**MHC PROTOCOL TEMPLATE v11.28.16**

**HOW TO USE THIS TEMPLATE**

This **template** is a guide designed to assist you in developing a protocol document for an investigator-initiated clinical trial; it should be **tailored according to your study procedures / specifications.**

**General instructional text is provided in blue text boxes throughout this document**:

* When you see this symbol some instructions may also be here , click on it an enter text as directed.
* Text within a blue box that is in Arial font (and in black) indicates that language is being provided for you to copy and paste into your document*, if it is applicable to your study*.
* Language that is NOT in a blue box is language that MUST be present in ALL protocol documents, and must remain in your document as is.
* Instructional text boxes are intended to provide you information on what should be included in a particular section and should be deleted once read and replaced with your information.

**TIPS FOR PREPARING YOUR PROTOCOL DOCUMENT**

* **Study Title** - -Include any of the following elements that apply to your study:
* **Phase** (phase I, phase II, etc.)
* **Design** (randomized, double blind, placebo controlled, etc.)
* **multi-center**
* **investigational drug**, and **target diseases and stage** (e.g. advanced, relapsed, refractory)

**EXAMPLE TITLE**: A phase II, randomized, double-blind, placebo-controlled, multi-center study of the effects of XXXX on infarct size in subjects with diabetes mellitus presenting with acute myocardial infarction.

* Ensure the headings and content remain in the order provided in this template.
* Be mindful of redundancy and repetitive language, as this can lead to an unnecessarily lengthy document.
* Ensure the final protocol document is in Arial 11 pt. font; and in black
* Carefully review the final protocol document to ensure ALL information regarding your project is relayed accurately.

**PRIOR TO SUBMISSION TO THE IRB:**

* **PROOFREAD YOUR DOCUMENT FOR SPELLING, GRAMMAR, AND FORMATTING ERRORS**
* **REMOVE ALL INSTRUCTIONAL TEXT BOXES BY CLICKING ON THE BORDER OF THE BOX AND HITTING THE DELETE BUTTON**

**Insert full study title**

**Principal Investigator:** PI Name

**Address:** PI Address

**Phone:** PI Phone #

**Email:**  PI email

**Protocol version: This should be the final date**

**Provide requested information for EACH of the following, as applicable**, **then copy and paste into your document. For any non-local personnel, include the name of their institution.**

**Sub-Investigator(s):** Sub-I Name

**Biostatistician:** Name

l

**Complete any of the following that apply to your study, then copy and paste into your document:**

**Study Drug/Study Device: Generic name followed by marketed name**

**IND/IDE Number: IND / IDE#**

**IND/IDE Holder Name: IND / IDE Holder Name**

**Funding Source**: **Also provide grant #, if applicable**

**NOTE: List ALL sources of funding for investigational agent / device (from sponsor, etc.)**

**Amended: Date revised**

**TO REMOVE INSTRUCTIONAL TEXT BOXES:**

**Click on the border of the box and hit the delete button**

**Biostatistician:** Name

l

**Complete any of the following that apply to your study, then copy and paste into your document:**

**Study Drug/Study Device: Generic name followed by marketed name**

**IND/IDE Number: IND / IDE#**

**IND/IDE Holder Name: IND / IDE Holder Name**

**Funding Source**: **Also provide grant #, if applicable**

**NOTE: List ALLsources of funding for investigational agent / device (from sponsor, etc.)**

**Amended: Date revised**

**TO REMOVE INSTRUCTIONAL TEXT BOXES:**

**Click on the border of the box and hit the delete button**

**Provide requested information for EACH of the following, as applicable**, **then copy and paste into your document. For any non-local personnel, include the name of their institution.**

