INSERT TITLE OF THE PROTOCOL

*[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)**]*

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.

Regulatory Sponsor:	*Insert the Name of the Sponsor-Investigator* *Insert Department Name* *Insert Address* *Insert Phone Number*
Funding Sponsor:	*Insert the Name of Primary Funding Institution* *Insert Address* *Insert Phone Number*
Study Product:	*Insert Study Drug Name – Generic, followed by marketed name if applicable*
Protocol Number:	*Insert Protocol Number Used by Sponsor*
IND Number:	*Insert IND Number if applicable*

Initial version: [date]
Amended: [date]
Amended: [date]

Table of Contents

List of Abbreviations

Study Summary

Title	*Full title of protocol*
Short Title	*Shortened title, if one is typically used by you or your Center/Dept.*
Protocol Number	*The standard protocol number used to identify this study.*
Phase	*Clinical study phase (e.g. Phase 1, 2, 3 or 4)*
Methodology	*Design attributes such as 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 (e.g. from start of screening to last subject processed and finishing the study)*
Study Center(s)	*Single-center or multi-center. If multi-center, note 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 (e.g. not for simply one site, rather for entire study, all sites combined)*
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, Dose, Route, Regimen	*Study drug name (generic name, though can also state marketed name if name-brand used in the study). Also dose, dose route and dose regimen*
Duration of administration	*Total duration of drug product administration (including any open-label lead-in, if applicable).*
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. (As few lines as possible).*

1 Introduction

The introduction should open with remarks that state that this document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable Medical center research requirements. The rest of the introduction is broken out into subsections. Example language for the first paragraph under "Introduction" and before the section "1.1 Background":

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

This section should contain a background discussion of the target disease state to which the investigational product(s) hold promise, and any pathophysiology relevant to potential study treatment action.

1.2 Investigational Agent

This section should contain a description of the investigational product, its make-up, chemical properties and any relevant physical properties, including any available pharmacologic data. (A good example for this section is the "Description" and "Pharmacology" sections for drugs listed in the Physicians' Desk Reference)

1.3 Preclinical Data

Summarize the available non-clinical data (published or available unpublished data) that could have clinical significance.

1.4 Clinical Data to Date

Summarize the available clinical study data (published or available unpublished data) with relevance to the protocol under construction -- if none is available, include a statement that there is no available clinical research data to date on the investigational product.

1.5 Dose Rationale and Risk/Benefits

Describe the rationale used for selection of the dose for the protocol under construction. This should be based on non-clinical and clinical data available to date. It should include justification for route of administration, dosage, dosage regimen, and dosage period. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and/or knowledge that might reasonably be expected from the results.

2 Study Objectives

Describe the overall objectives and purpose of the study. This should include both primary and any secondary objectives, e.g.:

Primary Objective
To assess the efficacy of XXXX on decreasing infarct size as measured by Sestamibi scanning.

Secondary Objective
To assess the safety and tolerability of two doses of XXXX in subjects with acute myocardial infarction.

3 Study Design

3.1 General Design

Include:

- The type/design of the study (e.g. Phase, randomized, double-blind, parallel group, etc.)
- A schematic diagram of the trial design, procedures and stages is advisable
- Expected duration of subject participation
- A summary description of the sequence and duration of all trial periods including follow-up, if any

3.2 Primary Study Endpoints

Describe the primary endpoint to be analyzed in the study (e.g. could be safety or efficacy, depending on the main objective of the study).

3.3 Secondary Study Endpoints

Describe any secondary endpoints to be analyzed in the study

3.4 Primary Safety Endpoints

All studies should include the primary safety endpoints to be measured. If the primary objective of the study is a safety study and therefore the Primary Endpoint(s) of the study are safety endpoints, then it should be noted in section 3.2 above and this subsection 3.4 can be deleted.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Create a numbered list of criteria subjects must meet to be eligible for study enrollment (e.g. age, gender, target disease, concomitant disease if required, etc.) Generally should include items such as: "subjects are capable of giving informed consent", or if appropriate, "have an acceptable surrogate capable of giving consent on the subject's behalf."

4.2 Exclusion Criteria

Create a numbered list of criteria that would exclude a subject from study enrollment. If appropriate, should generally include that subjects cannot be homeless persons, or have active drug/alcohol dependence or abuse history. If exposure to certain medications or treatments at screening is prohibited, that must be noted in the exclusion criteria—if these are also prohibited concomitant medications during the study period that should be noted here as well.

4.3 Subject Recruitment and Screening

Describe how subjects will be recruited for the study, e.g. from investigator or sub-investigator clinical practices, referring physicians, advertisement, etc. Note in this section that information to be disseminated to subjects (handouts, brochures, etc.) and that any advertisements must be approved by the EC/IRB for the site; include a sample of such information in the attachment section of the protocol. Also in this section, list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria (greater detail of timing, etc. can be included later in section 6 "Study Procedures" section of the protocol).

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Describe the scenarios under which a subject may be withdrawn from the study prior the expected completion of that subject (e.g. safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.) Also, if abrupt termination of study treatment

could affect subject safety (e.g. in an antihypertensive study, abrupt withdrawal without other intervention might cause hypertensive rebound), describe procedure to transition subject off the study drug or to alternate therapy.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be give to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. IT MUST BE A HIGH PRIORITY TO TRY TO OBTAIN AT LEAST SURVIVAL DATA ON ALL SUBJECTS LOST TO FOLLOW-UP AND TO NOTE WHAT METHODS SHOULD BE USED BEFORE ONE CAN STATE THE SUBJECT IS TRULY LOST TO FOLLOW-UP (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.).

