomized, individually randomized group treatment, stepped wedge)*
- *The phase of the trial*
- *Study population*
- *Study location (e.g., in-patient or out-patient, clinic, community)*
- *The number of study groups/arms including sample size (including a table, if appropriate)*
- *Single- or multi-center*
- *Specific unit(s) of assignment and unit(s) of observation*
- *Specific statement of the primary and secondary outcomes (must be consistent with Study Objectives)*
- *Approximate duration of enrollment period and follow-up (specify individual participant vs. entire trial)*
- *Description of intervention and administration*
- *Changes in scheduling, such as dose escalations*
- *Randomization, blinding and any restrictions on randomization (e.g., matching, stratification, constrained randomization)*

- *Other protocol specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)*

Briefly describe the study design and indicate, in general terms, how the design will answer the question posed by the study. You may choose to use diagrams to explain design complexities.

For Pilot Studies: Preliminary Study

- *Specify the objectives and endpoints (e.g., feasibility, pharmacodynamics, etc.).*
- *Specify the maximum total accrual (often no larger than 10 participants and almost never larger than 20 participants).*
- *Provide a justification of the sample size. Invocation of the term "pilot study" does not exempt the investigator from justifying their choice of sample size.*
- *Provide statistical considerations whenever possible.*
- *Specify the statistical methods that will be used in the data analyses.*
- *Explain how data and tests will be interpreted.*
- *Explain how the information gathered from the pilot study will be used to design and optimize subsequent clinical trials.*

For Phase I Study: Evaluation of Toxicity

- *Specify the study design and primary endpoints.*
- *Include information on how toxicity will be graded and reported, and state that all participants who receive any amount of the study drug will be evaluable for toxicity.*
- *State the toxicities that are dose-limiting (DLT).*
- *Define the maximum tolerated dose (MTD), the dose below that which produced an unacceptable rate of DLT, and state if this will be the dose used for further testing in Phase II studies.*
- *Explicitly describe the escalation scheme: the number of participants at each dose, a minimum suspension time between doses, and a decision rule for dose escalation, de-escalation, or further exploration of a dose given observed toxicity.*
- *Specify the various possible values of the true toxicity rate, the chance of observing toxic events, and hence of escalating or de-escalating, at a given dose.*
- *If an additional group of participants (usually fewer than 15) is to be treated at the MTD once it has been determined, state how many participants will be included in this expansion cohort and the maximum width of a 90% exact confidence interval for the true but unknown toxicity rate.*
- *Specify the maximum total accrual (approximately 15-30 participants), the accrual rate and anticipated time to study completion even though the study completion depends on observed toxicity and the need to suspend accrual after each dose.*

For Phase II Study: Treatment Efficacy

- *Specify the primary endpoint that should reflect the first stated objective of the study. The primary objective may be to "investigate", "estimate", or "describe" the endpoints of interest. The verbs "determine" and "establish" should be avoided, as such goals are not consistent with the exploratory nature of a Phase II study. Other goals include determination of feasibility of administering a treatment, classification of toxicity, etc.*

- *Specify the study design, that is, whether participants will be accrued in one stage, two or more stages, or some other formal sequential design.*
- *Explicitly state any early stopping rules. If a multistage design is used, criteria for moving onto subsequent stages of accrual, and for determining if the treatment is promising after the final stage of accrual must be outlined.*
- *State the planned total sample size, the expected accrual rate and accrual period, and the expected duration of follow-up. The statistical considerations section must include a justification for the proposed sample size and the design parameters. It is not appropriate to suggest that a Phase II study will continue to accrue beyond its specified accrual goal.*
- *State whether the total sample size should be adjusted to allow for participants who never begin protocol therapy, ineligibility, inevaluability, participant drop out, and/or pathology exclusions.*
- *If a Phase III investigation is planned, contingent upon the outcome of the Phase II study, this should be explicitly stated in the protocol.*
- *Specify which outcomes (e.g., how many responses) will be regarded as indicating inactivity, and which will indicate efficacy, that is, the null and alternative hypotheses. These results should be based on literature or prior work and cited in the background section. Also, explicitly state the overall Type I error rate, and the power. Since the goal of a Phase II study is to determine whether or not to proceed with further testing, the probability of warranting further testing when the null hypothesis is actually true should be limited. Generally, Phase II designs use a 10% one-sided type I error and have at least 90% power.*
- *The accrual goal is between 17 and 50 participants total in single arm trials or per arm in randomized phase II trials. If the study involves randomization, also state the randomization process and any stratification factors.*

For Phase III Study: Comparative Study

- *State the primary objective and provide a precise definition of the primary endpoint.*
- *Specify the projected accrual rates, total sample size (or maximum sample size in the case of sequential trials), and projected length of accrual and follow-up after termination of accrual. The accrual rate for a particular study should be estimated from other studies previously conducted by DF/HCC with the same disease (sub) types.*
- *Adjust the total sample size according to the expected rate of ineligibility, exclusion based on central pathology review, and drop out.*
- *Describe the randomization process and any stratification factors.*
- *Specify the type I error rates. Superiority trials should have type I error rates $\leq$ 0.05. For one-sided tests, type I errors of 0.025 are recommended. Equivalence or non-inferiority trials may have larger type I errors.*
- *Specify the alternative hypothesis of interest and the power. The alternative hypothesis used for sample size should represent the minimum treatment difference required to change clinical practice.*
- *Sample sizes must be sufficiently large to have at least 80% (85-90% if feasible) power to detect a clinically meaningful alternative to no treatment difference, in a reasonable time frame. In diseases where many cases may be accrued quickly, 90% power is recommended. Equivalence/non-inferiority trials may be designed with powers of 90-95%.*
- *State which participants will be included in the primary analysis. The primary efficacy analysis should be based on the intention to treat (ITT) principle, which groups participants based on assigned treatment, regardless of the treatment actually received.*
- *Clearly state the test (e.g., log rank) to be used for the primary analysis, including details such as stratification and whether the test is one-sided or two-sided. Any assumptions such as a*

proportional hazards model or a cure rate model made in calculating power should also be mentioned.

- *Clearly describe the sequential monitoring plan, including planned total information, how analysis times will be determined, how critical values for rejecting the null will be determined, and if appropriate, describe rules for stopping in favor of the null hypothesis. If no interim analyses are planned, a justification should be given.*
- *Explicitly state any early stopping rules.*
- *Discuss the power for each endpoint to be analyzed. Usually this includes survival, even when it is not the primary endpoint.*

6.1.1 *End of Study Definition*

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

The following example text is provided as a guide. Please customize as needed:

A participant is considered to have completed the study when all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) has been completed.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

6.1.2 *Correlative Studies*

Please provide background information on each planned correlative study including the biologic rationale and hypothesis as well as the relevant preclinical and clinical data, if available. List the types of information and the number and types of specimens to be collected. Include a detailed explanation of the types of analyses to be performed. Include detailed instructions regarding processing and shipping of specimens either in the protocol, or as a separate manual, if applicable.

7.0 Enrollment

7.1 Informed Consent Process

The following subsections should describe the procedures for obtaining and documenting informed consent of study participants. State if a separate screening consent will be used. If a separate screening consent will not be used, the study consent must be signed prior to conducting study screening procedures.

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for

obtaining consent from speakers of language other than English. Any procedures for determining competency and assessing comprehension/understanding should be included here as well as procedures for obtaining surrogate consent for those unable to consent on their own behalf. This section should be consistent with ***Strategies for Recruitment and Retention,*** *when describing consent plans and special considerations for children or other vulnerable participants. Address re-consent processes for children who become adults or are emancipated during a study.*

EXAMPLE TEXT:

Potential subjects will be identified and recruited from the research study team's clinic. The consent process will be conducted in a private room. Potential subjects will be given a copy of the consent form to take home with them before making a final decision to participate.

The informed consent process will be initiated prior to the individual's agreement to participate in the study, and will continue throughout the individual's study participation. The possible risks and benefits of participation will be discussed extensively with the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant, and will answer any questions that may arise. All participants will receive a verbal explanation of the purposes, procedures and potential risks of the study, and of their rights as research participants in terms suited to their comprehension. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to think about the study and discuss it with their surrogates prior to agreeing to participate. The participant will sign the informed consent document prior to the start of any study-specific procedures. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to each participant. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the study, and will not have a conflict of interest.

7.1.1 *Consent/Assent and Other Informational Documents Provided to Participants*

This section should demonstrate that the consent form contains all required regulatory elements. List all consent and/or assent documents and materials submitted with this protocol. Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.

If needed, describe special documents or materials (e.g., Braille, another language, audio recording).

The following example text is provided as a guide. Please customize as needed:

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol <insert list>.

7.2 Study Population

Include a description of the study population. The study population should be appropriate for clinical trial phase/stage of the study intervention. It is essential that the population's characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities).

7.3 Participant Eligibility Criteria

If Inclusion Criteria/Exclusion Criteria are also listed in the Protocol Summary, please ensure that the text is the same in both places.

Select study-specific enrollment criteria through careful consideration. Please avoid copying and pasting criteria from other studies without updating and accounting for individual study characteristics.

Consider patient populations seen in the clinic and the benefits the proposed study can provide to them.

Use the following guidelines when developing participant eligibility criteria:

- *The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment.*
- *If participants require screening, distinguish between screening participants vs enrolling participants. Determine if screening procedures will be performed under a separate screening consent form.*
- *The risks of the study intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimized.*
- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).*
- *Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.*
- *If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal or barrier methods).*
- *If you have more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.*

7.3.1 *Participant Inclusion Criteria*

Inclusion criteria are characteristics that define the population under study, e.g., those criteria that every potential participant must satisfy, to qualify for study entry. Provide a statement that individuals must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion. Women and members of minority groups must be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects.

Some criteria to consider for inclusion are: provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, health status, specific clinical diagnosis or symptoms, background medical treatment, laboratory ranges, and use of appropriate contraception. Additional criteria should be included as appropriate for the study design and risk.

The following example text is provided as a guide. Please customize as needed:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged <specify range>
4. In good general health as evidenced by medical history or diagnosed with <specify condition/disease> or exhibiting <specify clinical signs or symptoms or physical/oral examination findings>
5. <Specify laboratory test> results between <specify range>
6. Ability to take oral medication and be willing to adhere to the <study intervention> regimen
7. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
9. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

7.3.2 *Participant Exclusion Criteria*

Exclusion criteria are characteristics that make an individual ineligible for study participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification, to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Limited English proficiency cannot be an exclusion criterion.

Some criteria to consider for exclusion are: pre-existing conditions or concurrent diagnoses, concomitant use of other medication(s) or devices, known allergies, other factors that would cause harm or increased risk to the participant or close contacts, or preclude the participant's full adherence with or completion of the study. Additional criteria should be included as appropriate for the study design and risk.

Include a statement regarding equitable selection or justification for excluding a specific population.

The following example text is provided as a guide. Please customize as needed (including adding a statement about equitable selection):

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current use of < specify disallowed concomitant medications>
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Febrile illness within <specify time frame>
6. Treatment with another investigational drug or other intervention within <specify time frame>
7. Current smoker or tobacco use within <specify timeframe>

8. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>

7.4 Research Participant Registration

A Central Registration system has been implemented effective January 2012 to ensure that all subjects who enroll on interventional drug or device studies are fully eligible before treatment is initiated. Prior to registration, a member of the study staff must scan and email the following documents to the Central Registration Mailbox (central.registration@mssm.edu) and Central Registrars:

- central registration form
- signed informed consent form (ICF)
- eligibility checklist
- clinical documentation of eligibility and
- documentation of investigator and sponsor approval

The above documents are reviewed by the central registration team to ensure accuracy, completeness, and compliance. They verify that all eligibility criteria have been met according to the study protocol, that the correct version of the ICF has been used, and that the ICF was properly signed before any study procedures were performed. If there is any concern or discrepancy noted, the study staff member who originated the central registration request will be contacted immediately for clarification. The research team submits all necessary eligibility documents to central registration for review before the participant can begin the study and study treatment. To ensure compliance, study drug cannot be released by the research pharmacy until the central registrar releases a formal registration letter referencing the study and subject via email to the principal investigator. If the potential participant is deemed eligible, enrollment of the participant in the study will proceed. The ICF is linked to the initial study visit encounter and uploaded to the "Media Manager" tab in Epic, and the electronic registration forms in the OnCore clinical trial management system (CTMS) are completed. A Confirmation Letter is generated and sent to the following individuals:

- Study team
- Treating Physician
- Research Infusion Nurse designee
- Research Pharmacy

7.5 Randomization and Blinding Procedures

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated). If adaptive randomization or other methods of covariate balancing/minimization are employed, include a cross link to the methods of analysis in ***Statistical Considerations****. In addition, details regarding the implementation of procedures to minimize bias should be included in this section. Please do not include details that might compromise these strategies. Design techniques to avoid bias can be found in the ICH Guidance for Industry E9 Statistical Principles for Clinical Trials.*

Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

Sometimes blinding is attempted but is known to be imperfect because of obvious effects related to study intervention or control product in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, and changes in laboratory data). Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by study staff shielded from information that might reveal study group assignment).

