

**Clinical Trial Template Instructions**:

This template is designed for investigator-initiated clinical drug trials. It is not intended for use with medical device trials or hematology-oncology trials.

Instructions on how to complete each section, and examples of relevant language are included in the template and appear in BLUE font. Example alerts appear in RED font.

Delete the instructions and example alerts. Modify the example text based on the needs of your protocol, or delete it if not applicable.

**5.2 Dose Delays and Modifications**

Instruction

Include information on dose delays or modification per the protocol design, dosing regimen.

*Example text provided as a guide, customize as needed:*

Sample Text

{Each subject will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Dose adjustments should be made according to the system showing the greatest degree of toxicity.}

NOTE: Some sections also include text in **BLACK** font. This indicates standard language for our institution and should be included in your study, unless it is not applicable.

Acknowledgment: This template is based on the Rogel Cancer Center protocol and the National Institute of Health (NIH) protocol templates.

Version: May 1, 2024

PROTOCOL HUM NUMBER: [assigned by eRESEARCH]

**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**, and **target disease(s) and stage** (e.g. advanced, refractory)

**Principal Investigator:** Name

Institution

Address

(Phone)

(Fax)

Email

**Sub-Investigator(s):** For local sub-Is include:

Name

Department/Division

For off-site sub-Is include:

Name

Institution

Address

(Phone)

(Fax)

Email

**Biostatistician**: Name

Institution

Address

(Phone)

(Fax)

Email

**Investigational Agent(s)/How supplied:** List generic study drug name, followed by marketed name (if applicable)/How supplied (Pharmaceutical company name, commercial supply, commercial supply purchased by study funds).

**Standard of Care Agent(s) (Commercial Supply):** List generic drug name followed by marketed name

**IND Number**: Insert IND number, if applicable

**Initial version:**  V 1.0 [date] (this should be the final version sent to IRB)

**Amended:** V [date]

Consider adding an Appendix to describe protocol modifications during public health or civil emergency or restrictions and add a note to introduce the Appendix:

*An example is provided as a guide, customize as needed:*

**{NOTE:** To effectively manage **restrictions** put in place during public health or civil emergency or restrictions **(**i.e. COVID-19 pandemic**)** changes to protocol-required items **are to be made** to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens). These changes are listed in **Appendix A** of the protocol (**Contingency Operation Plan**).}

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# ABBREVIATIONS

Examples (the list should be inclusive of the entire protocol):

For better readability, avoid using excessive abbreviations and acronyms

|  |  |
| --- | --- |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ALC | Absolute Lymphocyte Count |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CMP | Comprehensive Metabolic Panel |
| CT | Computed Tomography |
| CTSU | Clinical Trials Support Unit |
| DSMC | Data and Safety Monitoring Committee |
| HRPP | Human Research Protections Program |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IV (or iv) | Intravenously |
| MOP | Manual of Procedures |
| MTD | Maximum Tolerated Dose |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PI | Principal Investigator |
| po | per os/by mouth/orally |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| UaP | Unanticipated Problem |
| WBC | White Blood Cells |

# STUDY SYNOPSIS

|  |  |
| --- | --- |
| Title | Insert the full title of protocol |
| Phase | Insert the clinical study phase (e.g., Phase I, II, III) |
| Study Design | Design attributes such as single blind, double blind or open label; randomized, placebo or active placebo control; cross-over design, etc. |
| Study Duration | List the estimated time (in months) of the following:  Enrollment duration: \_\_\_\_\_\_ months  Subject follow-up duration: \_\_\_\_\_\_\_ months  Overall study duration: \_\_\_\_\_\_ months  For overall study duration list the time from when the study opens to enrollment until completion of data analyses. |
| Study Center(s) | Specify if this is a single-center or multi-center; if multi-center, note number of projected centers to be involved. You do not need to include the names of the study center(s). |
| Objectives | Provide a brief statement of study objectives. Please note that specific measurable outcomes will need to be identified within the body of the protocol. |
| Number of Subjects | List the number of evaluable subjects projected for the entire study (i.e., not for simply one site, rather for all sites combined) |
| Disease/condition | Briefly describe the disease state/condition under study |
| Inclusion/Exclusion Criteria | See Section 3.0 for a complete list of inclusion and exclusion criteria |
| Description of Study Intervention: | Describe the study intervention. For a drug or biologic, include the name (generic, though can also state marketed name if name-brand used in the study) dose, route and regimen. Also include non-drug therapy (i.e., counseling, surgery). Identify the comparator product, if any, used as a reference. It may be an investigational or marketed product (i.e., active control or placebo). |
| Duration of Intervention | List the total duration of intervention expected in order for a participant to complete the trial (including any open-label lead-in, if applicable). Include total time of all interventions not just drug administration. |
| Statistical Methodology | Provide a very brief description of the main elements of the statistical methodology to be used in the study (as few lines as possible) |

# STUDY SCHEMA

The schema should represent your study design, along with corresponding descriptive text, as applicable.

*An example is provided as a guide, customize as needed:*

Prior to Enrollment

Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.

Perform baseline assessments.

<List the main procedures>

<Refer to Section 6.1, Time and Events Table

Administer initial study intervention (if applicable)>

Administer initial or repeat study intervention (if applicable).

<List the main procedures>

<Refer to Section 6.1, Time and Events Table>

Repeat study intervention (if applicable) and perform follow-up assessments of study endpoints and safety

<List the main procedures>

<Refer to Section 6.1, Time and Events Table>

Repeat study intervention (if applicable) and perform follow-up assessments of study endpoints and safety

<List the main procedures>

<Refer to **Section 6.1, Time and Events Table>**

Randomize

Arm 1

N

Arm 2

N

Final Assessments

<List the main procedures>

<Refer to Section 6.1.

Visit 1

Time Point

Visit 2

Time Point

Visit 3

Time Point

Visit 4

Time Point

Visit X

Time Point

# BACKGROUND AND RATIONALE

Include relevant references to support the information in this section. If you list numerically, then make reference list numerical.

## Disease Background

Provide disease background information particularly relevant to your study. Questions to be addressed may include the current standard of care and any relevant treatment issues or controversies. Please justify why an investigational therapy or approach is warranted.

## Study Agent(s) Background and Associated Known Toxicities

Please provide relevant background information about the study agent(s) that you are planning to use in the study and known toxicities. The following briefly explains what is required in this section:

* A summary of findings from non-clinical in vitro/in vivo studies that have potential clinical significance including information on mechanism of action, pharmacokinetics and safety. This is particularly important for investigational agents, and may not be necessary for commercially available drugs (FDA approval information and indication should also be included), and/or drugs with sufficient clinical data.
* A summary from relevant published clinical studies or study results posted on ClinicalTrials.gov, with focus on those that provide information for your study. Please include important safety information, **the rationale for the starting dose(s)**, information on clinical pharmacokinetics, and major route(s) of elimination. If available, please include information on the metabolism of the agent(s) in humans and address any potential for drug interactions.