**Sub-Investigator(s):** Sub-I Name

**Biostatistician:** Name

l

**Complete any of the following that apply to your study, then copy and paste into your document:**

**Study Drug/Study Device: Generic name followed by marketed name**

**IND/IDE Number: IND / IDE#**

**IND/IDE Holder Name: IND / IDE Holder Name**

**Funding Source**: **Also provide grant #, if applicable**

**NOTE: List ALLsources of funding for investigational agent / device (from sponsor, etc.)**

**Amended: Date revised**

**TO REMOVE INSTRUCTIONAL TEXT BOXES:**

**Click on the border of the box and hit the delete button**

 **document. For any non-local personnel, include the name of their institution.**

**Sub-Investigator(s):** Sub-I Name

**Biostatistician:** Name

l

**Complete any of the following that apply to your study, then copy and paste into your document:**

**Study Drug/Study Device: Generic name followed by marketed name**

**IND/IDE Number: IND / IDE#**

**IND/IDE Holder Name: IND / IDE Holder Name**

**Funding Source**: **Also provide grant #, if applicable**

**NOTE: List ALLsources of funding for investigational agent / device (from sponsor, etc.)**

**Amended: Date revised**

**TO REMOVE INSTRUCTIONAL TEXT BOXES:**

**Click on the border of the box and hit the delete button**

**NOTE: All protocol documents should contain a table of contents (TOC) for ease of navigation.**

**\*\*\*REMEMBER TO TAILOR THE TOC TO YOUR PROJECT\*\*\***

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 7

STUDY SCHEMA 7

STUDY SUMMARY 7

1.0 BACKGROUND AND RATIONALE 8

1.1 Disease Background 8

1.2 Study Agent(s) Background and Associated Known Toxicities 8

1.3 Other Agents 8

1.4 Rationale 8

1.5 Correlative Studies 8

2.0 STUDY OBJECTIVES 9

2.1 Primary Objectives 9

2.2 Secondary Objectives 9

2.3 Exploratory Objectives 9

2.4 Endpoints 9

3.0 PATIENT ELIGIBILITY 10

3.1 Inclusion Criteria 10

3.2 Exclusion Criteria 11

4.0 TREATMENT PLAN 11

4.1 Treatment Dosage and Administration 11

4.2 Toxicities and Dosing Delays/Dose Modifications 12

4.3 Concomitant Medications/Treatments 14

4.4 Other Modalities or Procedures 14

4.5 Duration of Therapy 14

4.6 Duration of Follow Up 15

4.7 Removal of Patients from Protocol Therapy 15

4.8 Patient Replacement 15

5.0 STUDY PROCEDURES 15

5.1 Screening/Baseline Procedures 15

5.2 Procedures During Treatment 16

5.3 Follow-up Procedures 17

5.4 Time and Events Table 17

5.5 Removal of Subjects from Study 17

6.0 RESPONSE CRITERIA……………………………………………………………………………18

6.1 Safety/tolerability .18

7.0 ADVERSE EVENTS 18

7.1 Experimental Therapy 18

7.2 Adverse Event Monitoring 18

7.3 Definitions 19

7.4 Steps to Determine If an Adverse Event Requires Expedited Reporting 20

7.5 Reporting Requirements for Adverse Events 20

7.6 Unblinding Procedures 21

7.7 Stopping Rules 22

8.0 DRUG/DEVICE INFORMATION 22

8.1 Agent/Device 22

9.0 CORRELATIVES/SPECIAL STUDIES 23

10.0 SPECIMEN COLLECTION 23

10.1 Sample Collection Guidelines 23

10.2 Assay Methodology 23

10.3 Specimen Banking 24

11.0 STATISTICAL CONSIDERATIONS 24

11.1 Study Design/Study Endpoints 24

11.2 Sample Size and Accrual 25

11.3 Data Analyses Plans 25

12.0 STUDY MANAGEMENT 25

12.1 Conflict of Interest 25

12.2 Institutional Review Board (IRB) Approval and Consent 25

12.3 Data Management and Monitoring/Auditing 26

12.4 Adherence to the Protocol 26

12.5 Modifications to the Protocol 26

12.6 Record Retention 27

12.7 Obligations of Investigators 27

13.0 REFERENCES 27

14.0 APPENDICES 27

**Providing a list of abbreviations and acronyms is a helpful guide for those not familiar with your project.**

# LIST OF ABBREVIATIONS

Some common examples include:

|  |  |
| --- | --- |
| 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 |
| CR | Complete Response |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| DSMB | Data and Safety Monitoring Board |
| ECOG | Eastern Cooperative Oncology Group |
| H&P | History & Physical Exam |
| HRPP | Human Research Protections Program |
| IV (or iv) | Intravenously |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| p.o. | per os/by mouth/orally |
| PR | Partial Response |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SPGT | Serum Glutamic Pyruvic Transaminase |
| WBC | White Blood Cells |
|  |  |
|  | **ONCE YOU HAVE COPIED AND PASTED ALL NECESSARY VERBIAGE - DELETE THIS BOX** |

#

# STUDY SCHEMA

**Including a concise study schema is not required, but we suggest that you include one. It should represent the design of your study and a brief description. For example:**