If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Describe efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible. Measures to prevent unblinding by laboratory measurements, if used, should be described.

Include a description of your plans to manage and report inadvertent unblinding. If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained (e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias). If blinding is considered desirable but not feasible, the reasons and implications should be discussed.

7.6 Screen Failures

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures. Indicate how screen failures will be handled in the trial, including conditions and criteria upon which re-screening is acceptable, when applicable. Please specify that screen failures will not be counted in the total number of participants accrued to the study.

The following example text is provided as a guide. Please customize as needed:

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a <specify modifiable factor> may be rescreened. Rescreened participants should be assigned the same participant number *as for the initial screening.*

7.7 Patient Replacement

Explain whether or not inevaluable participants will be replaced. If inevaluable participants are to be replaced, describe the procedure for replacement. Discuss the impact of replacing participants who discontinue early, if allowed, on the statistical analysis/power calculations.

7.8 Strategies for Recruitment and Retention

Identify general strategies for participant recruitment and retention. This section may refer to a separate detailed recruitment and retention plan in the Manual of Procedures (MOP) and site specific plans could be included in a site-specific Standard Operating Procedures (SOP) document. Consider inclusion of the information below either in this section or the MOP. Please include:

- *Anticipated number to be screened, including women, minorities, and participants across the lifespan, in order to reach the target enrollment size (should be consistent with information contained in description of sample size determination)*
- *Anticipated enrollment sample size by gender, race and ethnicity, and age*
- *The anticipated accrual rate over the course of the study including accrual rate by any key subject characteristics such as by sex, age, or racial or ethnic minority group (e.g., 5 parent-child dyads per month over 24 months)*
- *Planned recruitment strategies (e.g. university student research pool, patient advocacy groups, online recruitment services, community advisors, national newspaper, local flyers). Include rationale for why the strategy will be appropriate for reaching the targeted study population.*
- *When applicable, consider and include strategies adapted to the cultural context of the study or population*
- *If recruitment or data collection procedures occur in a public setting, community-based outreach, or other similar settings, describe a plan for ensuring participants' and study staff's safety.*
- *For multi-site studies, description and number of recruitment sites (e.g., inpatient hospital setting, student health service, community center), and anticipated number of participants to be recruited from each site*
- *Procedure of how potential screening participants will be identified and approached*
- *Indicate whether an interview or a run-in period will be used to identify eligibility*
- *Specific strategies that will be used to recruit and retain historically under-represented populations in order to target sample size and conform with the NIH Policy on Inclusion of Women and Minorities and Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects. Include the number of women, minorities, and participants representing ages across the lifespan expected to be recruited, or provide justification on those rare occasions where women and/or minorities will not be recruited, and/or where age restrictions are justified.*
- *If the study requires multiple visits, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance)*

Include a section to address participant incentives:

- *Specify if participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation. Describe the type of incentive, amount, and timing of such compensation in relation to study activities (include financial and non-financial incentives).*
- *Describe steps to minimize coercion or undue influence, i.e., whether appropriate level of incentive is used so not to be viewed as coercive*

- *Describe who will receive incentives (if not the participant). For example, if participants are minors, state whether the minor or the parent/guardian will receive the incentive. If participants are incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.*

If appropriate, in a section for vulnerable participants include:

- *Justification for inclusion of vulnerable participants and recruitment strategy. Include safeguards for protecting vulnerable populations. Please refer to the Office of Human Research Protection (OHRP) guidelines when choosing the study population. Note that these regulations apply if any participants are members of the designated population, even if it is not the target population (e.g., if a participant becomes a prisoner during the study).*

Identify strategies for participant recruitment and retention.

Including the following information regarding recruitment:

- *Target sample size (Identify anticipated number to be screened in order to reach target enrollment)*
- *Anticipated accrual rate (i.e., annually)*
- *Number of sites and participants to be enrolled (both within U.S. and outside U.S.)*
- *Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, general public)*
- *Recruitment venues*
- *How potential participants will be identified and approached*
- *Types of advertisements planned*

EXAMPLE TEXT:

Potential subjects will be identified and recruited from the research study team's clinic. The consent process will be conducted in a private room. Potential subjects will be given a copy of the consent form to take home with them before making a final decision to participate.

If participants will be compensated or provided any incentives (e.g., vouchers, iPads) for study participation, describe the following characteristics of all compensation in relation to study activities (include both financial and non-financial incentives):

- *Amount*
- *Form*
- *Timing*
- *Recipient (if not the participant)*

7.8.1 *Inclusion of Vulnerable Participants*

Specify approach(es) for conforming to National Institute of Health (NIH) Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects.

Include numbers of women and minorities expected to be recruited, or provide justification if women and/ or minorities will not be recruited.

If appropriate, include justification for inclusion of vulnerable participants and recruitment strategy. Include safeguards for protecting the following types of vulnerable populations:

- *Mentally ill*
- *Prisoners*
- *Cognitively impaired*
- *Pregnant women*
- *Children*
- *Employee volunteers*

7.9 Lifestyle Considerations

Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, intake of caffeine, alcohol, or tobacco, or limits on activity). Describe what action will be taken if a participant has used prohibited medications, treatments or procedures (e.g., early withdrawal by study Investigator).

The following example text is provided as a guide. Please customize as needed:

During this study, participants are asked to:

- Refrain from starting medications or dietary supplements for weight or appetite control
- Refrain from brushing teeth, eating, or drinking 30 min prior to salivary cortisol collection
- Fast on the morning(s) that blood samples will be collected for <assay>
- Avoid caffeine and nicotine for 24 hours prior to study assessment visits]

8.0 Study Procedures

8.1 Schedule of Assessments Table

Information in this table should match the information found within the section below.

Protocol Template Guidance Document

Procedures / Assessments <<INSERT BELOW – Procedures as listed above and place "X" next to occurrences throughout the study >> *** Examples below ***	**Screening**	**Treatment Day (Cycle 1)** [a]		**Treatment Day (Subsequent Cycles)** [a]			**At completion of the study**	
	Days –28 to –1	**Day 1**	**Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 15**	**Cycle 3+ Day 1**	**End of study** [i]	**30-day post-treatment visit** [j]
Informed Consent and HIPAA Authorization	X							
Inclusion/Exclusion	X							
Medical/Cancer History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Physical Examination	X	X		X		X	X	X
Vital Signs (HR, temp, BP, HT,WT) [b]	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X		X		X	X	X
Tumor biopsy				X			X	
[Blood Tests]	X	X	X	X	X	X	X	X
[Study Drug] treatment		--X--	--X--	--X--	--X--	--X--		
[Imaging Tests]						X[j]		
[Tissue Sample]								
[Research blood]				X			X	
AE Monitoring		--X--	--X--	--X--	--X--	--X--	--X--	--X--

The schedule above is provided as an example and should be modified or replaced as appropriate.

The schedule of activities (SOA) must capture the procedures that will be accomplished at each study visit, and all contact with study participants (e.g., telephone contacts). This includes any screening procedures that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility, study objectives and endpoints. Other procedures should be done sparingly and with consideration, as they may add unnecessary complexity and participant burden. However, for feasibility or other studies that include an aspect of procedural refinement; those activities may be appropriate for inclusion herein and elsewhere in the protocol.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints (e.g., short-duration interventions and follow-up periods might require short outcome assessment windows, whereas longer follow-up periods of 6 months or longer might have a window of several weeks). In some cases, the protocol may include an unscheduled visit (e.g., if participants are asked to come to the clinic when they are experiencing specified symptoms). For unscheduled visits, specify all data that would be important to collect.

8.2 Pre-Treatment and Intervention Procedures

List and describe study procedures, measures, and assessments to be done to fulfill the objectives of the study. This section will include any non-safety baseline assessments (e.g., screening, eligibility, enrollment), even though they would not be affected by the intervention per se.

Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/evaluations must be performed (e.g., within 28 days prior to enrollment). If a separate screening protocol is developed, describe how the screening protocol will be used to identify participants for this study. In addition, discuss any special conditions that must be achieved during the enrollment and/or initial administration of study intervention.

Note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Include any definitions used to characterize outcomes (e.g., diagnostic criteria, sub-clinical symptoms, and change in health behaviors considered clinically-significant).

Note that the protocol should provide a high-level overview of all procedures, including administration, scoring, and psychometrics. When applicable, discuss any cultural adaptations that will be implemented and provide support for the validity of these adaptations. Additional relevant details can be provided in a MOP or SOP. Provide justification for any sensitive procedures (e.g., provocative testing, deception). In addition, note where approaches to decrease variability, such as centralized laboratory assessments or observational coding, are being employed. Indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.

This section may include (but is not limited to) a list and description of the following (example) categories:

- *Physical examination-based assessments (e.g., height and weight, organ systems, motor or visual acuity assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*

- *Performance-based assessments (e.g., physical function – gait, balance; sensory testing – pain perception, proprioception; neuropsychological/cognitive assessments – dementia assessment, executive function, memory performance tests)*
- *Administration of questionnaires, interviews, or other instruments for patient (or other, e.g., family, caregiver-) reported outcomes, such as a daily diary*
- *Ecological momentary assessment (real-time repeat sampling of a person's behaviors, symptoms, or experiences typically outside of the clinic setting often using an application or other device, physical activity/sleep monitor or other sensor)*
- *Radiographic or other imaging assessments State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study's MOP or a separate SOP.*
- *Biological specimen collection and laboratory evaluations - Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study's MOP.*
- *Special assays or procedures required (e.g., 3-D image capture of facial emotional expression, video recording of standardized family interaction tasks, a food choice task after laboratory intervention). Special instructions for the preparation, handling, storage, and shipment of raw data and/or specimens should be briefly explained in this section with detailed discussion in the study's MOP.*
- *Assessment of adverse events Describe provisions for identification and follow-up of ongoing AEs/SAE. If support staff will have contact with individuals, indicate how they should report identified AEs/SAE to the study te*am.
- *Procedures that will be completed during the study as part of regular standard of clinical care*

Include in this section a discussion of the results of any study-specific procedures that will be provided to participants (e.g., radiographic or other imaging or laboratory evaluations). Address when endpoints will be assessed with respect to timing of rescue medication/therapy, if applicable.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used as a part of collection of trial data, Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements should be followed, as applicable. If this is the case, this section should note which information is to be obtained through review of existing data.

8.2.1 *Screening Evaluation*

Describe only the procedures/evaluations necessary to assess whether a participant meets eligibility criteria

Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the time frame prior to enrollment within which screening procedures/ evaluations must be performed

Helpful Hint: consider typical clinic "flow" when writing these sections so there will be less chance of protocol deviations.

EXAMPLE TEXT:

Screening Visit (Day –X to Day –Y) <include appropriate window>

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form
- Review medical history to determine eligibility based on inclusion/ exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria
- Collect blood/urine for <<specify tests>>
- Schedule study visits for participants who are eligible and available for the duration of the study
- Provide participants with <<specify instructions needed to prepare for first study visit>>

8.2.2 *Enrollment/Baseline Evaluation*

- *Describe the procedures/evaluations necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled.*
- *Describe the procedures/evaluations that are required at baseline for later endpoint comparison after study intervention.*
- *Discuss the sequence of events that should occur during enrollment and/ or initial administration of the study agent. List any special conditions that must be achieved at this visit.*
- *List the procedures for administering the study agent and follow-up procedures after administration.*

EXAMPLE TEXT:

- Enrollment/Baseline Visit (Visit 1, Day 0)
- Obtain informed consent of potential participant verified by signature on study informed consent form
- Verify inclusion/exclusion criteria
- Obtain urine pregnancy test
- Obtain demographic information, medical history, medication history, alcohol, and tobacco use history
- Record vital signs, results of examinations, other assessments

- Collect blood/ urine for <<INSERT specify baseline laboratory tests required for the study>>
- Administer the study treatment.
- <<INSERT specify procedures, instructions provided to participants, observations after the intervention>>

8.3 Evaluation During Treatment/Intervention

Please describe the assessments and evaluations that will be conducted at each time point during the study intervention.