## Other Agents

This section may be required if your study focuses on either an investigational agent in combination with commercially available products, or if your primary objective focuses on only one of several commercial agents included in the study. If needed, please provide background information on other agent(s) and/or treatments in this study that are not described in Section 1.2 including rationale for including them in this study, their mechanism of action, information to support safety issues and the rationale for the proposed starting dose scheme, if applicable. For commercially available agents, detailed information on adverse events and potential risks should be deferred until Section 9.0 (Drug Information).

## Rationale

Discuss the reasoning behind conducting the study, and your study design. Include justification of your study outcomes. This section should link the disease background with the study agent(s) under evaluation. Include study population and starting dose rationale and risk/benefit assessment, particularly if focusing on a subset within the disease population (e.g., relapsed or elderly subjects).

## Correlative Studies

If applicable, provide the background information on the planned correlative study(ies) including the biological rationale and hypothesis.

# STUDY DESIGN, OBJECTIVES AND OUTCOME MEASURES

Include a brief description of the study design including phase, single vs multisite, randomization, blinding, and other characteristics, as applicable.

Include a detailed description of Primary and Secondary objectives of the study. Be discerning about what is classified as Primary, Secondary, and Exploratory. If it’s not certain that reliable data can be collected for a given outcome measure, do not list it as a Primary or Secondary outcome. Rather, classify it as an Exploratory outcome. Each objective should receive a separate number, e.g., 1, 2. As an example, the following guidelines can be used to describe these objectives:

Statement of purpose: e.g., to describe, to measure, to compare, to estimate

General measure: e.g., efficacy, safety, immunogenicity, pharmacokinetics

Specific measure: e.g., dose-response, superiority to placebo

Note: Sometimes one or more (often the primary or first) objective from/for a grant forms essentially a first study in its own right, e.g., to ***design*** an educational, behavioral or clinical intervention. The outcomes for that “design” objective may be completely separate from the primary and secondary outcomes of the clinical trial testing the intervention. And indeed, that initial stage of the project may not be a clinical trial at all. Only those objectives that relate to the actual clinical trial belong in the protocol. In drafting the protocol for a clinical drug trial, it is important to have the hierarchy of the outcome measures relate to the definitions in 42 CFR 11: primary outcome measure means the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation.

Most clinical trials have one primary outcome measure, but a clinical trial may have more than one. Secondary outcome measure means an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan for evaluating the effects of the intervention(s) under investigation in a clinical trial and is not specified as an exploratory or other measure.

Each objective (whether primary, secondary or exploratory) should receive a separate number and should generally have one or more outcome measures. A notable exception would be when the objective can be met by doing a different analysis based on data collected and already listed in another outcome measure. (For example, if an exploratory objective were to analyze the different impact of age on the metabolism of the drug, where the metabolic endpoints were already included in the secondary outcome measure, there would not need to be an additional endpoint for that exploratory objective.)

To meet ClinicalTrials.gov quality standards, ensure that every outcome measure is specific and measurable. List each outcome separately. Remember – any trial that reports results in ClinicalTrials.gov will be required to upload the final protocol for the public to view.

While coherence with grant language is important, it bears understanding that secondary outcome measures will need to be listed and report results in ClinicalTrials.gov, whereas exploratory outcome measure do not. Therefore, while all necessary secondary outcome measures should be listed, in accordance with scientific and bio statistically sound principles, care should be taken not to throw in extra secondary measures just “in case” they might be interesting. Such measures would belong in Exploratory outcomes.

## Primary Objectives

*Example text for a Phase II trial is provided as a guide, customize as needed:*

### {To determine the efficacy of [Study Drug X] when administered in combination with [Study Agent Y] in subjects with [condition Z].}

### **Primary Outcome Measure:**

*Example text is provided as a guide, customize as needed:*

{A typical outcome measure might be overall survival at one year, or percent change from baseline to Week 12 in fasting HDL, etc.}

## Secondary Objectives

Typical secondary objectives for a phase I trial may include (add details):

* Safety
* Pharmacokinetics
* Pharmacodynamics
* Preliminary clinical responses

Include one secondary outcome measure per each objective.

Example text for secondary objectives and outcome measures for a Phase I trial are provided as a guide, customize as needed:

### {To assess the bioequivalence of two dosing regimens.}

**Secondary Outcome Measure:**

{Geometric Mean Ratio of the AUC between the high and low dose of [Study Drug X].

The Geometric Mean Ratio and 90% confidence interval around this value permit an assessment of the bioequivalence of two dosing regimens in the same group. The geometric mean is computed based on the ratio of the AUC value from the high dose compared to the AUC value from the low dose for each individual. This ratio provides a more robust interpretation of the differences between the two dosing arms because each individual serves as their own control.}

### {To describe the adverse events associated with [Study Drug X] when administered with [Study Drug Y]}

**Secondary Outcome Measure:**

{Number of subjects experiencing one or more Serious Adverse Events related to study drug at Week 12.}

## Exploratory Objectives

If applicable, please include objective(s) for your correlative studies

*Example text is provided as a guide, customize as needed:*

### {To understand whether weight gain is attributable to [Study Drug X] when administered with [Study Drug Y].}

**Exploratory Outcome Measure:**

*Example text is provided as a guide, customize as needed:*

{The difference between subject weight from Baseline to Week 12.}

# SUBJECT ELIGIBILITY

Subjects must meet all of the selection criteria to be enrolled to the study. Study treatment may not begin until a subject has been consented and meets the eligibility criteria.

If eligibility needs to be confirmed more than once (for example in case of a long washout period), include a timeline for eligibility confirmation here.

## Inclusion Criteria

Each criterion should be assigned (or given) its own number (e.g., 1, 2, etc.). All criteria should be written in a manner that you answer YES to enroll.

For example:

1. Diagnosis and/or disease status criteria
2. Criteria for type and amount of prior therapy that is allowed
3. Male or Female [Age criteria]
4. Required lab and acceptable range criteria. This section could state ‘Adequate organ and marrow function as defined below:

|  |  |
| --- | --- |
| Lab A | Enter Criteria X or ’within institutional normal reference range’ |
| Lab B | Enter Criteria X or ’within institutional normal reference range’ |
| Lab C | Enter Criteria X or ’within institutional normal reference range’ |

1. Criteria for contraception usage if women of child-bearing potential are allowed to participate in the trial

*Example text is provided as a guide, customize as needed:*

{Subject agrees to the use of highly effective contraception starting at screening, during study participation and for at least [X] days/months/years after final study treatment administration}

1. Male contraception requirements and sperm donation including timeline
2. Other study-specific criteria
3. For oral medications, ability to take oral medication and be willing to adhere to the study intervention regimen
4. Ability to understand and willingness to sign a written informed consent.
5. If applicable, indicate that the subject must understand/read/speak English

## Exclusion Criteria

Each criterion should be assigned (or given) its own number, e.g., 1, 2, etc. All criteria should be written in a manner that you answer NO to enroll. If they are YES, the subject will be excluded.