**NEXT: Complete the Study Summary table below.**

**Replace instructional text** (in blue) **with information specific to your study design / plan.**

# STUDY SUMMARY

|  |  |
| --- | --- |
| Title | Full study title |
| Short Title | Acronym for your study (should match short title provided on clinicaltrials.gov application |
| Protocol Number | Protocol # used for this study (IRB# or sponsor#) |
| Phase | Clinical study phase (Phase 1, 2, 3 or 4) |
| Methodology | Design attributes (single blind, double blind or open label; randomized, placebo or active placebo control; cross-over design, etc.). |
| Study Duration | Estimated duration for the main protocol (from start of screening to last subject processed and finishing the study) |
| Study Center(s) | Single-center or multi-center (list number of projected centers to be involved) |
| Objectives | Brief statement of primary study objectives |
| Number of Subjects | Number of subjects projected for the entire study (all study sites) |
| Diagnosis and Main Inclusion Criteria | Note the main clinical disease state under study and the key inclusion criteria (i.e., not the entire list that will appear later in the protocol, rather only the key inclusion criteria) |
| Study Product(s), Dose, Route, Regimen | List generic name for study drug(s) (marketed name may be used if name-brand is used in the study) and/or description of non-drug therapy (i.e., radiation, surgery, etc.); include dose, route and regimen |
| Duration of administration | Total duration of drug product administration  |
| Reference therapy | Note if there is a standard reference therapy against which the study product is being compared, or if the reference is a placebo |
| Statistical Methodology | A very brief description of the main elements of the statistical methodology to be used in the study (be as concise as possible) |
|  |  |

# BACKGROUND AND RATIONALE

## Disease Background

Provide disease background information relevant to your study. This section should include:

* Current standard of care
* Treatment issues or controversies
* Justification for the investigational therapy or approach.

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

##

Provide relevant background information about the study agents / devices and any known toxicities:

* Summary of findings from **non-clinical** in vitro / in vivo studies that have potential clinical significance, including mechanism of action, pharmacokinetics and safety. (Particularly important for investigational agents, **may not** be necessary for commercially available drugs, and/or drugs with sufficient clinical data).
* Summary of relevant **clinical studies** that provide background for your study. Include safety information, the rationale for the starting dose(s), information on clinical pharmacokinetics, and major route(s) of elimination. If available, include information on the metabolism of the agent(s) in humans and address any potential for drug interactions.

## Other Agents/Devices

##

Provide background information on any agents and/or treatments in this study that were not already described in section 1.2. Include the following information for each:

* Basis for inclusion in this study
* Mechanism of action
* Information to support safety issues
* Rationale for the proposed starting dose scheme (f applicable)

**NOTE**: Detailed information on adverse events / potential risks for commercially available agents/devices should be provided in Section 8.0 (Drug/Device Information).

**\*\*THIS SECTION MAY BE OMITTED IF IT IS NOT RELEVANT TO YOUR STUDY\*\***

## Rationale

##

**Provide**:

* Basis for conducting the study
* Study design

Justification of the study endpoints

Link the disease background with the study agents under evaluation, including the rationale for the study population, particularly if focusing on a subset within the disease population (e.g., relapsed or elderly patients).

## Correlative Studies

Provide background information on any planned correlative studies including their biological rationale and hypothesis.

**\*\*THIS SECTION MAY BE OMITTED IF IT IS NOT RELEVANT TO YOUR STUDY\*\***

# STUDY OBJECTIVES

Describe primary and secondary objectives of the study, using the following guidelines:

* Statement of purpose: to describe, to measure, to compare, to estimate
* General purpose: efficacy, safety, immunogenicity, pharmacokinetics
* Specific purpose: dose-response, superiority to placebo

## Primary Objectives

Describe the primary objective of your study. Ensure each objective has a separate number (i.e. 2.1.1, 2.2.2, etc.).

**Example of a primary objective for a Phase I trial:**

2.1.1 “To determine the dose-limiting toxicity (DLT) and maximally tolerated dose for (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable).”

**NOTE**: ClinicalTrials.gov strongly encourages having only 1 primary objective and endpoint.

## Secondary Objectives

Describe the secondary objectives of your study. Ensure each objective has a separate number (i.e. 2.2.1, 2.2.2, etc.).

**Examples of typical secondary objectives for a Phase I trial:**

2.2.1 “To describe the adverse events associated with (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable)”

2.2.2 “To describe the pharmacokinetics associated with (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable)”

2.2.3 ”In patients with measurable disease, to describe any preliminary evidence of anti-tumor activity by assessment of objective response as determined by (insert response criteria) in patients with (insert tumor type, etc.)”

## Exploratory Objectives

Describe any exploratory objectives for your study.Ensure each objective has a separate number (i.e. 2.3.1, 2.3.2, etc.).

**\*\*THIS SECTION MAY BE OMITTED IF IT IS NOT RELEVANT TO YOUR STUDY\*\***

## Endpoints

Specify endpoints that will be used to answer the primary objective, the secondary objectives and exploratory objectives described above.

**NOTE**: **Include endpoints for all objectives provided in Sections 2.1 - 2.3**

# PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

## Inclusion Criteria

Describe all inclusion criteria for your study. List each criteria individually, as shown below.