Example text:

Visit 2 (Day X+/-Y) *<include a window that is appropriate for the study>*

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Collect blood/urine for <specify follow-up laboratory tests>.
- Administer the study agent or provide additional medication to the participant, in accordance with <specify procedures, instructions provided to participants>.
- Record participant's adherence to treatment program

8.4 Final Study Visit

Include a discussion of procedures/evaluations required to assess or confirm study endpoints and study evaluations. Define when the final study visit should occur. Describe provisions for follow-up of ongoing AEs/SAEs. Consider discussing if or when participants will be informed of study results. Consider specifying an appropriate range of time, or visit window, when the visit should occur to allow feasible scheduling, data collection and study completion considerations.

Final Study Visit (Visit X, Day X+/-Y) *<include a window that is appropriate for the study>*

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Collect blood/urine for <specify final laboratory tests>.
- Record participant's adherence to treatment regimen.
- Provide <specify final instructions> to participant

8.5 Follow-up Evaluation

- *Describe procedures/evaluations required to assess or confirm study endpoints and study evaluations*
- *Discuss the sequence of events that should occur during the visit, if applicable. Include appropriate windows for each study visit*

EXAMPLE TEXT:

Follow-up Visit (Visit 2, Day X+/-Y)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <<specify examinations or other assessments and include information to be recorded>>
- Collect blood/ urine for <<specify follow-up laboratory tests>>
- Administer the study agent, or provide additional medication to the participant, in accordance with <<specify procedures, instructions provided to participants>>
- Record participant's adherence to treatment program

Follow-up Visit (Visit 3, Day X+/-Y)

- Record adverse events as reported by participant or observed by investigator
- Record vital signs, results of <<specify examinations or other assessments, including information to be recorded>>
- Administer the study agent or provide additional medication to the participant, in accordance with <<specify procedures, instructions provided to participants>>
- Record participant's adherence to treatment program

8.6 Early Termination Visit Evaluation

Specify which procedures/evaluations should be done at an early termination visit, if one occurs.

8.7 Unscheduled Visit Evaluation

Specify how unscheduled visits will be handled and documented.

8.8 Justification for Sensitive Procedures

If applicable, provide justification for any sensitive procedures (e.g., use of placebo, medication withdrawal, provocative testing, deception).

9.0 Study Intervention Plan

9.1 Study Intervention Description

Please include a description of each study intervention (procedure, study agent, placebo, device, etc.)

Describe in detail the planned intervention to be carried out on the participants registered to this research study. Carefully explain which procedures are considered routine and which are deemed experimental and carried out solely for the purpose of research. The Treatment/Intervention Plan should include the appropriate days/time intervals, measures, amounts, potential adjustments to treatment/intervention plan, and a window of time that would be considered acceptable to avoid protocol deviations.

If appropriate, include which specimens (and amount that) will be taken (e.g., tumor acquisition, pharmacology). If necessary, the information can be written in bullet form.

Specify which scans (e.g., disease assessment imaging, image-guided biopsies) are standard-of –care (SOC) and which are investigational. For those scans that are considered investigational, include applicable dosimetry information in the Appendices Section.

Each defined step/procedure should be described independently, and also in terms of how it will interact with the entire treatment/intervention plan. If appropriate, this section can include where the intervention will take place (i.e.,, in-patient, out-patient), time period required (including information per visit, cycles, and intended duration of intervention), how long study is expected to last (from start to finish), and if applicable, what makes participants evaluable, whether patient can receive continued treatment past progression, and any special notifications regarding intervention that should be noted.

9.2 Availability, Acquisition and Accountability

Describe the availability of the study agent and control product, and how they will be acquired and shipped to the investigator (e.g. supplied by the manufacturer, approved products from hospital pharmacy, etc.).

Please describe:

- *How the study agent will be distributed*
- *Who will distribute the study agent*
- *Participation of drug repository or pharmacy*
- *Frequency of product distribution*
- *Documentation of adequate and safe handling*
- *Plans for return of unused product*

9.3 Formulation, Appearance, Packaging, and Labeling

Describe the following characteristics of both the study and control agents (usually found in the Investigator's Brochure (IB) or package insert):

- *Formulation*
- *Appearance*
- *Packaging*
- *Labeling (per 21 CFR 312.6)*
- *Availability (e.g., investigational or commercially marketed)*

Describe if the product is available for human use in the form, route, and dose planned in this trial or if the product must be formulated to meet the trial plan.

9.4 Product Storage and Stability

Describe the requirements regarding the following parameters as they pertain to the study agent(s) and control product:

- *Temperature*
- *Humidity*
- *Security*
- *Container*

If applicable, include stability and expiration information for studies that use multi-dose vials.

9.5 Preparation

Describe the following aspects of the preparation of the study agent(s) and control product:

- *Thawing*
- *Diluting*
- *Mixing*
- *Reconstitution*

Specify what is required of the study staff and study participant.

Detailed information can be provided in a separate Manual of Procedures (MOP) or standard operating procedure (SOP).

9.6 Route of Administration

Describe the planned route of administration (e.g., oral, nasal, intramuscular).

9.7 Dosing and Administration

Describe the procedures for selecting each subject's dose of study agent and control product.

- *Timing (time of day, interval)*
- *Relation to meals*
- *Specific instructions about how or when to take the dose.*

Provide instructions regarding missed dose or vomited dose, if fasting is required, must take with or without food, can or cannot take with other daily medications (i.e., blood pressure medication), etc.

If appropriate, include maximum hold time once thawed/ mixed before administration of the dose.

9.8 Starting Dose and Dose Escalation Schedule

Please Include:

- *Starting dose of the study agent(s) and control product*
- *Dose escalation scheme and treatment regimen (use exact dose, not percentages), if applicable.*
- *Describe any minimum period required before dose increase.*

9.9 Dosing Delays and Modifications

If applicable, state the conditions under which a dose change will be made, for instance:

- *Toxic or negative changes in specified indicators (e.g., white blood cell count)*
- *Dose modifications for specific abnormal laboratory values or other AEs known to be associated with the study agent*
- *Anticipated dose-limiting effects (state explicitly)*
- *Criteria used to determine dose escalations*
- *Specify whether treatment will progress to higher doses if a subject is responding positively.*

9.10 Criteria for Discontinuing Study Intervention

Please list the criteria for discontinuing study intervention.

9.11 Duration of Therapy

Discuss the duration of therapy for each active phase and what duration is the minimum necessary for a participant to be considered evaluable.

Explain whether or not inevaluable participants will be replaced.

9.12 Device Considerations

If conducting a study with a device, please include the following information:

- *Device size(s)*
- *Device model(s)*
- *Device settings and programming (if applicable)*
- *Duration of implant or exposure (if applicable)*
- *Frequency of exposure (if applicable)*

9.13 Concomitant Interventions and Supportive Care Guidelines

Please describe the data that will be recorded regarding concomitant medications, treatments, and procedures. Include details about when the information will be collected (e.g., screening, all visits).

Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints) and how to ascertain the independent effects of concomitant therapies and study agents.

Please also list and describe any dietary supplements that will be prohibited during the study.

Example Text:

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

9.13.1 *Allowed Interventions*

9.13.1.1.1. Prophylactic Interventions

Please list all medications, treatments, and procedures that will be provided as prophylaxis on study, if applicable.

9.13.1.1.2. Precautionary Interventions

If applicable, please list all medications, treatments, and procedures for which there are precautions for concomitant use with the study agents. Include:

- *Instructions for dose modifications, if appropriate.*
- *Description of drug and food interactions*
- *Toxicities for standard agents likely to be given in conjunction with this protocol*

9.13.2 *Required Interventions*

If applicable, please list and describe all required concomitant medications, treatments and procedures.

9.13.3 *Prohibited Interventions*

Please list all medications, treatments, and procedures that are NOT permitted on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study.

Please describe what action will be taken if prohibited medications, treatments, or procedures are indicated for care (e.g., early withdrawal).

Example Text:

Treatment with <<INSERT - list specific drugs>> will not be permitted unless discussed with and approved by the <<INSERT – Role of individual who will make this determination (i.e., study monitor / sponsor / investigator)>>.

9.14 Duration of Follow-up

Please describe the follow-up interval, time points, and required assessments.

9.15 Study Intervention/Follow-up Compliance/Adherence Assessment

Discuss what procedures will be in place to monitor dosing and adherence for each participant.

9.16 Participant Access to Study Intervention at Study Closure

Describe obligations to continue beneficial interventions after participants are no longer enrolled in the study, if applicable.

10.0 Criteria for Premature Termination or Suspension of the Study (Study Stopping Rules)

State the stopping rules relevant to the intervention.

Describe safety findings that would prompt temporary suspension of enrollment and/or study agent until a safety review is convened. The safety review will determine whether the study:

- *Should continue per the protocol*
- *Should proceed with caution*
- *Should be further investigated*
- *Should be discontinued*
- *Should be modified before proceeding*

EXAMPLE TEXT (if applicable):

Administration of a study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the <<INSERT – Role (not name) of individual/entity>>. The <<INSERT – Role (not name) of individual/entity>> will notify the study sponsor and PIs immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMC members within 24 hours of this occurrence and will provide the DSMC with AE listing reports. The DSMC will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor. The study sponsor will inform the FDA of the temporary halt and the disposition of the study, if applicable.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <<INSERT – Names of people and/or entities that must be notified (Lead PI, funding agency, the IND/ IDE sponsor, and regulatory authorities)>>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/ or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, DSMC, and/ or FDA.

11.0 Criteria for Removal from study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Participant voluntarily withdraws from treatment (follow-up permitted)
- Participant withdraws consent (termination of treatment and follow-up)
- Participant is unable to comply with protocol requirements
- Participant demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator)
- Participant experiences toxicity that makes continuation in the protocol unsafe
- Treating physician judges continuation on the study would not be in the patient's best interest
- Participant becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study
- Participant is lost to follow-up

11.1 Lost to Follow-up

If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

12.0 Criteria for outcome assessment and endpoint evaluability/Measurement of Effect

Please provide response criteria. Please select the appropriate criteria from the text below, or, if none of these are applicable, provide agent- or disease-appropriate criteria with references.

For phase 1 protocols only: Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every [# of weeks] weeks. In addition to a baseline scan, confirmatory scans will also be obtained [# of weeks] weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

Please define the criteria to be utilized for evaluation (iwCLL, RANO, RECIST, other) and, if necessary, provide justification.

For the purposes of this study, participants 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.

If using RECIST, please state:

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

12.1.1 *Definitions*

Evaluable for Target Disease response: Only those participants 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 target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants 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.

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

If using RECIST, please include the following:

12.1.2 *Disease Parameters*

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm 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 in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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 participant, these are preferred for selection as target lesions.

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

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

12.1.3 *Methods for Evaluation of Measurable Disease*

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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 in 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 thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of 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.

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.

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.

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

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 data 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 from 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 participant 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.

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 28 days 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 when both methods have been used to assess the antitumor effect of a treatment.

12.1.4 *Response Criteria*

Replace this section with other response scales when applicable.

12.1.4.1.1. 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.

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. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.1.4.1.2. 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 short axis).

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

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

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

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

12.1.4.1.3. Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

12.1.4.1.4. 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 Participants with Measurable Disease (*i.e.*, Target Disease)

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

See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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 Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.1.4.1.5. 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

12.1.4.1.6. 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. Suggested text is provided below and should be modified as necessary.

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12.1.5 *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 participants' files and radiological images is the best approach.

12.2 Antitumor Effect- Hematologic Tumors

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

Responses will document surrogate clinical activity and will also be reported consistent with iwCLL 2008 guidelines (see Appendix #/letter).

Baseline disease assessments will occur as previously indicated. Final Response assessment will be assessed per iw-CLL criteria with clinical CRs confirmed by bone marrow biopsy and CT scan should be performed if previously abnormal. The primary efficacy point is response assessed following 3 cycles of treatment.

Primary Efficacy/ Response assessment - clinical response following 3 cycles of treatment. If patient is clinically in CR (without or with cytopenias) peripheral blood should be assessed for clonal lymphocytes.

Final Response Assessment- Will occur two months following completion of treatment with sorafenib. It is acknowledged that to meet iwCLL Guidelines for response in CLL, a response assessment must be performed 2 months from therapy to document responses including a bone marrow to confirm CR and a CT maybe indicated or recommended. Therefore, those patients that clinically appear to be in CR will have a bone marrow and possibly a CT scan to confirm complete responses at least 3 months after all treatment.

12.3 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events (Appendix #/letter).

12.4 Other Response Parameters

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

13.0 Statistical Considerations

13.1 Study Design and Description of Statistical Methods

State the proposed formal design of the study (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). Address the following as appropriate:

- *Descriptive statistics: describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range)*
- *Inferential tests: indicate the p-value for statistical significance (Type I error) and whether one- or two-tailed*
- *Indicate whether covariates will be pre-specified in the sections below or later in the Statistical Analysis Plan (SAP).*
- *State whether checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests).*

13.2 Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints.