For example:

1. Criteria for previous treatment
2. Comorbidity or intercurrent illness exclusion criteria
3. History of allergic reaction exclusion criteria
4. Current use of [specify disallowed concomitant medications]; provide time line for discontinuation
5. Pregnancy or nursing female exclusion criteria
6. Exclusion criteria for participation in other investigational trials (include a timeline e.g., current participation, participation in the past 3 months etc.]

# SUBJECT SCREENING, ENROLMENT, AND RECRUITMENT

Describe study registration procedures in this section. You may create and distribute a Manual of Procedures (MOP) that includes contact information and details that may change over time and therefore, should not be included in the protocol.

If the protocol is for a multi-site trial where the University of Michigan is the coordinating center, you may include the enrollment process here or in the MOP. For multisite studies, the UM IRBMED requires a MOP.

*Example text provided as a guide, customize as needed:*

{A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine subject eligibility prior to enrollment. After subject eligibility has been determined, a signed statement (i.e. eligibility checklist) by the site investigator attesting eligibility will be included in the subject file. In addition, source documentation supporting each eligibility criteria will be placed within the subject file.}

## 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. Indicate if screen failures will be replaced.

*Example text provided as a guide, 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, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. 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.}

## Randomization

If the treatment plan includes randomization, include the details here. Describe the process and include information on stratification, if applicable. For block randomization, do not include the block sizes.

## Blinding

If the treatment plan includes blinding, include the details here. Also include who is blinded (e.g., subjects and investigators, care providers, outcome assessors, monitors, only subjects) and who is unblinded. Describe the blinded drug assignment procedure (e.g., code with subject numbers, blinded envelops, etc.)

## Subject 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 procedure (SOP). Consider inclusion of the information below either in this section or the MOP.

* Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public)
* Recruitment venues
* How potential participants will be identified and approached
* Types of recruitment strategies planned (e.g. patient advocacy groups, national newspaper, local flyers; social media, specific names of where advertisements may be planned are not needed)
* If the study requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).
* Specific strategies that will be used to recruit and retain historically under-represented populations in order to meet target sample size and conform with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects, if applicable. Include the number of women and minorities expected to be recruited, or provide justification on those rare occasions where women and/or minorities will not be recruited. If you need assistance with subject recruitment, see the following site: https://www.michr.umich.edu/rdc/category/Participant+Recruitment

# TREATMENT PLAN

If the treatment plan includes washout periods, confirmation of eligibility or other requirements that need to be met, create a new section and include the details.

## Treatment Dosage and Administration

Describe the procedures for selecting each participant's dose of study intervention and control product. For drugs, that includes the timing of dosing (e.g., time of day, interval), the duration (e.g., the length of time study participants will be administered the study intervention), the planned route of administration (e.g., oral, nasal, intramuscular), and the relation of dosing to meals. If multiple drugs/interventions are administered on the same day, indicate the order of drug administration and the wait time between drugs/interventions, if applicable.

State the starting dose and schedule of the study intervention and control product, including the maximum and minimum duration for those participants who continue in the study.

### For complicated studies (e.g., multiple treatment phases) please first provide a summary of the entire treatment plan. This should be a few sentences, which provide a “snapshot” of the treatment plan. Details will be described below. If the treatment plan includes randomized drug assignment or blinding, include a randomization plan in Section 7.2 and refer to this section here.

### Please provide a full description of the treatment and how it will be administered (inpatient/outpatient basis). Include a description of any definite required or recommended/suggested supportive care medications.

See the example below for how the planned treatment regimen may be presented. If multiple drugs/interventions are administered on the same day, list the drugs in the order of administration and include the wait time between drugs/intervention as illustrated in the table below. Please provide separate regimen descriptions for different treatment groups of subjects as necessary.

If the dose needs to be rounded to the closest tablet or capsule size, include rounding instructions.

*Example text provided as a guide, customize as needed:*

Table 1. Treatment Plan

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Agent** | **Premedications; Precautions** | **Dose** | **Route** | **Schedule** |
| Agent A | Premedicate with DRUG for 3 days prior to Agent A. | 5mg/kg in 500 mL 0.9% NaCl | IV over 2 hours before Agent B | Day 1 every 4 weeks for \_\_\_\_ weeks |
| Agent B | Avoid exposure to cold (food, liquids, air) for 24 hrs. after each dose. | 100mg in 250 mL D5W | IV 1 hour after completion of Agent A; separate IV line required | Day 1 only |
| Agent C | Take with food. | 50 mg tablet | PO in the morning. | Daily, continuously for weeks |

If applicable, describe a dose escalation scheme and the rationale for selecting that particular type of dose escalation schema. Describe the dose regimen (using exact dose, rather than percentages). State any minimum period required before a participant’s dose might be raised to the next higher dose or dose range. Provide criteria that will be used to determine dose escalations. If a participant is responding positively to the intervention, the protocol should specify whether study intervention administration would progress to still higher doses.

Any specific instructions to study participants about when or how to prepare and take the dose(s) should be described. Include any specific instructions or safety precautions for administration of the study intervention. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration.

State any special precautions or warnings relevant for agent administration (e.g., incompatibility of agent with commonly used intravenous solutions, pre-medications, hydration, use of in-line filter, whether any monitoring of vital signs during or shortly after treatment is required, etc.). If treatment will be self-administered (i.e. oral drug or self-injection), please reference any subject tools that will be implemented (study medication diary, subcutaneous injection instruction sheets, questionnaires etc.); remember to submit all materials that are given to patient to IRB for approval. Also state how delayed, missed, interrupted, or vomited doses should be handled.

* + For injectables include: information on flushing the line, need for special tubing like DEHP free tubing, need for in-line filter [if applicable], whether central line is required, whether the drug is a vesicant, and extravasation precautions [if applicable]
  + For oral medication include administration in relation to food

## Toxicities and Dosing Delays/Dose Modifications

Include information on dose delays or modification per the protocol design, dosing regimen. If using a commercially available drug product, you should be following the label instructions for dosing delays and or dose-modifications.

*Example text provided as a guide, customize as needed:*

{Each subject will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Dose adjustments should be made according to the system showing the greatest degree of toxicity.}

If applicable, the protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count). Address dose modifications for specific abnormal laboratory values of concern or other adverse events (AEs) that are known to be associated with the planned study intervention. The protocol must state explicitly the dose-limiting effects that are anticipated. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.

