Investigator-Initiated Study Protocol

Title:

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 Sites:	*List the names of the participating sites*
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*
Funding Source(s):	*List the name(s) and contact information of the funding sponsor(s)*
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*

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Statement of Compliance

The signature below constitutes the approval of this protocol and the associated documents, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Sponsor-Principal Investigator: _____
Print/Type Name

Signature: _____ ***Date:*** _____

1.0 Summary

1.1 Synopsis

Protocol Title:	
Objectives:	***Primary Objective:*** ***Secondary Objectives:***
Endpoints:	• ***Primary Endpoint:*** • ***Secondary Endpoints:***
Population:	• ***Sample size:*** ***XX*** participants • ***Gender:*** • ***Age:*** • ***Demographic group:***
Study Type:	*e.g. Prospective, Interventional, Investigator-Initiated, Cancer-Related, etc.*
Participating Sites:	*Mount Sinai Hospital*
Description of Study Intervention:	*Please describe any diagnostic, treatment, behavioral, or other types of interventions.*
Study Duration:	*e.g. 1 year*
Participant Duration:	*e.g. 1 year*
Enrollment Period:	*e.g. 3 months*
Accrual Rate:	*e.g. 50 participants/month*

2.0 Hypothesis and Specific Aims

Please state the primary objective or main hypothesis to be tested. This is the main question to be answered through the conduct of the study. 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.

List any secondary objectives or goals that will provide further information.

List any tertiary or exploratory objectives that will serve as a basis for explaining or supporting findings of primary analyses, or serve as a basis for suggesting further hypotheses for later research.

Quality of Life objectives should be included when applicable.

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).

The study design should describe an adequate plan for answering the primary study question.

3.0 Outcome Measures

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.

Please clearly specify the secondary endpoints. 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.

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.

4.0 Background and Scientific Rationale

Explain the background of this project so that IRB and other review committees will understand why it is important to perform this research project. Include:

- *Summary of study disease(s) and previously published data and pilot studies. Be sure to include a discussion of any data that does not support hypothesis. If a study similar to the one being proposed has already been completed, explain why the proposed study is necessary.*
- *For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternate modes of therapy.*
- *Please provide the scientific rationale/justification for conduct of the study*
- *If not obvious, explain why human subjects are necessary.*
- *Include references for all published data cited.*

5.0 Potential Risks and Benefits

5.1 Potential Risks

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).

5.2 Potential Benefits

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

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

Please provide justification for the study procedures to be conducted, and the data collection tools to be used.

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 Study Design and Research Methods

Describe the study design and indicate how the design will answer the question posed by the study.

- *Specify the objectives and endpoints.*
- *Specify the maximum total accrual, accrual rate, accrual period, and expected duration of follow-up.*
- *Provide a justification of the 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 will be used to design and optimize subsequent clinical trials.*

7.0 Study Population

Please describe the study population to be enrolled.

7.1 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>

7.2 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>

8.0 Study Procedures and Evaluations

Please describe the study procedures and evaluations. Include when, where, and how often they will occur, and who will conduct them.

Example:

Screening

1. *Informed Consent*
2. *Confirmation of Eligibility*

Baseline

1. *Enrollment*
2. *Study Survey Administration*
3. *Data Collection*

Follow-Up

1. *One-month follow-up telephone call*
2. *Data Collection*

8.1 Schedule of Activities Table

Procedures	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 14 ±7	Visit 3 Day 28 ±7	Visit 4 Day 42 ±7	Visit 5 Day 56 ±7	Visit 6 Day 365 ±30	Unscheduled Visit
EMR Review Eligibility	X	-	-	-	-	-	-	-
Informed Consent	-	X	-	-	-	-	-	-
Demographics	-	X	-	-	-	-	-	-
Clinical history	-	X	-	-	-	-	X	-
Height & Weight	-	X	X	-	-	-	X	-
Outcome Evaluation	-	-	-	-	-	-	-	-
Pain Assessment (Brief Pain Inventory)	-	X	-	-	X	-	X	X
Quality of Life Questionnaire	-	X	X	X	X	X	X	-
Randomization	-	X	-	-	-	-	-	-
Control & Experimental Interventions – Occupational therapy	-	X	X	X	X	-	-	-
Adverse Events Reporting	-	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.