- *Specify the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response)*
- *Specify the time period for which each endpoint will be analyzed*

13.3 Sample Size and Accrual Rate

Include number of participants to recruit, screen, and enroll to meet a goal of evaluable participants for the study. Provide all information necessary to validate calculations and to judge the feasibility of enrolling and following the necessary number of participants. Specify:

- *Outcome measure used for calculations (generally the primary variable)*
- *Test statistic*
- *Null and alternate hypotheses*
- *Type I error rate (alpha)*
- *Power level (e.g., 80% power)*
- *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
- *Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., with justification*
- *Approach to handling withdrawals and protocol violations, i.e., whether participants will be included in the ITT population*
- *Statistical method used to calculate sample size, with a reference for it and for any software utilized*

- *Method for adjusting calculations for planned interim analyses, if any*

Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

Consider discussing whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses.

13.4 Analysis of Outcomes and Endpoints

13.4.1 *Analysis of the Primary Endpoint(s)*

For each primary endpoint:

- *Define the measurement or observation and describe how it is calculated.*
- *Describe the scale (nominal/binary/categorical, ordinal, interval) and state if it is measured as a single endpoint/summary measure or repeated measure.*
- *Describe the statistical procedures that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. Reference the Statistical Analysis Plan (SAP) if appropriate.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat).*
- *Describe details to check assumptions required for certain types of data (e.g., proportional hazards, transformations or nonparametric tests if non-normal).*
- *Describe the Analysis Set for which the analysis will be conducted.*
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and loss to follow-up.*

13.4.2 *Analysis of the Secondary Endpoint(s)*

For each secondary endpoint:

- *Define the measurement or observation and describe how it is calculated.*
- *Describe the scale (nominal/binary/categorical, ordinal, interval) and state if it is measured as a single endpoint/summary measure or repeated measure.*
- *Describe the statistical procedures that will be used to analyze the endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. Reference the SAP if appropriate.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat).*

- *Describe details to check assumptions required for certain types of data (e.g., proportional hazards, transformations or nonparametric tests if non-normal).*
- *Describe the Analysis Set for which the analysis will be conducted.*
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and loss to follow-up.*

13.4.3 *Safety and Toxicity Analyses*

Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores form baselines such as shift tables).

If the study is evaluating a formal safety endpoint, include all factors from the analysis of the primary endpoint here as well.

For Adverse Events (AEs), describe:

- *Coding (e.g., Medical Dictionary for Regulatory Activities)*
- *Calculation (e.g., each AE counted once for any given participant)*
- *Presentation (e.g., severity, frequency, and relationship of AEs to study agent will be presented by System Organ Class)*
- *What information will be reported about each AE (e.g., start date, stop date, severity, relationship, outcome, and duration)*
- *How AEs will be identified*

13.5 Stratification Factors

Please describe any criteria and methods used to stratify participants, and the rationale for stratification.

13.6 Data Analysis Plans

State whether there will be a formal Statistical Analysis Plan (SAP). If so, this should be completed prior to database lock and unblinding of the data.

13.6.1 *Analysis Datasets*

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

For example:

- *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
- *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one does of investigational product and/or have some particular amount of follow-up outcome data)*
- *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of investigational product)*
- *Evaluable or Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would*

be likely to represent the effects of treatment according to the underlying scientific model (e.g., participants who took at least 80% of investigational product for 80% of the days within the maintenance period)

- *Other Datasets*

13.6.2 *Baseline Descriptive Statistics*

Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Discuss planned baseline descriptive statistics. Indicate whether inferential statistics will be used.

Adherence and Retention Analyses

Define how adherence to the protocol will be assessed, calculated, and verified.

Describe measures and calculations for assessing:

- *Participation*
- *Study retention/loss to follow-up*
- *Frequency of discontinuation*
- *Reasons for discontinuation*

13.6.3 *Planned Interim Analyses*

13.6.3.1.1. Safety Review

Specify, to the extent possible, the criteria that would prompt an interim review of safety data. Describe who performs the statistical analysis. Discuss whether this person or group is unmasked and how blinding is preserved.

- *Provide details of the proposed rules for halting study enrollment or study intervention/ administration of study product for safety.*
- *Indicate whether these rules pertain to the entire study, specific study arms or participant subgroups, or other components of the study.*
- *If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics.*
- *State which safety endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.*

13.6.3.1.2. Efficacy Review

Specify, to the extent possible, the criteria that would prompt an interim review of efficacy data. Describe who performs the statistical analysis. Discuss whether this person or group is unmasked and how blinding is preserved.

- *Provide details of the proposed rules for halting study enrollment or study intervention/ administration of study product for efficacy.*
- *Indicate whether these rules pertain to the entire study, specific study arms or participant subgroups, or other components of the study.*
- *If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics.*
- *State which efficacy endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.*
- *Discuss the impact of the interim analysis on the final efficacy analysis, particularly on Type I error.*
- *If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.*

13.6.4 *Additional Sub-Group Analyses*

Describe how the primary and secondary endpoints will be analyzed based on age, sex, race, ethnicity or other demographic characteristics.

13.6.5 *Multiple Comparison/Multiplicity*

Generally there should only be one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. However, if there is more than one primary endpoint, or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.

13.6.6 *Tabulation of Individual Response Data*

State whether individual participant data will be listed by measure and time point.

13.6.7 *Exploratory Analyses*

Describe any exploratory analysis. These cannot be used as confirmatory proof, and serve as a basis for supporting primary analysis findings and suggesting hypotheses for future research.
Provide a general description of how the conduct and progress of the clinical investigation will be monitored.

14.0 Biomarker, Correlative, and Special Studies

*Please briefly describe all planned correlative studies and indicate whether they are mandatory or optional. For additional information refer to the "Guidelines for Correlative Studies in Clinical Trials" available on the CTEP Web site (*http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary_correlatives*).*

Explicit instructions for handling, preserving, and shipping the specimens should be provided below. 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. A plan for statistical analysis of the results of the correlative study(ies) should be provided in the Analysis of Secondary Endpoints.

If development of diagnostic assays to identify participants 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. If samples will be shipped to a central laboratory for processing and analysis, responsible parties and contact information should be provided below in addition to instructions for handling, preserving, and shipping the specimens.

*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.*

A suggested format for presentation of the required information is shown below and may be used or modified as required. 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.

14.1 Biomarker Studies

If the protocol includes any biomarker studies using in situ *hybridization (ISH) and/or immunohistochemistry (IHC) techniques, refer to the "ISH Biomarker Template" and/or the "IHC Marker Template" for guidance. These templates can be downloaded from the CTEP website (*http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary_correlatives*).*

Biomarker studies should be summarized in this section. Please specify whether these studies are "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 participant disposition. Note especially that if integral markers are to be used to make individual participant decisions, then CLIA regulations will apply (*http://wwwn.cdc.gov/clia/regs/toc.aspx*).*

The description for all proposed biomarker studies, if applicable, should include specific information, as outlined below.

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 validity and appropriateness for the study*
3. *Describe the investigator's experience and competence with the proposed assays*
4. *Provide the data supporting the degree of biomarker "fit for purpose" and clinical qualification*

5. *Justify the number of participants and specimens:*
    a. *To demonstrate feasibility*
    b. *To demonstrate that studies are likely to produce interpretable and meaningful results*
6. *Give thoughtful consideration to the risk to the participant of obtaining samples, specimens, or data for biomarker studies in the context of data on biomarker validity and degree of clinical qualification*

14.2 Correlative Studies

Include the following collection/processing details when developing this section: (a) amount and type of specimen collected; (b) number, size, and type of tubes or cryovials used for collection; and (c) processing instructions.

1. *Title – Laboratory Correlative Study #1*
    1. Collection of Specimen(s)
    2. Handling of Specimens(s)
    3. Shipping of Specimen(s)
    4. Site(s) Performing Correlative Study

2. *Title – Laboratory Correlative Study #2*
    1. Collection of Specimen(s)
    2. Handling of Specimens(s)
    3. Shipping of Specimen(s)
    4. Site(s) Performing Correlative Study

14.3 Special Studies

Special assays or procedures required (e.g., immunology assays, pharmacokinetic and pharmacodynamic studies, flow cytometry assays, microarray, DNA and RNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this or in the study Manual of Procedures.

1. *Title – Special Correlative Study #1*
    5. Outcome Measure
    6. Method of Assessment
    7. Timing of Assessment
    8. Method of Data Recording
    9. Timing of Data Recording

14.4 Pharmacokinetic Studies

Include the following collection/processing details when developing this section: (a) amount and type of specimen collected; (b) number, size, and type of tubes or cryovials used for collection; and (c) processing instructions.

14.5 Pharmacodynamic Studies

Include the following collection/processing details when developing this section: (a) amount and type of specimen collected; (b) number, size, and type of tubes or cryovials used for collection; and (c) processing instructions.

14.6 Genetic/Genomic Analysis

Include the following collection/processing details when developing this section: (a) amount and type of specimen collected; (b) number, size, and type of tubes or cryovials used for collection; and (c) processing instructions.

14.7 Quality of Life Assessment

Selection of Quality of Life (QOL) instruments should be justified from scientific and psychometric perspectives and instrument validation and experience in previous studies should be described. Instruments should be age appropriate. Scoring of instruments should be included. Timing of the administration of the QOL instrument(s) should be discussed and windows for completion of instruments should be provided. Statistical considerations should include: justification for the sample size, power statements, clinical significance of the effect size that can be detected, variability of the instrument(s), expected compliance rate, method of analysis (e.g., longitudinal), and a clear outline of how missing data will be handled.

15.0 Investigational Device Information

For IDE Protocols Only

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

16.0 Safety Surveillance

16.1 Serious Adverse Events (SAEs)

16.1.1 *Serious Adverse Event Identification and Classification*

Serious Adverse Events (SAEs) will be identified and monitored by the clinical investigators, study team, and study monitors. At each study visit, the clinical investigator will inquire about the occurrence

of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All event reports will be captured on the appropriate case report forms (CRFs) and submitted to federal and local regulatory agencies as required and as detailed below. Events will also be entered into a secure database that includes search, collation and retrieval capabilities.

Serious adverse events will be classified by the study investigator using three criteria: seriousness, expectedness and relatedness to the investigational intervention. These criteria are defined below.

16.2 Serious Adverse Event Definition

An adverse event (AE) is any undesirable experience associated with the use of a medical intervention in a human study participant, whether or not considered intervention-related. The event is considered serious and should be reported to federal and local regulatory agencies when the outcome of the event is:

Death
Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening
Report if suspected that the participant was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical intervention might have resulted in the death of the participant.

Hospitalization (initial or prolonged)
Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event). **Please Note:** Hospital admission for a planned procedure/disease treatment is not considered a SAE.

Disability or Permanent Damage
Report if the adverse event resulted in a substantial disruption of a participant's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect
Report if you suspect that exposure to a medical intervention prior to conception, or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)
Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical intervention.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the participant and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events. Other important medical events include pregnancy, adverse events of special interest, and secondary malignancies, etc.

16.2.1.1.1. Definition of "Expected" and "Unexpected" SAE Classifications

Describe the method for determining the expectedness of a serious adverse event. Please note that expectedness refers to awareness of previously observed adverse events, not what might be anticipated from the properties of the study intervention. Please also note that if an IB is not available, then the adverse event is, by default, considered unexpected.

<<INSERT – Role (not name) of individual>> will be responsible for determining whether a Serious Adverse Event (SAE) is expected or unexpected.

Definition of "Expected"
A serious adverse event will be considered expected if it is common and known to occur with use of the study intervention.

Definition of "Unexpected"
A serious adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. A serious adverse event is considered unexpected if:

- It is not listed in the Investigator Brochure (IB)
- It is not listed in the IB at the specificity or severity observed

16.2.1.1.2. Definition of Relationship to Study Intervention

Please describe the method of determining the relationship of a SAE to the study agent. All SAEs will be assessed for relatedness using this method. Evaluation should consider the following:

- *Natural history of the underlying disease*
- *Concurrent illness*
- *Concomitant therapy*
- *Study-related procedures*
- *Accidents*
- *Other external factors*

NOTE: In a clinical trial, the study agent must always be suspect.

All serious adverse events must be assessed to determine if there is a causal relationship between the SAE and the study intervention.