If there are multiple agents being used in the study, provide a detailed description of toxicity grades and method of dose modification for all agents. In the event that more than one study agent could be responsible for a given toxicity, address in what order each agent should be modified/delayed and provide justification (if available). You may also want to refer reader to the appropriate section in the protocol that contains more detailed information on the potential adverse events and risks associated with each agent (either in Section 1.2,1.3 or 9.0). All treatment modifications should be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose (e.g., mg/m2, mcg/kg, x mg, etc.). Please also address how many missed days of treatment or missed cycles warrants removal of the subject from the study. If subjects may remain on study after missed days or cycles, please specify when treatment under study may resume. For FDA approved drugs dosing delays and dose modifications should be consistent with the package labeling.

You may also want to consider breaking out your dose modification schema for hematological versus non-hematological criteria. Use of a table format is recommended if applicable.

*Example text provided as a guide, customize as needed:*

*Example 1 Hematological Toxicities for Single Agent*

Table 2. Hematological Toxicity Dose Reductions for [Agent A]

|  |  |  |
| --- | --- | --- |
| **ANC** | **Platelets** | **Action** |
| ≥ 1,500/µL or | >100,000/µL | None. |
| 1000-1499/µL or | 75,000-99,000/µL | * 1st Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. * 2nd Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. * 3rd Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. * 4th Occurrence: Discontinue protocol therapy. |
| 500-999/µL or | 50,000-74,000/µL | * -1st Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. * -2nd Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. * -3rd Occurrence: Discontinue protocol therapy. |
| <500/µL or | <50,000/µL | -1st Occurrence: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/L. Restart next treatment at TBD dose. -2nd Occurrence: Discontinue protocol therapy. |

*Example 2 Non-hematological Toxicities (multiple agents)*

Table 3. Non-Hematological Toxicity Dose Reductions for [Agent A, B, and C]

|  |  |  |  |
| --- | --- | --- | --- |
| **Toxicity** | **Agent A** | **Agent B** | **Agent C** |
| AST and/or ALT >ULN to <3xULN | No change from original starting dose (Note any exceptions here and address in text) | No change from original starting dose (Note any exceptions here and address in text) | No change from original starting dose (Note any exceptions here and address in text) |
| AST and/or ALT > 3xULN to <5xULN | Hold until resolved to ULN, then reduce to TBD dose | Hold until resolved to ULN, then reduce to TBD dose | Hold until resolved to ULN, then reduce to TBD dose |
| AST and/or ALT >5xULN | Remove subject from trial | Remove subject from trial | Remove subject from trial |

*Example 3 Non-hematological Toxicities (separate table for each agent)*

Table 4. Non-Hematological Toxicity Dose Reductions for [Agent A]

|  |  |
| --- | --- |
| **Event** | **Action** |
| AST and/or ALT >ULN to <3xULN | None |
| AST and/or ALT > 3xULN to <5xULN | Hold dose until bilirubin is down to <1.5xULN and decrease dose to TBD\_ |
| AST and/or ALT >5xULN | Discontinue treatment |

## Concomitant Medications/Treatments

List all relevant concomitant drugs and/or treatments that are prohibited including information on interacting drugs and cytochrome P450 interactions.

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria. If any medications may be used, but only with caution, please address that in this section.

## Other Modalities or Procedures

If applicable, provide a detailed description of any other modalities or procedures (e.g., counseling, surgery diet) used in the addition to study drug treatment. Please distinguish between those modalities that comprise standard of care, and those under investigation within your protocol.

## Duration of Therapy

This section should unambiguously define the duration of therapy and reasons for ending protocol therapy.

*Example text provided as a guide, customize as needed:*

{In the absence of treatment delays due to adverse events, treatment may continue for [XX weeks] or until one of the following criteria apply:

* + Disease progression as defined in Section 7.0
  + Inter-current illness that prevents further administration of treatment
  + Unacceptable adverse event(s)
  + Subject voluntarily withdraws from treatment OR
  + General or specific changes in the subject’s condition render the subject unacceptable for further treatment in the judgment of the investigator}

## Off Treatment Criteria

*Example text provided as a guide, customize as needed:*

{Subjects will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending protocol therapy and the date the subject was removed from treatment. All subjects who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.}

## Duration of Follow-Up

Include information regarding follow-up, for example, “Subjects will be followed for [time frame] after removal from treatment or until death, whichever occurs first. Subjects need to be followed for adverse events for at least 30 days after the last dose of study drug. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event”.

For Phase I studies, subjects are usually “off study" at 30 days from last treatment. Follow-up in Phase II studies will vary (e.g., 2 to 5 or even 10 years or more) depending on whether subjects are followed for a survival endpoint. Please think this through carefully as following subjects until death may require considerable resources, and may not be necessary. Please also state the nature and frequency of follow-up (e.g., visits every 3 months, by phone call every 6 months, etc.).

## Off Study Criteria

*Example text provided as a guide, customize as needed:*

{Subjects can be taken off 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 from study will be documented and may include:

1. Subject withdraws consent (termination of treatment and follow-up);
2. Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
3. Subject is unable to comply with protocol requirements;
4. Treating physician judges that continuation on the study would not be in the subject’s best interest;
5. Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
6. Lost to Follow-up. If a research subject cannot be located for 2 years, the subject may be considered “lost to follow-up.” All attempts to contact the subject during the two years must be documented;
7. Termination of the study by The University of Michigan, Sponsor, or the Food and Drug Administration (FDA);
8. Subject completes protocol treatment and follow-up criteria.

## Subject Replacement

Include guidelines describing when and how enrolled subject may be replaced in the study or state that subjects will not be replaced.

# STUDY PROCEDURES AND EFFICACY ASSESSMENT

## Study Procedures and Efficacy Assessments

List and describe all study procedures and evaluations to be done as part of the study to support the determination of feasibility, safety and/ or efficacy, as per the primary and secondary, and any exploratory objectives, outlined in this protocol, making sure not to introduce any inconsistencies in categorization of outcome measures from that listed in Section 2. 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. Include the procedures for administering the study intervention and follow-up procedures after administration, as well as any specifics about subsequent follow-up visits, and unscheduled visits. Also, note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully. This section should match Section 6.3. Avoid duplications that can lead to inconsistencies.

For participants that may discontinue or withdraw early, it is important to capture the rationale during the final visit. See Section 5.8, Off Study Criteria, for details.

Note that the protocol should provide a high-level discussion of all procedures, whereas detailed information can be further provided in a Manual of Procedures (MOP) or Standard Operating Procedures (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, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in Section 6.3, Time and Event Table and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.