**EXAMPLES OF INCLUSION CRITERIA:**

1. Diagnosis/disease status
2. Allowable type and amount of prior therapy
3. Age ≥ 18 years.
4. Performance status
5. Adequate organ and marrow function as defined below:

- leukocytes: ≥ 3,000/mcL

- absolute neutrophil count: ≥ 1,500/mcL

- platelets: ≥ 100,000/mcl

- total bilirubin: within normal institutional limits

- AST(SGOT)/ALT(SPGT): ≤ 2.5 X institutional upper limit of normal

- creatinine: within normal institutional limits

1. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

**3.1.6.1** A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

* Has not undergone a hysterectomy or bilateral oophorectomy; or
* Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).
1. Other study-specific criteria
2. Ability to understand and the willingness to sign a written informed consent.

## Exclusion Criteria

Describe all exclusion criteria for your study. List each criteria individually, as shown below.

**EXAMPLES OF EXCLUSION CRITERIA:**

1. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
2. Patients may not be receiving any other investigational agents.
3. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Agent(s) or other agents used in study.
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Patients must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

# TREATMENT PLAN

## Treatment Dosage and Administration

Describe treatment dosage and administration, numbering them individually as shown below:

**4.1.1** For complicated studies (e.g., studies with multiple treatment phases) first provide a summary of the entire treatment plan. This should be a few sentences, which provide a “snapshot” of the treatment plan.

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. State any special precautions or warnings relevant for agent administration such as:

* incompatibility of agent with commonly used intravenous solutions
* necessity of administering agent with food
* pre-medications, hydration, whether any monitoring of vital signs during or shortly after treatment is required, etc.

For self-administered treatments (i.e. oral drug or self-injection):

Include subject tools that will be implemented for administration, such as a study medication diary, injection instruction sheets, etc. This should also include information regarding how missed (or vomited) doses should be handled.

## Toxicities and Dosing Delays/Dose Modifications

Describe toxicities and dosing delays / dose modifications using the guidelines (in red) below.

**NOTE: If you will be including a Time and Events table (recommended) in your protocol, complete the following sentence and copy and paste into beginning of this section**:

Any patient who receives treatment on this protocol will be assessed for the development of toxicity according to the Time and Events in tableClick here to enter text..

Treatment modifications / dosing delays, and the factors predicating treatment modification should be explicit and clear. For Phase I studies, there should be consistency between toxicities which mandate dose reductions, and those events which are considered a DLT.

* **If dose modifications or treatment delays are anticipated** - provide a dose de-escalation schema.
* **If multiple agents are being used in the study** - provide a detailed description of toxicity grades and method of dose modification for each agent separately.
* **If more than one study agent could be responsible for a given toxicity** -indicate the order in which each agent should be modified/delayed and provide justification (if available).
* Express treatment modifications as a specific dose or amount rather than as a percentage of the starting or previous dose.
* Identify how many missed days of treatment or missed cycles warrant removal of the patient from the study.
* If patients may remain on study after missed days or cycles, specify when study treatment may resume.

It is advisable to include a reference to the sections of the protocol that provide detailed information regarding potential adverse events / risks associated with each agent (as noted in sections 1.2,1.3 or 8.0).

A dose modification schema can also be included for hematological versus non-hematological criteria. (For hematological toxicity, please address guidance on use of growth factors). It is best to provide this information in a table format.

**\*\*\*\*The following tables are examples. If used, tables should be modified to appropriately fit your study and copied and pasted into this section.**

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

**Example 1 Hematological Toxicities**

|  |
| --- |
| **Hematological Toxicity Dose Reductions for Agent A** |
| **ANC1** | **Platelets** | **Action** |
| ≥ 1,500/μL | 100,000/μL | None. |
| 1000-1499/μL | 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 | 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 | <50,000/μL | *-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at TBD dose.*-2nd Occurrence*: Discontinue protocol therapy.  |
| 1Note: G-CSF (Filgrastim) may be added for low ANC on day of treatment *BEFORE* a dose reduction is instituted at treating physician’s discretions. Neulasta® is NOT allowed. |

**Example 2 Non-hematological Toxicities: Modifications for several agents may be presented at once. Any exceptions should be further explained in the text of the protocol.**

|  |
| --- |
| **Non-hematological Toxicity Dose Reductions** |
| **NCI CTC Grade** | **Agent A** | **Agent B** | **Agent C** |
| 0-2 | 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)** |
| 3  | Hold until resolved to < Grade 2, then reduce **to TBD dose** | Hold until resolved to < Grade 2, then reduce **to TBD dose** | Hold until resolved to < Grade 2, then reduce **to TBD dose** |
| Second episode of grade 3 or 4 toxicity | Hold until resolved to < Grade 2, then reduce **to TBD dose** | Hold until resolved to < Grade 2, then reduce **to TBD dose** | Hold until resolved to < Grade 2, then reduce **to TBD dose** |
| Third episode of grade 3 or 4 toxicity | Remove subject from trial | Remove subject from trial | Remove subject from trial |