For all SAEs, the clinician who examines and evaluates the participant will determine the SAE's causality based on temporal relationship to the study intervention and clinical judgment. The degree of certainty about causality will be graded using the categories below:

Relationship to Study Intervention

Related: The SAE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the SAE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the SAE.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Not Related: There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

- **Unlikely to be Related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related:** The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

16.2.2 *Serious Adverse Event (SAE) Reporting*

<<Insert procedure for actions to be taken in response to SAEs. Please include time frames for SAE reporting, a flowchart for the reporting procedure, if desired, the regulatory agencies to which the SAE should be reported, the staff who will be responsible for completing and signing off on reports, the online systems, databases and forms that should be used for SAE reporting, and who will receive notification of SAEs >>.

All SAEs must be reported as follows:

Clinical investigators will be responsible for conducting SAE assessments, making determinations regarding causality, and signing off on SAE reports.

All members of the clinical research team are responsible for properly documenting and reporting SAEs as detailed below.

SAEs must be reported to the study sponsor, IRB, and Mount Sinai DSMB within 24 hours of initial notification.

SAE reporting is required as soon as the participant signs the informed consent form. SAE reporting is required throughout the study until 30 days after the participant's last day of study participation. In addition, any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must also be reported.

Serious adverse events (SAEs) will be followed by the clinical investigators, study team, and study monitors. At each study visit, the clinical investigator will inquire about the occurrence of AEs/SAEs since the last visit. All serious adverse events observed will be documented noting the severity, relationship to the research study intervention, start date, date of notification, and any medical care given to manage the adverse event. Events will be followed for outcome information until resolution or stabilization. The stop date will be recorded, if applicable. All event reports will be captured in the participant's research chart, and on the appropriate case report forms (CRFs), and will be submitted to federal and local regulatory agencies as required and as detailed below. Events will also be entered into a secure database that includes search, collation and retrieval capabilities.

All SAE reports should contain the following information:

- Protocol number
- Principal Investigator Name
- Participant code
- The SAE event term and description
- The date the serious adverse event occurred
- The severity and grade of the event

- The relationship of the serious adverse event to the study intervention
- Whether or not the SAE was expected
- If applicable and available, the resolution or stabilization date of the SAE
- Detailed text that includes the following:
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Whether or not the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

Any additional SAE reporting information required by the study funding sponsors or drug suppliers should be included in this section.

For reportable deaths, the investigator should supply the sponsor and IRB with any additional requested information (i.e. autopsy reports, death certificates, and terminal medical reports).

16.3 Adverse Events (AEs)

16.3.1 *Adverse Event Identification and Classification*

Adverse Events (AEs) will be monitored by the clinical investigators, study team, and study monitors. At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All event reports will be captured on the appropriate case report forms (CRFs) and submitted to federal and local regulatory agencies as required and as detailed below. Events will also be entered into a secure database that includes search, collation and retrieval capabilities.

Non-serious adverse events are classified by the study investigator using three criteria: severity, expectedness and relatedness to the investigational intervention. These criteria are defined below.

16.3.2 *Adverse Event Definition*

An adverse event (AE) is any undesirable experience associated with the use of a medical intervention in a human study participant, whether or not considered intervention-related (21 CFR 312.32 (a)).

16.3.2.1.1. Severity

Please describe the method for grading an AE. For example:

For this study, the clinician will evaluate the severity of AEs using the NCI CTCAE version 5.0 grading scale.

For AEs not included in the NCI CTCAE version 5.0 grading system, the following guidelines will be used to describe severity:

- Mild: Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt the participant's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening, or incapacitating.

16.3.2.1.2. Expectedness

Describe the method for determining the expectedness of an adverse event. Please note that expectedness refers to awareness of previously observed adverse events, not what might be anticipated from the properties of the study intervention. Please also note that if an IB is not available, then the adverse event is, by default, considered unexpected.

<<INSERT – Role of individual>> will be responsible for determining whether an Adverse Event (AE) is expected or unexpected.

Definition of "Expected"
An adverse event will be considered expected if it is common and known to occur with use of the study intervention.

Definition of "Unexpected"
An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. An adverse event is considered unexpected if:

- It is not listed in the Investigator Brochure (IB)
- It is not listed in the IB at the specificity or severity observed

16.3.2.1.3. Relatedness

Please describe the method of determining the relationship of an AE to the study agent. All AEs will be assessed for relatedness using this method. Evaluation should consider the following:

- *Natural history of the underlying disease*
- *Concurrent illness*
- *Concomitant therapy*
- *Study-related procedures*
- *Accidents*
- *Other external factors*

NOTE: In a clinical trial, the study agent must always be suspect.

All adverse events must be assessed to determine if there is a causal relationship between the AE and the study intervention.

For all AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship to the study intervention and clinical judgment. The degree of certainty about causality will be graded using the categories below:

Relationship to Study Intervention

Related: The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Not Related: There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

- **Unlikely to be Related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related:** The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

16.3.3 *Adverse Event Reporting*

Adverse Events (AEs) will be monitored by the clinical investigators, study team, and study monitors. At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All event reports will be captured in the participant's research chart, and on the appropriate case report forms (CRFs), and submitted to federal and local regulatory agencies as required and as detailed below. Events will also be entered into a secure database that includes search, collation and retrieval capabilities.

Adverse event reporting is required as soon as the participant signs the informed consent form.

All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

Non-serious AE reporting is required for 7 days after the participant's last day of study participation. At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The AE report should contain the following information:

- Protocol number
- Participant code
- The name of the adverse event
- The date the adverse event occurred
- If available, the resolution or stabilization date of the AE
- The severity and grade of the event
- The relationship of the adverse event to the study intervention
- Whether or not the AE was expected
- Detailed text that includes the following:
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Whether or not the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the AE is an Unanticipated Problem

Any additional AE reporting information required by the study funding sponsors or drug suppliers should be included in this section.

16.3.4 *Expected Adverse Events*

If appropriate, please describe in detail any expected adverse events (AEs) that may be related to the intervention. Please classify these adverse events according to seriousness, and, if possible, include the likelihood and anticipated frequency of occurrence of these adverse events. Tables may be used for clarity.

16.3.5 *Routine Reporting*

All adverse events are to be reported annually as part of regular data submission.

16.4 Unanticipated Problems (UPs)

16.4.1 *Definition of Unanticipated Problems*

An unanticipated problem (UP) is any incident, or experience of outcome, that is unexpected, related, or possibly related, and places the study participant or others at greater risk of harm than was previously known or recognized.

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human participants, and reported to the Institutional Review Board (IRB), only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

According to the FDA only the following AEs should be considered as unanticipated problems that must be reported to the IRB:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). It is recommended that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem

involving risk to human subjects. It is recommended that a discussion of the divergence from the expected specificity or severity accompany the report.

- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). It is recommended that a discussion of the divergence from the expected rate accompany the report.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. It is recommended that an explanation of the conclusion accompany the report.

16.4.2 *Reporting Unanticipated Problems*

Describe the unanticipated problem reporting procedures (include time frames, regulatory groups to whom the UP must be reported, study staff responsible for completing and signing off on reports, who will receive notification of UPs).

Investigators must report all unanticipated problems to the IRB. An investigator participating in a multicenter study may rely on the sponsor's assessment of AEs from multiple sites and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

The UP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name
- A detailed description of the event, incident, experience, or outcome
- An explanation why the event was classified as a UP
- A description of any changes to the protocol, or other corrective actions, that are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs that are SAEs will be reported to the IRB and to the Lead PI within 24 hours of notification.

All other UPs will be reported to the IRB and to the Lead PI within 5 days of notification.

All UAPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), [if applicable] the supporting agency head (or designee), and ISMMS within <<INSERT - timeline in accordance with policy>> of the IRB's receipt of the report of the problem from the investigator.

16.4.3 *Reporting AEs to IRBs in Clinical Trials of Devices Under the IDE Regulations*

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature,

severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)). The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

16.5 Safety Reporting for IND/IDE protocols

External study sponsors must directly notify study investigators, in an IND/IDE safety report, of any unanticipated problems and important safety information that has implications for the conduct of the research.

For all Mount Sinai Tisch Cancer Institute Investigator-Initiated Trials and externally sponsored pilot, Phase I, and Phase I/II clinical trials, it is the responsibility of the sponsor-investigator to review all IND/IDE safety reports.

It is the external sponsor's responsibility to provide an explanation of why an event was determined to be an unanticipated problem, and clearly indicate the implications for the conduct of the study. Sponsors must provide sufficient information to support a substantive review by investigators and the IRB for any event that results in changes to the study conduct or the informed consent document.

16.5.1 *IND Safety Reporting to the IRB*

The principal investigator will follow the IRB's policy on receipt and review of IND Safety Reports to determine how and when events from other sites must be reported to the IRB. The principal investigator will notify the IRB of any potential serious risks as soon as possible when deemed necessary.

16.5.2 *IND Safety Reporting to the FDA*

The sponsor must notify the FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. (21 CFR 312.32(c)(2)).

The sponsor must notify the FDA and all participating PIs, in an IND safety report, of other potential serious risks as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. (21 CFR 312.32(c)(1))

The study clinician will complete a SAE Form within the following timelines:

All deaths and immediately life-threatening events, and other SAEs whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution, or until the site PI deems the event to be chronic or stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

16.5.3 *IDE Safety reporting to IRB and FDA for Device Protocols:*

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

16.6 Events of Special Interest

Describe any other events that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies (e.g., pregnancy, secondary malignancies, second malignancy)

16.6.1 *Reporting of Pregnancy*

State the study's pregnancy-related policy and procedure including, as applicable:

- *Mechanisms for reporting to the sponsor, study leadership, IRB, and regulatory agencies.*
- *Provide modifications to study procedures (e.g., discontinuing treatment while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).*

16.6.2 *Secondary Malignancy*

State the study's secondary malignancy policy and procedure including, as applicable:

- *Mechanisms for reporting to the sponsor, study leadership, IRB, and regulatory agencies.*

- *Provide modifications to study procedures (e.g., discontinuing treatment while continuing safety follow-up).*

16.6.3 *Second Malignancy*

State the study's second malignancy policy and procedure including, as applicable:

- *Mechanisms for reporting to the sponsor, study leadership, IRB, and regulatory agencies.*
- *Provide modifications to study procedures (e.g., discontinuing treatment while continuing safety follow-up).*

17.0 Study Management

17.1 Safety Oversight

Appropriate safety oversight should be considered for each trial. This could include a Data Safety Monitoring Committee (DSMC), Data Safety Monitoring Board (DSMB), and/or a Medical Monitor.

***DSMC**: An independent group of experts that advises the study investigators for Phase I and some Phase II trials. The primary responsibility of the DSMC is to monitor participant safety. The DSMC considers study-specific data as well as relevant background information about the disease, test agent, and target population under study.*

***DSMB**: An independent group of experts that advises the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. For example, a DSMB may be convened if a study meets one or more of the following criteria: will generate randomized, blinded data; is a multi-center protocol which presents more than minimal risk to participants; uses gene transfer or gene therapy methodology; or requires special scrutiny because of high public interest or public perception of risk.*

***Medical Monitor**: An independent medical expert that advises the study investigators and monitors participant safety. A study may choose to employ the services of, or may be appointed a Medical Monitor. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons.*

Independent oversight is an important component to ensure human subjects' protection and should be considered for each study. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety in the study and the frequency of meetings. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership,

responsibilities and administration of the DSMB. The DSMB Charter should be provided with protocol to FDA and NIH for review.

For more information on determining the need for a DSMB and other information about the constitution and management of a DSMB, see the FDA Guidance Document: "Guidance for Clinical Trial Sponsors on the Establishment of Clinical Trial Data Monitoring Committees"

www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

17.1.1 *Data and Safety Monitoring*

The Data Safety Monitoring Committee (DSMC) at Tisch Cancer Institute (TCI) at the Icahn School of Medicine at, Mount Sinai Medical Center (MSMC) will serve as the DSMB for this trial. The DSMC will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor investigator, statistician and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

Independent audits will be conducted by the Mount Sinai DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the clinical monitoring plan, as defined below.

Data Monitoring Plan

List the name(s) of the individual(s) at the Icahn School of Medicine at Mount Sinai (ISMMS) who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information.

ISMMS Principal Monitor:

Identify if this will be the PI, Team Member, or Independent

Last Name:
First Name:
Academic Title:
Department:
Mailing Address:
Phone:
Fax:
E-mail:

ISMMS Additional Monitor:

Identify if this will be the PI, Team Member, or Independent

Last Name:
First Name:
Academic Title:
Department:
Mailing Address:

Phone:
Fax:
E-mail:

- Justify your choice of principal monitor in terms of the assessed risk to the research, and subject's health and well-being. In high-risk studies when the principal monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and the rationale for selection.
- List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).
- Indicate the frequency at which accumulated safety and data information will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.
- Where applicable, describe rules which will guide interruption or alteration of the study design.
- Where applicable, indicate dose selection procedures that will be used to minimize toxicity.
- List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).
- Describe procedures that will be used to assure data accuracy and completeness.
- Should a temporary or permanent suspension of your study occur, in addition to the PPHS, to whom (NIH, FDA, sponsor, IRB) will you report the occurrence?