This section may include a list and description of the following procedures/evaluations, as applicable:

* Physical examination (e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination. Include exams to assess efficacy.
* 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, along with any specific preparation that is required of the research subject (e.g. fasting blood draw, clean catch UA, etc.) 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 investigational 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., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA 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 section with detailed discussion in the study’s MOP. The discussion for each assay should include whether any laboratory tests are investigational or are commercially available.
* Administration of questionnaires or other instruments for subject-reported outcomes, such as a daily diary or surveys. If you are planning to utilize a validated instrument or questionnaire, please obtain appropriate permissions prior to use for your study.
* 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 participant (e.g., radiographic or other imaging or laboratory evaluations). Address when endpoints will be assessed with respect to dosing of rescue medication, if applicable.

## Safety/Tolerability

Analyses will be performed for all subjects having received at least one dose of study drug (See Section 8.0). Include exams and tests to assess safety.

## Time and Events Table

List the specific day or days if appropriate. Ensure that the table reconciles with study objectives, eligibility criteria, and assessments listed in Section 6.1 and 6.2. Be sure to include any +/- windows for study events. Consider allowing flexibility to conduct phone or virtual visits and assessments, when possible.

*Example text provided as a guide, customize as needed:*

Table 5. Time and Events

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Visit number |  |  |  |  |  |  |
| Visit Description | Screening | Baseline | Monitoring | Monitoring | Off Treatment | Follow-Up |
| Time point | Day -30 to 0 | Day 0 | Month 1 | Month 3 |  | 3 months post Off Treatment |
| Visit Window | 30 days | NA | +/- 3 days | \_+/- 7 days | +/- 14 days | +/- 14 days |
| Informed Consent | X |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |
| Eligibility | X | X |  |  |  |  |
| History | X |  |  |  |  |  |
| Physical Exam | X | X | X | X | X |  |
| Height a and Weight | X | X | X | X |  |  |
| Vital Signs b | X | X | X | X | X |  |
| Dental Exam | X |  |  |  |  |  |
| Pregnancy Test c | X |  |  |  |  |  |
| Serum Chemistry d | X | X | X | X | X |  |
| CBCe | X | X | X | X | X |  |
| <Specify other required labs> |  |  |  |  |  |  |
| Urinalysis | X |  |  |  | X |  |
| Chest x-ray | X | X |  |  | X |  |
| ECG | X |  | X |  | X |  |
| Radiology/Imaging Assessment | X |  | X |  | X |  |
| QOLf | X |  | X |  | X |  |
| Include Correlative Procedures (if applicable) | X |  |  |  | X |  |
| Concomitant Medication Review | X | X | X | X | X |  |
| Randomization |  | X |  |  |  |  |
| Study Intervention |  | X | X |  |  |  |
| Other Assessments (immunology assays, pharmacokinetics) (please select appropriate visits) |  |  |  |  |  |  |
| Drug Adherence Assessment |  |  | X | X | X |  |
| Subject Diaries |  |  | X | X | X |  |
| Adverse Events | X | X | X | X | X | X |

\*Include any necessary notes detailing specifics of procedures outlined in table.

1. Height is only measured and recorded at screening
2. Temperature (specify route), blood pressure, heart rate, respiratory rate
3. Serum pregnancy test (women of childbearing potential) (specify serum and/or urine)
4. (specify labs)
5. (specify labs)
6. (specify tests here or refer to protocol Section that provides details)

# CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to indicate if submission of samples for correlative studies is mandatory/optional. Also, indicate in this section if you plan to do any QOL questionnaires. Provide justification and information about the questionnaires. Some specific information may be included in MOP.

## Sample Collection Guidelines

Describe what kind of samples will be collected and what containers/tubes will be used. You must include samples to be collected within your protocol; however, specific processes (i.e. containers/tubes to be used) may be listed here or within your laboratory manual or MOP.

*Example text provided as a guide, customize as needed:*

{Samples will be labeled with the subject’s de-identified study number, collection date, time, and delivered to: [Insert Location/Address]}

Specify instructions for preparation and shipment (types of tubes, spun, frozen, on wet/dry ice or at room temperature, sent by overnight mail or batched, etc.) Add any restrictions on specimen receiving times (e.g., after hours, weekends, holidays).

*Example text provided as a guide, customize as needed:*

Specimens should be spun at 3000 rpm for 10 minutes, and plasma transferred to a 7mL tube for shipment. A minimum of 3mLs per sample is required. Store between 0-6 degrees C until shipment. Pack specimens on wet ice. Send shipments Monday-Thursday via FedEx.

Specify the collection time points.

*Example text provided as a guide, customize as needed:*

{[Sample] will be collected at the following time points (+/- window):

* (Within 28 days) prior to study treatment.
* On Day 0
* On Day 30 (+/- 1 day)
* etc.

## Assay Methodology

Mention any special assays that are used to analyze samples in the protocol. Include the assay name and company and specify whether the assay is FDA-approved or cleared.

## Specimen Banking

*Example text provided as a guide, customize as needed:*

{Subject samples collected for this study will be retained at [specify location here]. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University policy governing tissue sample collection, ownership, usage, and disposition within all UMMS research repositories.

http://msa.med.umich.edu/policies/governing-tissue-sample-collection-ownership-usage-disposition-within-all-umms-research}

# ADVERSE EVENTS

## Experimental Therapy

*Example text provided as a guide, customize as needed:*

{For the most recent safety update, please refer to the current Investigator’s Brochure or Study Agent Label.}

## Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study [treatment administration or intervention] through [30] days after the last [dose of study treatment or study intervention]. Any serious adverse event that occurs more than [30] days after the last study [treatment or intervention] and is considered related to the study [treatment or intervention] must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

* Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
* There is satisfactory explanation other than the study [treatment or intervention] for the changes observed; or
* Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study [treatment administration or intervention] is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study [treatment administration or intervention] through [30] days following the last [dose of the study treatment or study intervention] must be recorded as an adverse event in the subject’s source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study [treatment or intervention].

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the subject begins study [treatment or intervention] is also considered an adverse event.

Review of AE and SAE data will be performed on a routine basis by the Independent Medical Monitor and the Data and Safety Monitoring Board (DSMB) as described in section 14.0.

## Definitions

### **Adverse Event**

**Adverse Event Definition**

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Consider the addition of the following language

*Example text provided as a guide, customize as needed:*

{Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

* Symptoms of the original or targeted disease are not to be considered adverse events for this study. The following symptoms are indicative of underlying disease [list name of disease to be studied here] and will not be reported as adverse events (unless the event is considered serious):
  + [List of symptoms of targeted disease here]
* Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.}

### **Serious Adverse Event**

An adverse event is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

* Death  
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
* A life-threatening adverse event  
  An adverse even is considered ‘life-threatening’ if, in the view of either the investigator [or sponsor], its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
* Inpatient hospitalization or prolongation of existing hospitalization for > 24 hours.
* A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
* A congenital anomaly/birth defect
* Important medical event  
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event.” Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the subject’s medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

### **Expected Adverse Events**

An adverse event (AE) is considered “expected” if:

* For approved and marketed drugs, those adverse events are described in the approved Prescribing Information (Label).
* For investigational new drugs, those adverse events are described in the Investigator’s Brochure.
* In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

### **Unexpected Adverse Event**

An adverse event (AE) is considered “unexpected” if it is not described in the Prescribing Information, Investigator’s Brochure, in published medical literature, in the protocol, or in the informed consent document.