**Example 3 Non-hematological Toxicities:** **Each agent to be modified may have a separate table.**

|  |
| --- |
| **Example of non-hematological Toxicity Dose Reductions** |
| **Event** | **Action** |
| **Name of Toxicity** |
| Grade 1-2 | None |
| Grade 3 | Insert dose modification, may want to specify if first allow attempt at control, e.g., with anti-emetics prior to dose modification |
| Grade 4 |  |
|  |  |
| **Name of Separate Toxicity** |
| Grade 1-2 |  |
| Grade 3 |  |

## Concomitant Medications/Treatments

List all relevant concomitant drugs and/or treatments that are prohibited; as well as any medications that may be used, but only with caution.

**NOTE: This section should be consistent with the medications/ restrictions in the inclusion / exclusion criteria.**

## Other Modalities or Procedures

Provide a detailed description of any other modalities or procedures (e.g., surgery, radiotherapy, hematopoietic stem cell transplantation) used in the protocol treatment. Distinguish between those modalities that comprise standard of care, and those being investigated within your protocol.

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

## Duration of Therapy

**This section should clearly define the “end of protocol therapy.” For example:**

In the absence of treatment delays due to adverse events, treatment may continue for Click here to enter text. or until:

* Disease progression
* Inter-current illness that prevents further administration of treatment
* Unacceptable adverse event(s)
* Patient decides to withdraw from the study, OR
* General or specific changes in the patient’s condition that, in the judgement of the investigator, render the patient unacceptable for further treatment.

## Duration of Follow Up

Describe the nature and frequency of follow up. (E.g. visits every 3 months, phone call every 6 months, etc.) For example:

* Patients will have follow up office visits once every three months.
* Patients will receive follow up phone calls every 6 months.
* Patients will be followed for 12 months after removal from treatment or until death**\*\*\***, whichever occurs first.
* Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

\*\*\*Following patients until death may require considerable resources, this should be carefully considered before deciding if such follow up is necessary.

**Follow up in Phase I studies**: Subjects are usually “off study" at 30 days from last treatment.

**Follow up in Phase II studies**: Follow up will vary (e.g., 2 to 5 or even 10 years or more) depending on whether patients are followed for a survival endpoint.

## Removal of Patients from Protocol Therapy

Provide procedures for removing patients from therapy. For example:

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. The Principal Investigator must be notified, and the reason for removal and date subject was removed from the study must be documented in the Case Report Form. The patient should be followed-up per protocol.

## Patient Replacement

Include guidelines for how and when and enrolled patients may be replaced in the study. Some sample language is listed below:

* Three patients within a dose level must be observed for one cycle (28 days) before accrual to the next higher dose level may begin.
* If a patient is withdrawn from the study prior to completing 22 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level.
* Patients missing 7 or more doses due to toxicity will not be replaced since these patients will be considered to have experienced a dose limiting toxicity.

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

# STUDY PROCEDURES

## Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. All screening procedures must be performed within Click here to enter text. days prior to registration unless otherwise stated. The screening procedures include:

## Procedures During Treatment

Describe all procedures to be done during the treatment period.

Treatment may be broken down by cycle(s) or phase(s) – whichever makes the most sense given the overall plan. Treatment phases might include neoadjuvant, adjuvant, initial, maintenance, etc. Ensure each procedure is listed / explained individually as shown, adjusting the section numbers accordingly:

### 5.2.1 Prior to Each Treatment Cycle

* Physical exam, vital signs
* Hematology
* Serum chemistries

### 5.2.2 Day 1

* Provide procedure description

### 5.2.3 30 days after treatment termination

* Physical exam, vital signs
* Hematology
* Serum chemistries

Describe all screening and baseline procedures. Ensure each procedure is listed / explained individually as shown, adjusting the section numbers accordingly. For example:

**5.1.2** Medical history

Complete medical and surgical history, history of infections

**5.1.3 Demographics**

Age, gender, race, ethnicity

**5.1.4 Review subject eligibility criteria**

**5.1.5 Review previous and concomitant medications**

**5.1.6 Physical exam including vital signs, height and weight**

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

**5.1.7 Performance status**

Performance status evaluated prior to study entry according to Appendix #/letter.

**5.1.8 Adverse event assessment**

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

**5.1.9 Hematology**

**5.1.10 Blood draw for correlative studies**

See Section 9.0 for details.

**5.1.11 Serum chemistries**

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

**5.1.12 Pregnancy test (for females of child bearing potential)**

See section 3.1.6 for definition.

**5.1.13 Other**

Describe any other screening procedures not listed above.