When appropriate, describe the DMC. Provide the number of members of the DMC, their names and area of professional expertise. DMC reports must be made available to the local PI and the TCI's DSMC. The report need not contain specifics of the study or data, but there must be assurance that subject safety is not being compromised and that the results of treatment do not warrant early termination of the study.

17.1.2 *Medical Monitoring*

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

17.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

• What protected health information (PHI) will be collected from subjects in this study

• Who will have access to that information and why

• Who will use or disclose that information

• The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

17.3 Ethical Considerations

17.3.1 *Institutional Review Board (IRB) Approval*

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study. The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require. Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

17.3.2 *Ethical Conduct of the Study*

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

17.3.3 *Informed Consent*

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject′s signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

17.4 Data Handling and Record Keeping

Provide details regarding the type(s) of data capture that will be used for the study. Specify if paper or electronic, distributed or central, batched or ongoing processing, and any related requirements.

- *Describe steps to ensure that data are accurate, consistent, complete, and reliable (following ICH E6 is acceptable, but not required per US federal regulations).*
- *Describe responsibilities for data handling and record keeping with regard to the sponsor, clinical site(s), laboratories, etc.*

17.4.1 *Source Documents and Access to Source Data/Documents*

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Each site will maintain appropriate medical and research records for this trial, in compliance with FDA regulatory and institutional requirements for the protection of confidentiality of participants.

A study team can choose to also follow ICH recommendations, but should note that ICH includes a higher level of reporting obligations than does the FDA. If the protocol is to include ICH language, consider stating the applicability of ICH to the extent it has been adopted by and is in accordance with FDA regulations.

Describe who will have access to records.

Each site will permit authorized representatives of regulatory agencies to examine clinical records for quality assurance reviews, audits, and valuation of study safety, progress, and data validity.

17.4.2 *Case Report Forms*

State what data will be collected on CRFs and what data will be collected from other sources.

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Access to case report forms (eCRFs) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents, or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <<INSERT - specify name of data capture system>>, a 21 CFR Part 11-compliant data capture system provided by the <<INSERT - specify name>>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

If using REDCap: Electronic Case Report Forms and study data management will be performed using the REDCap Study data will be collected and managed using REDCap (Research Electronic Data Capture), a HIPAA-compliant research data management system.

If using OnCore:
Electronic Case Report Forms and study data management will be performed using Oncore.

17.4.3 *Records Retention*

Specify the length of time for record retention for all records pertaining to this study. Indicate whether permission is required, and from whom, prior to the destruction of records.

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

17.5 Study Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Ethics Committee (EC)/Institutional Review Board (IRB), study sponsor (if applicable), government regulatory bodies, and institutional compliance, quality assurance, and quality control monitors of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

17.5.1 *Quality Assurance and Quality Control*

Describe the plans for quality management, including quality assurance (QA) and quality control (QC).

Each site, both clinical and laboratory, should have standard operating procedures (SOPs) for quality management that describe:

- *How data will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.*

- *The documents to be reviewed, who is responsible, and the frequency for reviews.*
- *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with the protocol) and QC issues (e.g., correcting errors in data entry).*
- *Staff training methods and how such training will be tracked.*
- *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*

17.5.1.1.1. Internal Quality Assurance Reviews

The primary goal of the Mount Sinai Cancer Clinical Trials Office (CCTO) Quality Assurance Program (QAP) is to ensure that TCI research activities are performed in accordance with institutional policies, as well as those policies promulgated by the National Cancer Institute (NCI) and the United States Food and Drug Administration (FDA), while adhering to good clinical practices (GCP). This centralized function includes education and training services, data auditing, assessment of subject eligibility via central registration, timely submission of study data and data and safety management (DSM) activities to ensure study participant safety. The following quality assurance activities have been implemented in pursuit of this goal.

The auditors perform internal audits of selected clinical trials on a monthly basis. Investigator-Initiated Trials (IITs), and studies associated with high and medium risk to participants, as deemed by the Mount Sinai Data and Safety Monitoring Committee (DSMC), are prioritized for auditing. The QA team will randomly select 5% of Investigator Initiated Trials (IIT) for review and/or a minimum of one IIT from each disease research team per quarter. Twenty percent, or at least three participants, will be audited. No trial will be audited more than once per year unless deemed for cause by TCI leadership. Any clinical trial with non-compliance or serious protocol violations will be audited.

Over the course of the audit, a review is done of study regulatory documentation, study participant charts, drug accountability, and verification of electronic case report form (eCRF) data against source documentation. For newly audited trials, all subjects accrued are reviewed for consent, eligibility, drug accountability, and serious adverse events (if applicable). Random subsets of subjects are reviewed in full. Trials which are re-audited are only reviewed for new subjects accrued since the previous audit and new study time points for existing subjects.

Internal Quality Assurance Reviews (ISMMS)
A quality assurance review will include four major objectives:

- Protocol adherence
- Data quality
- Response assessment
- Regulatory compliance

The review will encompass these major areas (including but not limited to):

- Drug and/or device accountability
- Review of all signed informed consent forms {JCF)
- Eligibility (meets inclusion/ exclusion criteria}

- Treatment (protocol specific regimen)
- Lab tests and study procedures
- Response (proper assessment and documentation per protocol}
- Reporting of all applicable adverse events
- Protocol deviations/violations
- Correlation of source documentation with case report forms
- Inspection of the study file binder
- Review of all monitoring reports

All concerns noted in the review will be assessed by designated TCI CCTO staff and leadership. The Principal Investigator and key members of the research team will be informed of all findings. This includes (but not limited to}: research nurse, clinical research coordinator, regulatory.

A corrective action plan (CAPA} will be created to address all issues and a deadline will be issued for addressing the deficiencies. The CAPA will include the names of research personnel responsible for implementing the plans, along with predicted dates of completion. The CAPA will be reviewed by a designated member of TCI leadership.

CCTO QAP Procedures:

- A quality assurance review will include four major objectives:
  - Protocol adherence
  - Data quality
  - Response assessment
  - Regulatory compliance
- The QA Manager will supervise the quality assurance reviews.
- The QA team will randomly select IITs for review and/or a minimum of one from the disease specific research teams. Ten percent or at least three patients will be audited. No trial will be audited more than once per year unless deemed by necessity.
- The review will encompass these major areas (including, but not limited to):
  - Test article accountability
  - Review of all signed informed consent forms (ICFs)
  - Eligibility (meets inclusion/exclusion criteria)
  - Treatment (protocol specific regimen)
  - Response (proper assessment and documentation per protocol)
  - Reporting of all adverse events (routine, serious and unanticipated)
  - Protocol deviations/violations
  - Correlation of source documentation with case report forms
  - Inspection of the study file binder
  - Review of all monitor reports

A preliminary audit report is generated summarizing audit findings as well as noted deficiencies with suggested corrective action plans that is reviewed with the Medical Director(s) of the CCTO, the principal investigator, and the research personnel. A copy of the final report is sent to the IRB of record and findings are presented to the DSMC and to the CRSC when applicable. The IRB of record will make final determinations on the necessity of reporting to official regulatory bodies such as the Office for Human Research Protections (OHRP) and the Federal Drug Administration

(FDA). Studies with poor compliance are re- audited as per the recommendation of the Medical Director(s), DSMC, CRSC and/or IRB.

- These findings will be reviewed at an "audit review meeting." Key people who work on the operations and data of the protocol and the principal investigator will be required to attend this meeting. The auditor will present the findings to the group in an official report with a signature page so that the protocol team signs off that they understand the deficiencies and will work towards correcting them.
- An action plan will be created to address all issues and a deadline will be issued for addressing the deficiencies. The action plan will include the research personnel responsible for implementing the plans, along with predicted dates of completion.
- On a continual basis, the QAP representative will monitor progress of completing the action plan.
- The action plan will be signed by the principal investigator or his/her designee.
- The action plan will be reviewed by the Medical Director or the Associate Medical Director.
- A letter/memo with the findings for each protocol audited will be reported to CRSC when applicable.
- If the action plan items are not completed within the specified time frame, the DSMC is formally notified. The DSMC can elect to suspend enrollment or terminate a trial resulting from noncompliance with recommendations to resolve audit discrepancies. This action is also reported to the IRB.

In an effort to maintain consistency when reporting audit findings to the research community, the following guidelines have been established to define commonly used terminology in the audit reports:

Types of Violations:

- Minor Violations: Instances of non-compliance that represent a violation of the protocol, Good Clinical Practice (GCP) Guidelines, federal regulations, Icahn School of Medicine at Mount Sinai or Cancer Clinical Trials Office Standard Operating Procedures. These violations are considered small deviations from the protocol or guidelines and do not impact overall data integrity or patient safety.
- Major Violations: Violations of the protocol, GCP guidelines, federal regulations, Icahn School of Medicine at Mount Sinai or Cancer Clinical Trials Office Standard Operating Procedures which could impact trial analysis, data integrity, effectiveness of treatment or evaluation of toxicities. Major violations include any study conduct that could result in regulatory agency action against the Principal Investigator or the Institution. Multiple minor violations of a similar infraction are also considered major violations (e.g. repeated non- compliance).

Audit Findings Scale:

- Acceptable: a few minor violations which are not of the same infraction type.
- Acceptable, needs follow-up: Multiple minor violations not of the same infraction type, 2 or less major violations and those findings that cannot be classified as an unacceptable finding.
- Unacceptable: 3 or more major violations, any violation which resulted in a life- threatening event, or any violation which raises concern for fraudulent data or gross study misconduct.

17.5.1.1.2. Mount Sinai Research Compliance Program (RCP)

The Research Compliance Program (RCP) is part of the Research Integrity Program of the Mount Sinai Health System whose role is to provide oversight, education and monitoring of the research activities at the Mount Sinai. The RCP conducts internal audits to ensure that the human subject research conducted at Mount Sinai meets federal as well as institutional regulations and to ensure that trial data is accurate, complete and verifiable. Components of the RCP audits include regulatory elements of Good Clinical Practices (GCP) (protocol, protocol amendments and case report forms; IRB submissions, correspondence, consent forms, HIPAA forms, assent forms, AEs, DSMB reports, source documentation and case report forms, CVs and licenses, clinical supplies and drug/storage, study reports and logs, sponsor correspondence, FDA forms, FDA annual report), subject billing, reimbursement, billing coverage analysis; verification of recruitment, storage of data, access to data as per institutional requirements; disclosure of financial interests. Reports of the audits are forwarded to the principal investigator of the study, the TCI Director, the TCI Executive Administrator, the CCTO Medical Director, the Mount Sinai Chief Compliance Officer, and the IRB.

17.5.1.1.3. Independent Auditing of High Risk Clinical Trials

Best practices indicate that independent auditing results in better quality data and regulatory compliance. The CCTO can outsource the independent auditing of high risk clinical trials to the Biomedical Research Alliance of New York (BRANY). BRANY auditors will ensure that the research trials are conducted and documented in accordance with regulatory requirements. BRANY provides detailed feedback to the Executive Director of Clinical Research Administration and the QA Manager for review and approval. Final reports of the audit are forwarded to the principal investigator of the study, the CCTO Medical Director and the IRB.

17.5.1.1.4. External Quality Assurance Reviews

When any member of a study team (Principal Investigator, Co-Investigator, Regulatory Coordinator, Clinical Research Coordinator, Research Nurse, or other CCTO personnel) is notified of an audit request this information should be immediately forwarded to the CCTO Executive Director, CCTO Medical Directors, CCTO Quality Assurance, and Administration (for coordinating/scheduling visit). Most industry sponsors require they are notified immediately upon knowledge of an FDA audit.

When scheduling an audit, care must be taken to ensure that all study team members, including the Pl and Pharmacy (if required), are available to meet with the auditor(s). When an audit date is confirmed by all relevant parties:

- A conference room or private work area will be booked for the day(s) of the auditors' planned visit
- If an external governing body requests the audit, the study sponsor is notified as soon as possible
- The study team will make all requested study-related documents available
- The study team will facilitate the audit, communicating directly with the external auditors prior to the designated audit date

Preparation:

The study team (and disease group manager if applicable) will meet with CCTO Directors and Quality Assurance to generate an organizational plan. Specific actions include:

- Responding to all outstanding data queries
- The creation of a Summary Page in the outer cover of each shadow chart that lists patient-specific study milestones
- Organization of study documentation into appropriate sections
- Tagging key study documentation (i.e. signed ICF, physical exam, etc.)