## Adverse Event Characteristics

### Terms and Grading

The severity or grade of an adverse event may be measured using the following definitions:

**Mild:**  Noticeable to the subject, but does not interfere with subject’s expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

**Moderate:** Interferes with the subject’s expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

**Severe:** Extremely limits to the subject’s daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve and may be life-threatening of fatal.

### Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE is clearly related to the study treatment/intervention.

Probable – The AE is likely related to the study treatment/intervention.

Possible – The AE may be related to the study treatment/intervention.

Unlikely – The AE is doubtfully related to the study treatment/intervention.

Unrelated – The AE is clearly NOT related to the study treatment/intervention.

## Serious Adverse Event Reporting Guidelines

### The Sponsor Investigator must be notified within one business day of study team’s knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment/intervention.

### The investigator must report all events meeting the criteria and definition of a serious adverse event as per the local IRB reporting requirements. All (or specify which SAEs) should be reported to Coordinating Center/Study Supporter. Serious Adverse Events will be reported to the University of Michigan Coordinating Center, if applicable, within one business day of the study team awareness. SAEs should be reported to the Study Supporter [add name if applicable or delete the supporter information] within [xx] days of the study team’s awareness.

*Example text provided as a guide, customize as needed:*

{For multi-site studies, all serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Sponsor Investigator and also to the Coordinating Center and Study Supporter [add supporter name if applicable or delete the supporter information]. All SAEs and UPs must be reported to the Coordinating Center within one business day of the study team awareness. They should be also reported to the Study Supporter [add supporter name if applicable or delete the supporter information] within [specify] of first awareness of the event.

Follow-up information for SAE and/or UPs should also be reported the Sponsor Investigator and Coordinating Center within one business day of receipt of the information by the investigator.

Participating sites should report all SAEs and UPs to their local IRB per current local institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within five business days of review of the information by the Sponsor Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug and unexpected. For IND/IDE trials, the Coordinating Center will be responsible for reporting of events to the supporter (if required by the supporter, add reporting requirements received from the supporter to here or delete).}

For IND/IDE trials: The [UM Coordinating Center or the Sponsor Investigator] will coordinate with the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Assistance Program (MIAP) office for the reporting of any and all IND safety reports to the FDA as per the requirements outlined in 21 CFR312.32. This includes reporting of all Serious Adverse Events (SAEs) that are both unexpected and related to the drug as soon as possible, but in no case later than 15 calendar days after the Sponsor Investigator determines that the information qualifies for reporting. If the unexpected and related SAE is either fatal or life-threatening, then the SAE must be reported as soon as possible but in no case later than 7 calendars days after the Sponsor Investigator’s initial receipt of the information. A summary of all non-expedited safety reports will be submitted in the annual report.

## Reporting of Unanticipated Problems

There are types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), an unanticipated problem is defined as a serious problem that has implications for the conduct of the study (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).

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience, or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to the IRB /FDA.

## Reporting of Pregnancy

Include content in this section if applicable, otherwise note as not-applicable. Pregnancy is not an adverse event, but some studies will require unique considerations if pregnancy was to occur during the study.

State the study’s pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the Coordinating Center, the IND or IDE sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).

## Unblinding Procedures

While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject’s safety. This section should clearly describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject’s source document. For investigators, other than the Sponsor Investigator, state that the investigator must inform the Sponsor Investigator of all subjects whose treatment was unblinded and describe the timelines for such reporting. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline requirements for investigator reporting of SAEs, (e.g., notification of Sponsor Investigator within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

## Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, rules should be developed that clarify the circumstances and procedures for interrupting or stopping the study with input from a statistician.

# DRUG INFORMATION

Include all drugs used in the study in this section.

## [Agent A]

For each drug provide the following:

* Other names for the drug: (include the chemical name (IUPAC name) and molecular formula, if available.
* Description: (For injectables include vial size in mg or concentration in mg/mL and number of mLs per vial. For oral medications include capsule/tablet size and number of units per bottle).
* Classification - type of agent:
* Mode of action:
* Pharmacokinetics: Briefly describe key pharmacokinetics parameters in humans, if available. At a minimum, include information on absorption (for oral drugs), half-life, and elimination (metabolism, if applicable).
* Contraindications: Include contraindications here and also address in the Exclusion Criteria, Treatment Plan, and Concomitant Medications/Treatments, if applicable.
* Special Warning and Precautions: Include warnings and precautions here and also address in the Exclusion Criteria, Treatment Plan, and Concomitant Medications/Treatments, if applicable.
* Side Effects: A brief summary of the adverse events most likely to occur in this study and associated with this agent should be inserted here. For commercially available drugs, refer the reader to the agent’s label and Investigator’s Brochure, if available, for a comprehensive list of adverse events.
* Drug Interactions: Briefly list interacting drugs. Make sure that these are consistent with the interactions listed in the selection criteria and concomitant medications sections.
* Storage and Stability: include specific temperature range, need to protect from light, if applicable. For drugs provided by a supporter or purchased using study funds and managed by the Research Pharmacy include the following statement:   
  [Agent name] must be stored in a secure, limited access area.
* Preparation Dispensing, and Labeling:   
  For injectables or for compounding liquid formulations include:
  + Reconstitution instructions including diluent name, diluent volume, final concentration, storage, and stability (expiration information).
  + If the drug needs to be further diluted, include diluent name, diluent volume or final concentration range, storage conditions and stability (expiration information).
  + Incompatibilities

For oral medication or prepackaged drugs, include:

* + Whether repackaging is allowed (e.g., counting into prescription bottle, need to used high-density polyethylene [HDPE] bottles)
  + Whether the drug is dispensed by bottle/kit number.
  + If the drug bottles include tear off labels, include instructions on handling the tear-off labels (e.g., attach to label pages in the pharmacy, attach to the CRFs).

If blinding is required, indicate how blinding is achieved.

Labeling: The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

* Availability: (e.g., “commercially available”, “provided by supporter”; specify if provided free of charge as this has implications for the consent form).

If the drug is provided by a supporter, indicate if commercial (lawfully marketed) or investigational drug supply will be provided.