## Follow-up Procedures

Describe the schedule and procedures for patient follow up. If necessary, ensure each procedure is listed / explained individually (as you did in Section 5.2 above).

**NOTE**: this schedule must be consistent with the information provided in Section 4.6.

## Time and Events Table

List the specific day or days (e.g. Day 1, Cycle 1 or Days 1, 7… etc.). Ensure table is consistent with study objectives, eligibility criteria, and assessments listed in sections 5.1-5.3. The following table can be adjusted to your study criteria and copied and pasted into this section:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SAMPLE**  | Pre-study | Week 1 or Day/Days | Weekly or Day/Days | q 6 Weeks | Off Treatment | Follow-up |
| Assessment |  |  |  |  |  |  |
| Informed Consent | X |  |  |  |  |  |
| History and PE | X |  |  | X | X | X |
| Performance Status | X |  |  | X | X | X |
| Toxicity (include DLT) Evaluations |  | X | X |  | X |  |
| Tumor Measurements | X |  |  |  | X |  |
| Chest x-ray | X | X |  |  | X |  |
| CBC | X | X | X | X | X |  |
| Other required labs |  |  |  |  |  |  |
| Include correlative Procedures (if applicable) | X |  |  |  | X |  |

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

## Removal of Subjects from Study

Describe criteria for removing patients from study, ensuring that each criteria is listed individually. You may adjust the language below to meet your study criteria:

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:

**5.5.1** Patient voluntarily withdraws from treatment (follow-up permitted);

**5.5.2** Patient withdraws consent (termination of treatment and follow-up);

**5.5.3** Patient is unable to comply with protocol requirements;

**5.5.4** Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

**5.5.5** Patient experiences toxicity that makes continuation in the protocol unsafe;

**5.5.6** Treating physician judges continuation on the study would not be in the patient’s best interest;

**5.5.7** Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

**5.5.8** 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*.*

# Response Criteria

Describe the criteria to document response and duration of response. For example:

## 6.1 Safety/tolerability

### Analyses will be performed for all patients having received at least one dose of study drug.

# ADVERSE EVENTS

## Experimental Therapy

Describe adverse events that may occur from experimental therapy. For example:

### For the most recent safety update, please refer to the current Investigator’s Brochure or Study Agent Prescribing Information.

### 7.1.1 Contraindications

### 7.1. 2 Special Warnings and Precautions for Use

### 7.1.3 Interaction with other medications

### 7.1.4 Adverse Reactions

## Adverse Event Monitoring

Data collection and monitoring are required for every clinical trial, and are done to ensure the safety of subjects currently enrolled in studies, as well as subjects who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial, or in an expedited manner, if necessary, to allow for optimal monitoring of patient safety and care. For example:

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

* The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
* Any abnormal laboratory values have returned to baseline;
* There is a satisfactory explanation other than the study drug for the changes observed; or
* Death.

## Definitions

### Below are some recommended adverse event definitions. Copy and paste as applicable to your study:

### 7.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

### 7.3.2 Severity of Adverse Events

The severity of an AE is graded as follows:

**Mild (grade 1)**: the event causes discomfort without disruption of normal daily activities.

**Moderate (grade 2)**: the event causes discomfort that affects normal daily activities.

**Severe (grade 3)**: the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

**Life-threatening (grade 4)**: the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

### 7.3.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

#### 7.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

#### 7.3.3.2 Is life-threatening. (i.e. The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

#### 7.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

#### 7.3.3.4 Results in persistent or significant disability or incapacity.

#### 7.3.3.5 Is a congenital anomaly/birth defect

#### 7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

#### 7.3.3.4 Results in persistent or significant disability or incapacity.

#### 7.3.3.5 Is a congenital anomaly/birth defect

#### 7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

## Steps to Determine If an Adverse Event Requires Expedited Reporting

This section should describe your process for determining if an Adverse Event requires expediting reporting. Copy and paste any of the language below that applies to your study; adjusting / adding verbiage as necessary:

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

* + Definite – The AE *is clearly related* to the study treatment.
	+ Probable – The AE *is likely related* to the study treatment.
	+ Possible – The AE *may be related* to the study treatment.
	+ Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. **For expedited reporting purposes only -**An adverse event is considered unexpected when either the type of event or the severity of the event is not listed in:

* the current known adverse events listed in the Agent Information Section of this protocol;
* the drug package insert;
* the current Investigator’s Brochure

## Reporting Requirements for Adverse Events

**Copy and paste any verbiage below that is relevant to your study, making adjustments as necessary:**

### 7.5.1 Expedited Reporting

* The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of last administration of the study drug.