CCTO Quality Assurance will conduct an internal audit prior to the planned external audit. The review will include the following major objectives:

- Protocol adherence/compliance
- Data quality/integrity.
- Chart organization
- Drug Accountability
- Regulatory compliance
- Review of original signed consent forms
- Eligibility (meets inclusion/exclusion criteria)
- Response (documentation of response per protocol}
- Reporting of all adverse events
- Reporting of protocol deviations/violations
- Source Verification
- Inspection of the regulatory file binder
- Review of JND Safety Reports

All concerns noted in the review will be assessed by CCTO Leadership. The principal investigator and the study team will be informed of all findings.

A corrective and preventive action (CAPA) Plan will be developed to address all findings within an established time frame and signed by the Pl. If necessary, appropriate training will be completed within a time period specified by the Pl or the designee.

On the day the audit begins, a member of the study team will greet the external auditors and guide the auditor(s) to the location of the introductory meeting. A designated team member will remain with the auditor(s) for the course of the audit.

The study team will:

- Maintain a list of all documents requested and copied
- Accompany the auditor(s) during tours and interviews
- Arrange for the auditor(s) to have EPIC access to the subject charts in advance, if needed
- Maintain a list of questions asked that require consultation with staff not readily available to answer
- Arrange for an exit interview at the conclusion of the audit.
- Arrange follow-up if required

Audit Exit Meeting:

The following individuals should participate in the exit interview with the auditor(s}:

- Principal Investigator (Pl)
    - It is the responsibility of the Pl to ensure that all questions posed by the auditors are answered
- Clinical Research Coordinator
- Clinical Research Nurse
- Regulatory Compliance Coordinator
- Pharmacy representative
- Clinical Trials Manager (if applicable)
- CCTO Quality Assurance
- CCTO Executive Director
- Additional personnel as required

Audit Follow up:
Within 30-60 days following the conclusion of the audit, a finalized Audit Report is generated by the external auditors and sent to the Pl.

The Pl will draft a formal response with input from the study team, QA and CCTO Leadership. The written response will include the formulation of a CAPA Plan with timelines for completion.

Quality Control (QC) procedures will be implemented beginning with the data entry system. Data QC checks that will generated from the study database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

17.5.2 *FDA Audits*

Notification

Upon receipt of notification from the FDA of an inspection, the Principal Investigator {Pl) or personnel contacted will immediately notify the following: CCTO Executive Director, CCTO Medical Directors, CCTO Quality Assurance, and Administration (for coordinating/scheduling visit). Most industry sponsors require they are notified immediately upon knowledge of an FDA audit.

- The Pl will ensure research staff immediately begin to retrieve and assemble any requested trial-related records.
- The Pl must be available in person during FDA inspection. If the Pl is unavailable during the proposed date of the audit, and the date must be rescheduled, the Pl or designee may contact the

FDA investigator to request rescheduling at a mutually convenient time. This request and response should be made in a timely fashion and should be documented together with the agency's response. If a new date is agreed upon, the rescheduled inspection must be communicated to all involved, as noted above.

Preparing for the inspection:

- All study personnel will be available to answer questions for which they have direct knowledge.
- A private conference room will be reserved, if available, for inspector to conduct their required review.
- A liaison will be designated to facilitate the audit and communicate directly with the FDA inspector prior to the designated audit date (if possible).

The liaison will:

- Provide requested documents
- Accompany auditor(s) during tours and interviews
- Maintain a list of questions asked that require consultation with staff not readily available to answer
- Maintain a list of documents requested
- Maintain a list of documents copied
- Assist the inspector(s) as needed
- Arrange for a debriefing at the conclusion of the audit
- Arrange follow-up if required

Conducting the inspection:

- The Pl or designee will greet the FDA inspector(s) and verify identification/credentials. The inspector will provide an FDA Form 482 (Notice of Inspection). If FDA does not provide the 482, notify CCTO leadership and the compliance team immediately. The team should be prepared to provide a tour of the facility if one has been requested.
- Provide access to subject charts and/or electronic medical records.
- Provide requested documents. The liaison will make two (2) copies of each record requested by
- FDA; one for FDA, and one for retention on site following the inspection.
- Assist in ensuring that each question is answered by person(s) most knowledgeable of the issue.
- Arrange for follow-up as required for any unanswered questions or outstanding document reports.
- FDA inspectors should not be allowed to enter patient care areas or research staff workspace areas unescorted at any point during the inspection.

Post-inspection:

- The Pl or liaison should request an end of day discussion during each day of the inspection with the FDA Inspector to review any preliminary findings.
- The liaison will document any questions whose answer could not be provided, along with appropriate follow-up to obtain the requested information.
- If the Pl receives a Form FDA 483 (report of observations) after the audit, consult CCTO leadership on how to respond and provide the sponsor with an opportunity to assist in the response.

- A copy of the FDA Form 483 and the response to the observations will be sent to the sponsor representative of the research (if applicable).
- The Pl will prepare a written response with input from CCTO leadership and send the response to the FDA within the time specified by FDA. The written response should:
- Address each observation and explain what steps have been implemented or will be implemented to remedy the observation, and prevent future occurrences of similar observations.
- The response should be factual and the tone should be respectful, professional and cooperative
- The Pl or designee should attempt to obtain a copy of the official FDA investigator's field audit report [Establishment Inspection Report (EIR)] under the Freedom of Information Act {FOIA Request). This request can be made at the conclusion of the 483 response. FDA typically will not respond to an EIR request until the matter is formally closed.

On-going readiness

- The FDA can notify of audit at any time. Advance notice varies. Always be audit ready.
- Research Study File Maintenance including but not limited to:
    - Keep files organized at all times
    - Retain all correspondence from - sponsor, monitors, study subjects, letters, faxes, emails, memos, and phone contacts
    - Retain all test article accountability record.
    - Retain Shipping receipts, screening and enrollment logs, dispensing logs

- Chances of an FDA Audit increase in certain instances:
    - Studies with a high enrollment, where test article approval is pending
    - Studies with few or no adverse events.
    - PIs who have received an FDA Form 483 in the past.
    - Studies where other sites have had problematic inspections.

17.6 Monitoring

17.6.1 *Clinical Monitoring*

For brevity and to allow for amendments to the monitoring plan without amending the protocol, it is preferable to use a stand-alone clinical monitoring plan (CMP) and incorporate herein by reference.

The CMP should include:

- *Who will conduct the monitoring*
- *What type of monitoring will be used*
- *Frequency of monitoring*
- *Extent of monitoring*
- *Who will receive monitoring reports*

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the

trial is in compliance with the currently approved version of the protocol, with GCP, and with applicable regulatory requirements.

Monitoring for this study will be performed by <<Insert >> in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

17.7 Training

17.7.1 *Investigator Responsibilities*

The principal investigator will ensure that:

- Designated individuals are qualified by licensure, training and/or experience to perform their assigned research study tasks. Qualifications may be documented by licensure and/or on individual curriculum vitae
- All research personnel, including experienced individuals and replacement staff, are properly trained in how to conduct the duties that have been delegated to them, and that they have an understanding of the research
- There is adequate supervision and involvement in the ongoing conduct of the research
- All training is documented

The Pl will ensure there is adequate oversight of the study to ensure compliance with federal state, and institution regulations as well as to the protocol.

Investigators involved in clinical research will adhere to institutional and sponsor training requirements, including but not limited to: protocol, biomedical research, and GCP education requirements.

17.7.2 *Training and Education Sessions*

The Cancer Clinical Trials Office (CCTO) of the Tisch Cancer Institute (TCI) routinely organizes one-hour training and education sessions monthly, and all CCTO staff are encouraged to attend. Speakers come from a wide variety of disciplines relating to cancer research including physician-scientists and regulatory experts. On an as-needed basis, the QA Manager formulates and runs training and education sessions to discuss new standard operating procedures (SOPs), issues of general concern that arise from the sponsor's monitoring reports, central registration, or internal audit review processes. Training and education, along with an effective communication strategy for reaching investigators and research staff, are considered critical to conduct quality research.

17.8 Protocol Deviations and Non-Compliance

Describe plans for detecting, reviewing, and reporting deviations.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations within 5 business days of identification of the protocol deviation, or within 5 business days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to <<INSERT – names of all entities to which reporting is required (i.e., DSMC, IRB, study agent manufacturer, FDA, etc.)>>. Protocol deviations must be sent to the local IRB per IRB guidelines. The site PI and study staff are responsible for knowing and adhering to their IRB requirements. In accordance with local IRB requirements, the following information must be reported within five (5) business days.

- Non-compliance with federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Breach of confidentiality
- Premature suspension or termination of the research by the sponsor or investigator

Further details regarding the handling of protocol deviations may be included in a study procedures manual.

17.9 Participant Privacy and Confidentiality

This section will describe protections for maintaining confidentiality of participant data, including, but not limited to forms, records and samples and participant privacy.

Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per the sponsor's requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, representatives of the NIH Institute or Center (IC), IND/IDE sponsor, representatives from the IRB, regulatory agencies, and representatives of the pharmaceutical company supplying product to be tested. In addition, consider inclusion of the following information:

Describe whether identifiers will be attached to data/samples, or whether data will be coded or unlinked.

If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.

If research data/samples will be coded, describe how access to the "key" for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.

Include a discussion of the circumstances in which data or samples will be shared with other researchers.

Include a discussion of plans to publish participant's family pedigrees, with a description of measures to minimize the chance of identifying specific families.

Describe any situations in which personally identifiable information will be released to third parties.

State who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access.

Discuss any additional features to protect confidentiality (e.g., use of a certificate of confidentiality).

Approaches to ensure privacy of study participants

For some studies, a Certificate of Confidentiality (CoC) may be necessary. A CoC provides protection to researchers and research institutions from being forced to provide identifying information on study participants to any federal, state or local authority. Authorization comes from NIH through section 301 (d) of the Public Health Service Act (42 U.S.C. 241 (d)) which provides the Secretary of Health and Human Services the authority to protect the privacy of study participants. Refer to the NIH Certificate of Confidentiality Kiosk, for more details.

Example text provided as a guide, customization will be required to address all aspects that should be included in this section:

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other

proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.]

17.10 Study Discontinuation and Closure

List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, sponsor/funder decision, regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance; futility). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension.

When a study is prematurely terminated, refer to "Criteria for Discontinuing Study Intervention" and "Criteria for Removal from Study" for handling of enrolled study participants.

Example text provided as a guide, customize as needed:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- *Determination of unexpected, significant, or unacceptable risk to participants*
- *Demonstration of efficacy that would warrant stopping*
- *Insufficient compliance to protocol requirements*
- *Data that are not sufficiently complete and/or evaluable*
- *Determination that the primary endpoint has been met*
- *Determination of futility*

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and, as applicable, the Food and Drug Administration (FDA).

17.11 Future Use of Stored Specimens and Data

Describe the following:

- *Intended use of stored samples, specimen, or data.*
- *Storage: whether samples or data will be retained, list type of samples and location of storage.*
- *Tracking: describe method of tracking, such as the name of the software program or other logging/ tracking method.*

- *Disposition at the completion of the study: describe the disposition of specimens.*
- *Subject request for destruction of samples: Approach for responding to requests (if applicable).*

Example Text:

- Intended Use: Samples and data collected under this protocol may be used to study <<INSERT - specify condition>>. No genetic testing will be performed.
- Storage: Access to stored samples will be limited using <<INSERT - specify approach>>. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using <<INSERT - specify approach>>.
- Disposition at completion of the study: All stored samples will be sent to <enter location>. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

If residual specimens will be retained after the study is complete, include the provisions for consent and the options available for the participant to agree to the future use of their specimens. Specify location of storage and how long specimens and data will be stored.

Data collected for this study will be analyzed and stored at Mount Sinai. After the study is completed, the de-identified, archived data will be transmitted to and stored at <<Insert storage site information>>, under the supervision of <<<INSERT – Role (not name) of responsible person>>, for use by other researchers including those outside of the study. Permission to transmit data to <<Insert Facility>> will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the <<Insert Facility>>. These samples could be used for research into the causes of <<INSERT - specify condition(s)>>, its complications and other conditions for which individuals with <<INSERT - specify condition(s)>> are at increased risk, and to improve treatment.

With the participant's approval and as approved by local IRBs, relevant de-identified data may also be shared with <<Insert Facility>>. The <<Insert Facility>> will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

An individual participant can choose to withdraw consent to have biological specimens stored for future research.

When the study is completed, access to study data and/or samples will be provided through <<Insert Facility>>.