* If the drug is provided by a supporter include drug ordering information (e.g., drug order form, contact information). If a MOP or a Pharmacy Manual is provided for the study, this information can be included in the Pharmacy Manual.
* If the drug is purchased using study funds (e.g., drug used for the control arm), indicate it here.
* If the drug is provided by a supporter or purchased using study funds include the following statement: Under no circumstance will the study medication [Agent name] be used other than as directed by the protocol.
* Return and Retention of Study Drug:  
  Please include instructions on unused and used (empty vials or drug that is returned by subjects) drug disposition (return to supporter or destruction on site). If drug is to be returned to the supporter, include address and supporter/Pharma/collaborator contact here or refer to the MOP or Pharmacy Manual, if available. If remaining/expired/used or returned drug is to be destroyed on site, please state that the drug destruction is according to the institution standard operating procedure for drug destruction and that destruction will be documented on the drug accountability logs.
* Drug Accountability:  
  Please include the following language for drugs that are provided by a supporter or purchased by study funds and for IND drugs:

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug [Agent name]. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

If the UM Research Pharmacy is managing the drug supply and accountability logs you may include the following language:

The University of Michigan Research Pharmacy will manage the drug supply and accountability records according to the institution standard operating procedures.

# STATISTICAL CONSIDERATIONS

Here is where you describe the statistical aspects of the protocol in detail. This section should be written in coordination with the study statistician. It should precisely describe what results will be reported and how those results were calculated.

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of all analyses. The SAP will be finalized prior to database lock.

## Study Design/Study Outcome Measures

Please specify the study design. State clearly key design aspects, such as; is the study retrospective or prospective, blinded, randomized, single or multi-centered? Define all study outcomes and either leave out any language categorizing them as primary, secondary or exploratory, or make certain that is matches the categories used in Section 2.

If there are stopping rules for either safety or efficacy, describe the reasoning behind them, and how they might cause a suspension of study enrollment until a safety review has been convened. Show operating characteristics of the stopping rules (e.g., if true toxicity rate is \_%, \_% of trials will be stopped early). Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

For dose finding trials, model based designs such as the Continual Reassessment Method are preferred to algorithmic designs such as the 3+3 design. The reasons for this preference include better selection of the MTD and an increased proportion of subjects treated near the MTD (Garrett-Mayer, Clin Trials, 2006). The operating characteristics for model based designs should be presented, with the statistical assumptions necessary for their creation stated explicitly.

## Sample Size and Accrual

Justification for the number of subjects to be used in the study must be given. Please state precisely what the statistical power (or precision when the primary aim involves estimation) and sample size considerations are for the primary outcome measure and objective of the proposed study. The total accrual, the expected accrual rate and all relevant assumptions should be stated explicitly. How these numbers were calculated, including the software used, should be included. A reviewer should be able to duplicate the calculations given the information provided. Include anticipated number to be screened and accrual rate.

Define an evaluable subject (i.e., after how many doses of study drug/therapy is the subject considered evaluable for one or more endpoints).

While power calculations are often not performed for pilot studies, some rationale for running a pilot study should be given. Valid reasons include feasibility and obtaining preliminary data when none is available.

## Data Analyses Plan

Please describe in detail how each objective (particularly the primary objective) will be addressed by a particular data analysis plan and what data (from which subjects) will be included. Specify sub-populations of interest where applicable (e.g., intent-to-treat vs. per-protocol population). This is where the details of each data analysis plan (for each objective) are given – stating what statistical methods will be used, and under which assumptions. Every objective, every study outcome should have a plan associated with it. CT.gov requires a statistical plan for ALL secondary outcomes as well as primary outcomes. Further details concerning safety and/or pharmacokinetics, may be given here as well.

# DATA AND SAFETY MONITORING

All clinical trials must include a protocol specific data and safety monitoring plan (DSMP) and procedures for its implementation.

The protocol specific DSMP should include a description of the procedure that will be utilized to ensure data integrity and protocol adherence (e.g., scheduled meetings between the PI and the study coordinator) and the procedure for independent monitoring of trial safety.

Based on trial type, the study may have a DSMB, a Medical Monitor and/or an independent monitor. Include information on this activity here. Specific details of review/responsibilities should be contained within a separate document such as a DSMB Charter and/or Medical Monitor Expectations Document.

If the protocol is a multi-site trial where the University of Michigan is the coordinating center, investigators should include a plan for a multi-site study in this section.

*Example text provided as a guide, customize as needed:*

{At each site the study team is required to meet at least quarterly to discuss matters related to:

* Enrolment rate relative to expectations, characteristics of participants
* Safety of study participants (Serious Adverse Event & Adverse Event reporting)
* Adherence to protocol (protocol deviations)
* Completeness, validity and integrity of study data
* Retention of study participants

## Data and Safety Monitoring Board (DSMB)

If the study has a DSMB describe the Board below. If a DSMB is not applicable, delete this section:

*Example text provided as a guide, customize as needed:*

{Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including [list expertise]. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined}

## Clinical Monitoring Procedures

If the study has clinical monitoring procedure, include the text provided below. If a this is not applicable, delete this section.

To assure adequate protection of the rights of human subjects, per 21 CFR §312.50, 312.53, this study will be monitored by the University of Michigan Institute for Clinical and Health Research (MICHR). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. An initiation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the Sponsor Investigator.

Monitoring visits may be in the form of a site visit or a review of the site records. During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the MICHR representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. It is expected that the relevant investigational staff be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner.

The established monitoring plan will ensure the quality and integrity of the data through pre- investigation visits and periodic site visits to verify adherence to the protocol, completeness and accuracy of study data and samples collected, proper storage, dispensing and inventory of study medication, and compliance with regulations.Monitoring visits can be conducted onsite or remotely with appropriate electronic documentation provided to the study monitors for review.

# QUALITY ASSURANCE AND AUDITS

## Audits and Inspections

The DSMB can request a ‘for cause’ quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the study staff must immediately inform IRB, Medical School Regulatory Affairs, MIAP, and the Research Pharmacy (if providing study drug).

*Example text provided as a guide, customize as needed:*

{If this is a multisite study, the site investigator must immediately inform the Coordinating Center that such a request has been made.}

## Protocol Deviations

Plans for detecting, reviewing, and reporting deviations from the protocol should be described. A statement should be included to indicate that deviations are not allowed, unless a statement is included in the investigator agreement. Provisions for approval of deviations can be described.

*Example text provided as a guide, customize as needed:*

{A protocol deviation is any noncompliance with the clinical trial protocol, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within [specify number] working days of identification of the protocol deviation, or within [specify number] working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to [specify]. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.}

A report of all deviations from the approved protocol will be provided to the DSMB per the approved DSMB charter. Deviations will be reported to the IRB according to local IRB reporting guidelines.