**(cont’d on next page)**

**Copy and paste any verbiage below that is relevant to your study, making adjustments as necessary:**

* If applicable, insert terms for expedited reporting to the pharmaceutical company/entity if they are providing funding and require expedited reporting.
* The {institutional officials} must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPIRSO).
* Insert your local requirements below:

The following events meet the definition of UPIRSO:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.
	* + For IND/IDE trials: The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

### 7.5.2 Routine Reporting

* All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

## Unblinding Procedures

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 (with the exception of sponsor-investigators):

State that the investigator must inform the sponsor of all subjects whose treatment was unblinded – and describe the timelines for such reporting.

**(cont’d on next page)**

In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE. However, if unblinding was not associated with an SAE report these actions in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline as used for reporting of SAEs, (e.g., notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

**NOTE**: 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 (with the exception of sponsor-investigators):

State that the investigator must inform the sponsor 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, if unblinding was not associated with an SAE report these actions in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline as used for reporting of SAEs, (e.g., notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

NOTE: 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.

## Stopping Rules

If applicable to your study, describe the stopping rules for inadequate efficacy.

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. If a central Data and Safety Monitoring Board (DSMB) or Committee (DSMC) is set up for the study, the stopping rules should be incorporated into their safety analysis plan as well.

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

# DRUG/DEVICE INFORMATION

## Agent/Device Click here to enter text.

**Provide the following information for each drug/device:**

* Other names for the drug(s)/device:
* Classification - type of agent/device:
* Mode of action:
* Storage and stability:
* Protocol dose: (if a drug is given at different doses at different points in the treatment cycle, all doses should be indicated.)
* Preparation:
* Route of administration for this study:
* Incompatibilities:
* Availability: (e.g., commercially available, provided by sponsor)
* Specify if provided free of charge, as this has implications for the consent form
* 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. Refer the reader to the agent’s package insert for a comprehensive list of adverse events.
* Nursing implications

### Return and Retention of Study Drug/Device

Provide the address and sponsor/Pharma/collaborator contact for the drug return and destruction policy. If remaining drug is to be destroyed, please state the drug destruction policy according to {institutional pharmacy/investigational drug services} or other appropriate instructions.

**8.1.2** If applicable, include a section to provide plans for subject’s compliance with the study agent (e.g., questionnaire, patient diary, pill diary). This is necessary for all oral or self-administered investigational agents.

# CORRELATIVES/SPECIAL STUDIES

If applicable to your study, provide information for planned laboratory correlative studies

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

# SPECIMEN COLLECTION

## Sample Collection Guidelines

Describe what type of samples will be collected, and by what method:

* Be clear as to how samples will be labeled (e.g. with the subject’s de-identified study number and collection date).
* Specify where specimens will delivered for analysis, ensuring you provide the name and address of the location.
* 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.)
* Specify any restrictions on specimen receiving times (e.g., after hours, weekends, holidays). For example:

 Samples will be collected at the following time points (+/- window):

* (Within 28 days) prior to study treatment.

## Assay Methodology

Describe assay methodology for the device / drug under investigation.

## Specimen Banking

**If specimens will be banked for future use, provide the following information:**

* Where specimens will be stored (i.e. McLaren Flint Lab, etc.)
* Length of time specimens will be stored (e.g. indefinitely or until they are used up, etc).
* Information regarding use of specimens if future use is denied or withdrawn by the patient (e.g. Best efforts will be made to stop any additional studies and to destroy the specimens if use is denied or withdrawn by patient.)

**Include any of the following information, if applicable to your study:**

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain byClick here to enter text., the investigator or a collaborating researcher or entity.

The following information may be obtained from the subject's medical record and provided to research collaborators when specimens are made available:

* Diagnosis
* Collection time in relation to study treatment
* Clinical outcome – if available
* Demographic data

**IF THIS SECTION IS NOT APPLICABLE TO YOUR STUDY, YOU MAY REMOVE IT FROM THE DOCUMENT**

# STATISTICAL CONSIDERATIONS

Describe the statistical aspects of the protocol in detail, precisely describing what results will be reported and how those results were calculated.

**NOTE: It is advisable to coordinate with the study statistician when writing this section of your protocol**

## Study Design/Study Endpoints

Describe the study design. Clearly state key design aspects (e.g. is the study retrospective or prospective, blinded, randomized, single or multi-centered, etc.) and define all study endpoints.

**If there are stopping rules for either safety or efficacy:**

Describe the rationale for them and how they might cause a suspension of study enrollment until a safety review has been convened.

**Examples of findings that might trigger a safety review:**

* The number of SAEs overall
* The number of occurrences of a particular type of SAE
* Severe AEs/reactions
* Increased frequency of events.

## Sample Size and Accrual

State the following in this section:

* Justification for the number of patients to be used in the study.
* Precise statistical power and sample size considerations and which objective they address (should be the primary objective.)
* Total sample size and accrual
* Expected accrual rate and all relevant assumptions (be specific)
* How these numbers were calculated, including the software used. NOTE: A reviewer should be able to duplicate the calculations given the information provided.