17.12 Collaborative Agreements

Only include this section if applicable. Investigators in the NIH intramural program may participate in multi-site collaborations under which biospecimens or data are transferred from the intramural program to another site for research that is part of the approved protocol. Each institution participating in the study is bound by the terms of the protocol and their obligations under the statutes and regulations. Intramural

protocols are cleared by the IC Clinical Director. In such situations, use of an HM-MTA is not necessary for these transfers.

Explain any collaborations involved in the protocol.

*Explain whether identifiers will be shared and describe the mechanism for IRB review at the other site(s), if applicable. For studies that include the conduct of human participant research for this protocol being carried out at more than one institution, please contact the **IRBO** for guidance on requirements/procedures for use of a Single IRB and appropriate agreements.*

17.13 Conflict of Interest

This section should include a description of how the study will manage actual or perceived conflicts of interest.

Example text provided as a guide, customize as needed:

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the < Center> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any research personnel who has a conflict of interest with this study (patent ownership, intellectual property, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must declare their conflict of interest to the appropriate institutional review bodies. Local institutional conflict of interest policies will be followed for all research personnel associated with the research project.

17.14 Required Documentation

(For Cancer Clinical Trials Office-Managed Studies multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the CCTO by all sites.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values

- Executed clinical research contract (if applicable)

17.15 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

18.0 Publication of Research Findings

18.1 Publication and Data Sharing Policy

The publication and authorship policies should be described in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Please refer to your specific contract, grant, and/or Clinical Trials Agreements. The study must comply with:

- *The NIH Public Access Policy, the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, The Food and Drug Administration Amendments Act of 2007 (FDAAA), Clinical Trials Registration and Results Information Submission rule,*
- *The NIH Data Sharing Policy (if applicable),*
- *The NIH Genomic Data Sharing Policy, (if applicable), and*
- *The NIH Data Sharing Policy and Implementation Guidance,*
- *Any other relevant policies (e.g., NIH IC-specific data sharing or publication policy)*

Example text provided as a guide, customize as needed:

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

18.2 Human Data Sharing Plan

The data sharing plan (DSP) must describe provisions for protecting the subjects' privacy and the confidentiality of the data, including, if necessary, any limitations on secondary research with the data based on the original informed consent (if known) or other limits. If data are not appropriate for sharing on an individual level basis even with individually identifiable information removed, the DSP should include an explanation as well as an alternative for data sharing such as aggregate data sharing.

Your data sharing plan (DSP) should describe, at least, what data will be produced and shared, how and where data will be shared, and the timeframe for sharing (generally, no later than the time of publication of the main findings). It should include a commitment to share, at a minimum, the data underlying any publications resulting from the research or an explanation of why sharing is not possible, e.g., informed consent limits, intellectual property issues (e.g., patent filings) or contractual obligations that would preclude sharing.

Below is an example that can be used in the protocol (it is recommended that you delete the options that are not applicable for clarity):

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

18.3 Genomic Data Sharing Compliance

The Genomic Data Sharing (GDS) Policy applies to all NIH intramural research that generates large-scale human or non-human genomic data as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data.

Investigators are required to develop a Genomic Data Sharing Plan (GDSP) and ensure that they have appropriate consent language, if they are proposing research that will generate large-scale human and non-human genomic data for which the GDS policy applies. A Genomic Data Sharing Plan and the Institutional Certification should be complete and approved by your SD or designee PRIOR to starting the research. You may contact your IC's GPA for help. To find more information and locate your IC Genomic Program Administrator, click on this link.

Below is an example that can be used in the protocol (this is not the data sharing plan; it simply indicates compliance with the plan), when applicable:

This study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

19.0 Study Finances

19.1 Funding Sources

This section should describe how the study will be financed, but should not contain specific dollar amounts (e.g. "This study is financed through a grant from the US National Institute of Health", or "… a grant from the American Heart Association", etc. If referral treatments or counseling will be provided, note how the cost of the counseling or referral services will be paid.

19.2 Costs to the Participant

Describe and justify any costs that the participant will incur as a result of participating in the study. This section should clarify who will pay for procedures associated with the study (ex. agency grant versus departmental funds). Normally, participants should not have to pay for research procedures without direct

benefit. No charge may be made to participants if the costs are covered by a grant, contract, or other payment method.

19.3 Participant Reimbursements or Payments

If participants will be compensated or provided any incentives (e.g. vouchers, iPads) for study participation, describe amount, form and timing of any such compensation in relation to study activities (include financial and non-financial incentives). List the prerequisite condition(s) that must be fulfilled by subjects to receive these payments. The amount must be justified and not constitute undue inducement of the subject to participate in the research or to continue beyond a point that they would have otherwise withdrawn. Note: The IRB requires a prorated system for financial payments. This means that payments are accrued as the study progresses and that participants do not have to complete the entire study to be eligible to receive a payment. This is to protect the subject's right to withdraw without penalty. Describe who will receive incentives (if not the participant). For example, for minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adult, state if the incentive will be provided to the participant or to a guardian.

If there are none, either delete this section or state that there are no participant reimbursements or payments.

Examples of reimbursements and payments:

- *Reimbursement for time, travel, parking, meals, etc.*
- *Gifts- any tokens of appreciation given to a research subject, or their family, should be described here*
- *Payment to the subject for time, effort or inconvenience of being in the study*
- *Payment to subject family for time, effort or inconvenience of assisting a family member being in the study*

20.0 References

Please include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

Examples:

Journal citation
Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.

Whole book citation
Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.

Chapter in a book citation
Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.

Web Site citation

Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.

Electronic Mail citation

Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]

References to package insert, device labeling or investigational brochure

Cite date accessed, version number, and source of product information.

21.0 Appendices

21.1 List of Abbreviations

List any abbreviations, with their corresponding definitions, that will be commonly used throughout the protocol.

Abbreviation	Definition

21.2 Appendix I: Performance Status Criteria

21.3 Appendix II: Information on Possible Drug Interactions

21.4 Appendix III: Bioassay Templates

21.5 Appendix IV: Amendments

21.6 Appendix V: Multicenter Guidelines

GUIDELINES FOR PARTICIPATING INSTITUTIONS IN MULTICENTER STUDIES

Note: In this appendix, *central registrar* and *Multicenter Senior Clinical Research Associate* are used interchangeably.

Multi-site Communication:

The Icahn School of Medicine at Mount Sinai in New York, NY will serve as the coordinating center for the management of this trial under the guidance of the Principal Investigator<insert name> who will provide oversight and guidance on regulatory issues and trial management. This trial will be monitored closely by a Multicenter Senior Clinical Research Associate, who is also located at Icahn School of Medicine at Mount Sinai.

The Multicenter Senior Clinical Research Associate at Mount Sinai will coordinate routinely scheduled conference calls with all participating sites. Minutes will be taken. The following issues will be discussed as appropriate:

• Pre-screening information

• Enrollment information

• Cohort updates (i.e. DLTs)

• Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)

• Protocol deviations/violations

• Other issues affecting the conduct of the study

New Protocol Distribution, IRB Submission, Modifications and Annual Renewals:

Protocol specific documents will be distributed to participating sites once Mount Sinai IRB approval and the CDA from participating sites has been obtained.

The participating site must submit a draft of site specific revisions to the consent form document for review and approval by the Multicenter Senior Clinical Research Associate prior to submission to the local IRB. The site will be provided with confirmation via email that the consent is approved for local IRB submission.

Protocol amendments must be approved by participating site's local IRB within 90 days of distribution to the site by the coordinating center.

Regulatory Documents:

Regulatory documents may be sent to the Multicenter Senior Clinical Research Associate at the following address, if wet ink originals are required:

Icahn School of Medicine at Mount Sinai
Tisch Cancer Institute
Cancer Clinical Trials Office
202 East 96th Street
New York, NY 10128

Central Registration Procedures for Participating Institutions:

All participating institutions must register subjects with the Mount Sinai coordinating center prior to the administration of study drug/intervention/local institution registration. Please see instructions below:

The participating institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's Multicenter Senior Clinical Research Associate via telephone or email to notify of a pending registration request. Contact email will be provided to all sites.

The following documents should be submitted securely via email, which is done by including the word [secure] within square brackets in the subject line of the message. All registration submissions will be responded to within 24 hours (1 business day) by the Coordinating Center. The subject of the email should read, "Pending Subject Registration Request (PHI)".

• Completed registration form

• A signed participating site eligibility checklist (signed by the investigator)

• Redacted completed/signed IRB approved/stamped informed consent forms

• Redacted signed HIPAA (or institutional equivalent)

• Copy of required laboratory test and procedure reports (i.e., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

• Copy of pathology and surgical reports

• Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

Upon receipt of the above-mentioned documents, the Multicenter Senior Clinical Research Associate will review all documents and verify patient eligibility. If any questions arise during the review process queries will be emailed to the appropriate participating site study team personnel for clarification prior to enrollment.

The Study PI will review these documents to confirm eligibility and sign off as final reviewer of the eligibility checklist. Confirmations will be sent to respective sites research team via email. The confirmation email will include the study specific patient ID and dose level. This email notification should be filed in the patient research binder. Protocol therapy may not be initiated prior to receipt of this confirmation email from the coordinating center.

All screen failures, ineligible subjects, and subject withdrawals prior to enrollment or initiation of protocol therapy must also be submitted to the study Multicenter Senior Clinical Research Associate.

On-Site Monitoring:

Initial, recurrent, and close-out on-site monitoring visits will also be conducted at participating sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

The study Multicenter Senior Clinical Research Associate will communicate with the participating site coordinator/Principal Investigator to schedule the monitoring visit. The study Multicenter Senior Clinical Research Associate will provide a minimum of one week advanced notice in order to permit sufficient time to arrange for access to study materials and documentation.

The Multicenter Senior Clinical Research Associate will monitor this trial within 1 month after the first subject is enrolled at the participating site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Multicenter Senior Clinical Research Associate is responsible for conveying what information and documentation will be required for the visit(s). The Multicenter Senior Clinical Research Associate is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol.

The Multicenter Senior Clinical Research Associate will also verify that the data reported in the CRFs accurately reflect source documents, that all toxicities have been reported to date, and that all SAEs/unanticipated problems/deviations/violations have been reported according to Coordinating Center, local IRB and MSH DSMC requirements. The Multicenter Senior Clinical Research Associate will issue queries and ensure resolution in a timely and efficient manner.

The study monitoring visit log will be completed and signed by the Multicenter Senior Clinical Research Associate at each visit and will be filed in the regulatory binder.

Remote Monitoring:

If remote electronic medical record (EMR) access is available, source documentation will be reviewed in this manner. If unavailable, secure email exchange will be used. Regulatory and Pharmacy records can also be exchanged via secure email.

Dose Level Determinations:

The primary investigator/study statistician will review enrollment for each dose level cohort during the regularly scheduled conference call with participating sites and determine the dose level for newly enrolled subjects.

If a dose limiting toxicity (DLT) is identified in a subject, the participating site must notify the sponsor investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been observed within 1 business day.

Confidentiality:

Each participating site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g. 04-10). All sites will be required to enter their data in REDCap, the clinical trial database system used for clinical research on this protocol at MSH. All users must login with their own application username and password. Access will be granted by the ASPIRE MHS REDCap administrator. Prior to activation, the administrator will schedule remote REDCap training with research personnel assigned to data entry.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Mount Sinai must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier. If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

Data Reporting Plan:

Mount Sinai’s policies that pertain to patient data sharing conform to Mount Sinai IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, statistician, Data Safety and Monitoring Board, and, in other instances, the MSH IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the MSH's guidelines for Protecting the Rights and Privacy of Human Subjects.

Data Acquisition and Submission:

Informed consent, including HIPPA authorization, must be obtained for all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. REDCap will be used as the electronic clinical trials and data management system. Participating sites will enter data directly into REDCap via customized case report forms for the study. Data is expected to be entered into REDCap by all sites within 5 and no more than 10 business days. Failure to enter data and/or resolve queries in a timely manner may result in site enrollment suspension. The research staff will generate reports from REDCap to ensure timely submission of data by participating sites. This resource allows for the timely analysis of particular data sets for safety analysis.

21.7 Appendix VI: Protocol Contact List

The Protocol Template incorporates a Protocol Contact List, a document that needs to be maintained and updated throughout the duration of the study.

The Protocol Contact List should include all sub-investigators, study research personnel, research facilities, and other participating sites (if applicable) including Site PI, and site's key personnel (i.e., main contact personnel for clinical, regulatory, finance, etc.).

If applicable, list CRO contact information.

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *COMIRB Research Personnel Form*, and/or a *UCCC Protocol Contact List*, incorporated herein by reference.

22.0 Addenda