# REGULATORY

## Food and Drug Administration (FDA)

Prior to study commencement, an Investigator Initiated Investigational New Drug (IND), if needed, will be submitted to the FDA, for review and approval.

## Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed and approved by a properly constituted IRB. Any amendments to the protocol must be reviewed and approved by the IRB.

## Subject Information and Consent

Study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject’s legally appointed representative, if witnessed by a person not involved in the study, mentioning that the subject could not read or sign the documents. No subject can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

It is recommended that the MOP include more information describing the informed consent process. Informed consent is an ongoing process that begins with recruitment and continues through the completion of the study. For more information, visit the IRBMED website: https://research.medicine.umich.edu/our-units/institutional-review-boards-irbmed/informed-consent-assent-templates.

## Assent

If an Assent is not applicable, delete this section:

A reasonable effort will be made to enable the child to understand, to the degree they are capable, what their participation in this study will involve. Include ages for which children are expected to assent. See guidelines here: https://ummsoor.sites.uofmhosting.net/sites/default/files/resource-download/res\_irbmed\_child-assent\_guidelines\_0.pdf

Also include whether assent will be written or verbal only. Finally, if assent will not be obtained, provide justification as to why the subjects are unable to assent.

## Good Clinical Practice

*If the study receives NIH funding include the information below. Otherwise, delete this section*

This study will be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described below:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

# REFERENCES

List all protocol references.

# APPENDICES

Please list and include all relevant appendices in alphabetical order (e.g., Appendix A, Appendix B, etc.)

**Appendix A: Contingency Operation Plan**

The following changes may be implemented and/or adapted without causing a deviation during a public health or civil emergency or restrictions. HOWEVER, the usual protocol parameters must be reinstated when the emergency is over or whenever local authorities and policies permit.

It is important that specific information explaining the basis for missing data be recorded in the case report forms (indicating the relationship to the event/restrictions, as applicable).

Consider listing protocol modifications in case of contact or travel restrictions (i.e., contact restrictions during COVID-19) by addressing the following:

* + 1. Disease Testing:

Include if applicable.

*Example text provided as a guide, customize as needed:*

{Should testing be available/required for a public health or civil emergency or restrictions it is not currently being added to the protocol as part of the screening requirements, but may be done as part of the clinical assessment, as needed during the course of the event/restrictions. During the course of the study, tests/results are to be recorded in the subject’s source documents but are only to be added as an Adverse Event in the electronic case report form (eCRF) should the test yield a positive result.}

* + 1. New subject enrollment

Specify if enrollment will be paused or continue with modification (i.e., patients that require biopsies will not be enrolled).

*Example text provided as a guide, customize as needed:*

{Together with the study supporter [insert name], the Sponsor Investigator will evaluate the new benefit/risk for subjects on the trial and determine if study enrollment needs to be partially or completely paused.}

* + 1. Study visit schedule

Indicate if phone/virtual visits will be allowed and include a visit window or extend the visit window.

*Example text provided as a guide, customize as needed:*

{The following adjustments will be permissible per clinician/subject discretion and institutional/government allowance:

* Virtual office/clinic visits will be allowed per clinician/subject discretion
* Diagnostic and disease assessments to be scheduled per clinician/subject discretion
* Collection of correlative samples are to be performed per clinician/subject discretion and lab facility capacity/capabilities}
  + 1. Treatment plan

For drug(s) that are administrated in clinic, specify a treatment delay window and a plan to address a delay beyond the allowed window (deviation, or discontinuation) taking into account that some treatment cannot be stopped abruptly.

* + 1. Laboratory testing

Research labs: indicate whether research labs will continue to be collected and/or analyzed.

Safety labs: indicate whether safety labs can be done locally with the results reviewed by the study physician.

*Example text provided as a guide, customize as needed:*

{It may be possible that lab closure is required as a contingency measure during the course of a public health or civil emergency or restrictions. Should that occur:

* Correlative samples will not be collected unless they can be stored
* Patients will be allowed to have safety labs (routine standard of care labs) drawn at a local lab and results will be reviewed by the study physician.}
  + 1. Imaging

Indicate if imaging can be delayed and include a window. Indicate a plan to address a delay beyond the allowed window.

Indicate if imaging can be done locally with the results reviewed by the study physician.

* + 1. Study medications  
       For oral study medications or drugs that are self-administered, indicate if the study drug(s) can be shipped to the subject home and specify that the drug(s) will be shipped via certified temperature-controlled container for overnight delivery with tracking number and delivery signature required.

*Example text provided as a guide, customize as needed:*

{Adjustments for alternate drug dispensing will be permitted by the Supporter [insert name] and Sponsor Investigator, to allow for study medication to be shipped directly to subject’s home, via certified temp-controlled container for overnight delivery, with tracking number and delivery signature required.

* The drug accountability log will be updated, as required, noting direct shipment to subject
* Patients will be contacted to confirm that the drug shipment was received and in good condition and the communication documented in study records and available for monitoring
* Any non-receipt by subject must be reported to study staff immediately so that shipment can be tracked. Any missed dose of study medication is to be managed per protocol.}
  + 1. Follow up  
       Include a window for a follow up visits or assessments
    2. Informed Consent Form (ICF)

Include a plan to notify patients of the changes and if virtual consenting and digital signature will be allowed.

*Example text provided as a guide, customize as needed:*

{Consenting can be done virtually and digital signatures are allowed.

The study staff should communicate all changes to the research plan to the subject, as applicable, and must do so if the changes might affect the subject’s willingness to continue participation in the study. Communication can occur virtually or via an addendum to the informed consent as required by the IRB. If discussed, documentation of the discussion and the subject’s decision to continue/discontinue should be documented in the subject’s record.}

* + 1. Statistical Analytics Plan:

*Example text provided as a guide, customize as needed:*

{Should changes in the contingency operation plan and/or protocol lead to amending the statistical analysis plan for this study, consideration for doing so will include submission and/or consultation with the applicable committees and regulatory agencies for review.

The plan for protocol deviations related to public health or civil emergency or restrictions will be assessed as part of the pre-specified analyses, and statistical procedures for handling these deviations will be addressed in the statistical analysis plan prior to database lock. Revisions to the statistical plan will be updated in the protocol and/or the statistical analysis plan, as required.}

* + 1. Monitoring

Indicate that during national emergency monitoring could be conducted remotely.

*Example text provided as a guide, customize as needed:*

{Planned on-site monitoring visits may not be possible if the restrictions put in place limit travel and/or access to site location. As such, remote monitoring will be performed as necessary to maintain the defined monitoring schedule.}

* + 1. Safety and Protocol Deviation Reporting

*Example text provided as a guide, customize as needed:*

{All safety and protocol deviation reporting for the study remains in place, per protocol requirements. Documentation of required reporting timelines are to be utilized during monitoring.}