## Data Analyses Plans

Describe in detail how each objective will be addressed by a particular data analysis plan. Provide the details of each data analysis plan (for each objective); stating what statistical methods will be used, and under which assumptions.

Every objective and study endpoint should have a plan associated with it.

You may also provide further details concerning safety and/or pharmacokinetics in this section.

# STUDY MANAGEMENT

## Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) will disclose the conflict in accordance with McLaren Health Care policy MHC\_CC0137 Provider Conflict of Interest and Business Integrity. The conflict will also be disclosed to the IRB via the eProtocol submission system. Any changes in conflict of interest will also be reported to the MHC IRB via the eProtocol system.

## Institutional Review Board (IRB) Approval and Consent

IRB approval of the consent form, protocol document, data collection forms, and all other supporting documentation will be obtained prior to commencement of any research activities.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB‑approved consent form.

## Data Management and Monitoring/Auditing

Describe any QA activities and monitoring committee(s) responsible for the monitoring / management of your study data.

## Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### Emergency Modifications

Deviations from / changes to the protocol will be implemented without prior IRB approval, only if immediate hazards to trial subjects exist.

**NOTE TO INVESTIGATORS**: If emergency modification to the protocol is necessary to eliminate immediate hazards to subjects, a modification form must be submitted to the IRB within five (5) business days of implementation of the change.

It is advisable to also review the UPIRSO policy (MHC\_RP 0121 Reporting UPIRSO) in such cases to ensure any adverse events / unanticipated problems involving risks to subject or others are appropriately reported to the IRB.

### Other Protocol Deviations/Violations

**Describe your process for reporting deviations and violations to your protocol.**

**For example:**

All deviations / violations to the approved protocol will be reported to the IRB in accordance with MHC Human Research Protections Program (MHC HRPP) policy MHC\_RP0122 Protocol Violations and Exceptions.

**NOTE TO INVESTIGATORS REGARDING DEVIATIONS / VIOLATIONS:**

A protocol deviation is generally described as any unplanned variance from an IRB approved protocol that:

* Is generally noted or recognized after it occurs
* Has no substantive effect on the risks to research participants
* Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
* Did not result from willful or knowing misconduct on the part of the investigator(s).

Where as a violation is generally described an unplanned protocol variance that:

* Has harmed or increased the risk of harm to one or more research participants.
* Has damaged the scientific integrity of the data collected for the study.
* Results from willful or knowing misconduct on the part of the investigator(s).
* Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Detailed information regarding deviations and violations can be found in MHC HRPP Policy MHC\_RP0122. Basic guidelines are as follows:

**Protocol Violations:** Report violations to data and safety monitoring committees (DSMC) in accordance with their policies. Violations are to be reported to the IRB within ten (10) business days of the investigator becoming aware of the event.

**Protocol Deviations:**  Report deviations to sponsors or DSMCs in accordance with their policies. Per MHC HRPP policy, minor deviations should be reported to the IRB at the time of continuing review. It is advisable to create a deviation log to track such instances throughout each continuing review period. This will ease administrative burden while creating the application for continuing review.

## Modifications to the Protocol

**Describe your process for modifying procedures / processes / documentation for your study.**

Modifications must be submitted to the IRB for approval **prior to implementation**. Be sure to revise and submit to the IRB, any documentation affected by the change (e.g. the consent form, protocol).

## Record Retention

**Describe your process for retention / storage / destruction of study-related documentation.**

**NOTE TO INVESTIGATORS**:

Documentation must be retained in accordance with all federal, state, and institutional policies, regulations, and directives. In general, study documents should be kept on file until (7) years after the completion and final report of the study. Documentation includes:

* Case report forms
* Data collection forms
* Sponsor-Investigator correspondence
* Monitoring logs/letters
* Regulatory documents (e.g. protocol, IRB correspondence, signed consent forms). Source documents (recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study)

**For studies seeking regulatory approval and marketing of a drug**: Documentation must be retained for at least (7) years after the last approval of marketing application in an International Conference on Harmonization (ICH) region.

## Obligations of Investigators

**Provide information regarding specific obligations of study investigators. For example:**

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and documented on the case report forms. Periodically, monitoring visits will be conducted and the 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.

**NOTE**: The Principal Investigator is responsible for the conduct of the study at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI must:

* Personally oversee the treatment of all study patients.
* Assure that all study site personnel (sub-investigators, coordinators, etc.), adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

# REFERENCES

List all references used in the creation of your study.

# APPENDICES

List all relevant appendices in alphabetical order (e.g., Appendix A, Appendix B, etc.)

**For all self-administered investigational agents**: Include an appendix for a Pill Diary