9.0 Enrollment Procedures

9.1 Informed Consent Process

The following subsections should describe the procedures for obtaining and documenting informed consent of study participants.

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.

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.

9.1.1 *Consent 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>.

9.2 Enrollment

Please describe the process by which participants will be enrolled in the study.

Example text:

Enrollment will consist of the entry of de-identified participant information into the study REDCap database. 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 research staff will be secured and password protected. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at Mount Sinai.

9.3 Strategies for Recruitment and Retention

Identify general strategies for participant recruitment and retention.

- *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)*

9.4 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*

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

State the stopping rules relevant to the intervention.

EXAMPLE TEXT (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, study participants)>>. 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 the appropriate response criteria.

13.0 Statistical Considerations

13.1 Study Design and Description of Statistical Methods

State the proposed study design. 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*
- *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 the 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.*

13.5 Data Analysis Plans

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

13.5.1 *Analysis Datasets*

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

13.5.2 *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*

13.5.3 *Additional Sub-Group Analyses*

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

13.5.4 *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.

13.5.5 *Tabulation of Individual Response Data*

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

13.5.6 *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

13.6 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.

14.0 Regulatory, Ethical, and Operational Considerations

14.1 Safety Oversight

14.1.1 *Data Monitoring*

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.

Example Text (Please customize as appropriate):

The sponsor-investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at Mount Sinai. The DSMC is responsible for ensuring data quality and study subject safety for all clinical studies at the Mount Sinai Tisch Cancer Institute, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the Mount Sinai Tisch Cancer Institute's Executive Committee

Each participant's outcome will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Study data including number of participants will be discussed and documented in the meeting's minutes.

The sponsor-investigator will provide a DSM report to the Mount Sinai Tisch Cancer Center DSMC annually. The DSM report will include a protocol summary, current enrollment numbers, all protocol

deviations, and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this annual report by the DSMC will then be provided to the sponsor-investigator in a DSMC review letter. The sponsor-investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

14.1.2 *Clinical Monitoring*

Example Text *(Please customize as appropriate)*:

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 protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the Mount Sinai Cancer Clinical Trials Office Monitor 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.

14.1.3 *Protocol Deviations*

Example Text (please customize as needed):

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 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the Mount Sinai IRB. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.1.4 *Confidentiality and Privacy*

Investigators and study-associated staff will maintain patient confidentiality in accordance with institutional regulatory requirements.

Information about study participants 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 participants 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.

14.1.5 *Quality Assurance and Quality Control*

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/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.

14.1.6 *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.

14.2 Ethical Considerations

14.2.1 *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.

14.2.2 *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.

14.2.3 *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.

14.3 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.*

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

Example text (please customize as needed):

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.

14.3.2 *Case Report Forms*

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

Example text (please customize as needed):

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 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.

14.3.3 *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.

Example text (please customize as needed):

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.

14.3.4 *Future Use of Stored Data*

Describe the following:

- *Intended use of data.*
- *Storage: whether data will be retained, list type of data 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 (please customize as needed):

- Intended Use: Data collected under this protocol may be used to study <<INSERT - specify condition>>. No genetic testing will be performed.
- Storage: Access to data 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 data 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, relevant de-identified data may also be shared with <<Insert Facility>>.

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

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

14.4 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.

14.5 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.

14.6 Publication of Research Findings

14.6.1 *Publication and Data Sharing Policy*

The publication and authorship policies should be described in this section.

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:

Results will be published in peer-reviewed scientific journals in oncology, such as *Name*. Findings would also be presented at scientific meetings, such as *Name*.

14.7 Study Finances

14.7.1 *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.

15.0 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.

16.0 List of Abbreviations

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

Abbreviation	Definition