5 Study Drug

5.1 Description

This section should be a very brief synopsis of section 1.2 "Investigational agent", along with how the how the drug product will appear (e.g. as tablets or capsules of "X"mg, as a liquid with "X"mg dissolved in 10ml 5% dextrose and water, etc.)

5.2 Treatment Regimen

Describe dose, route of administration, and treatment duration.

5.3 Method for Assigning Subjects to Treatment Groups

Describe how a randomization number and associated treatment assignment will be made. This could be selection of a sequentially numbered drug kit/box, or communication with a randomization center that assigns a number associated with a specific treatment kit/box, etc.

5.4 Preparation and Administration of Study Drug

Describe in detail all the steps necessary to properly prepare study treatment. Include whether the drug preparation will be done in a pharmacy or by a study team member. Fully describe how the study treatment is to be administered. If study drug is stored, mixed/prepared or dispensed from the Dartmouth-Hitchcock Medical Center Investigational Pharmacy, that should be noted here, including the contact number to that service office. The Investigational Pharmacy can also provide standard language text for this section of the protocol.

5.5 Subject Compliance Monitoring

Describe how the study team will assess and track subject compliance with the study treatment regimen, and what procedures must be followed for any subject who is significantly non-compliant with the study treatment regimen.

5.6 Prior and Concomitant Therapy

In this section, describe:

- What prior and/or concomitant medical therapy will be collected (if applicable).
- Which concomitant medicines/therapies (including rescue therapies) are permitted during the study
- Which concomitant medicines/therapies are not permitted during the study (if applicable)

5.7 Packaging

- Describe how the study drug and any comparator agent will be packaged along with the amounts (e.g. “20 ml vials containing 30 mg”, or “bottles containing 30 tablets of …”, etc.) along with any associated labeling
- Describe if drug is to be shipped in bulk (e.g. Study drug will be shipped in boxes of 30 vials each, etc.) or as separate subject-specific kits/boxes
- When subject drug kits are constructed describe all the contents of the kit/box and associated labeling

5.8 Blinding of Study Drug

Describe how the drug is blinded (refer back to Section 8.4 “Unblinding Procedures”).

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Describe how drug will be obtained i.e. what entity will ship the drug to the investigative site, and to what location at the site, (e.g. investigational pharmacy, etc.)

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator’s site.

5.9.2 Storage

Describe storage temperature requirements, whether supplies must be protected from light, and the location of the supplies (e.g. study pharmacy). Describe any special handling requirements during storage

5.9.3 Dispensing of Study Drug

Describe how the drug will be assigned to each subject and dispensed. This section should include regular drug reconciliation checks (i.e. how much drug was assigned and whether subjects actually received assigned dose or received dose properly, how much remains, how much drug was inadvertently damaged, etc. --- eg. “Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.”)

5.9.4 Return or Destruction of Study Drug

This section should note the procedures for final reconciliation of the site’s drug supply at the end of the study, and whether study drug is to be shipped back to a source or destroyed on site. If drug is to be shipped back to a source, note the address and contact information here.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

In this section, describe all the procedures and treatments required at each visit, broken out by visit. Create a study procedures flowchart/table that describes the activities and procedures to be followed at

each visit. Include this flowchart/table in the Attachment section and refer to that attachment in this section.

6.1 Visit 1

6.2 Visit 2

6.3 etc.

7 Statistical Plan

7.1 Sample Size Determination

Describe the statistical methods for determining the sample size for the study

7.2 Statistical Methods

Summarize the overall statistical approach to the analysis of the study. The section should contain the key elements of the analysis plan, but should not be a reiteration of a detailed study analysis plan. The full Statistical Analysis Plan can then be a "stand-alone" document that can undergo edits and versioning outside of the protocol and therefore not trigger an IRB re-review with every version or edit –AS LONG AS THE KEY ELEMENTS OF THE ANALYSIS PLAN DO NOT CHANGE.

Be clear on primary as well as any applicable secondary analyses

7.3 Subject Population(s) for Analysis

This section should be very specific in defining the subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses. Examples of such populations include:

- *All-randomized population: Any subject randomized into the study, regardless of whether they received study drug*
- *All-treated population: Any subject randomized into the study that received at least one dose of study drug*
- *Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing*

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

This section describes the requirements for reporting specific types of unanticipated problems including adverse events. Since this protocol template is likely being use to create a protocol for a Dartmouth faculty study sponsor, the sponsor may elect to require that participating investigators report <u>all</u> serious adverse events to be more complete (i.e. individual sites may not consider a given serious adverse event related to study participation, but by collecting all serious adverse events, the sponsor may note an unexpected increase in a specific serious event that may therefore indeed be related to the study drug). Alternatively the sponsor may elect to only require that investigators report the minimum information required by FDA regulations. This section is written with the more conservative approach requiring participating investigators to report all serious adverse events to the study sponsor, so should be adjusted if this is not the approach to be taken.

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

This section is written with the more conservative approach requiring participating investigators to report all serious adverse events to the study sponsor, so should be adjusted if this is not the approach to be taken. This section also describes the use of a "Serious Adverse Event Form" as the document for recording and reporting such events. This is meant to be a form you create for this study. If you are using a FDA Form 3500A, please adjust the template language below accordingly.

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

[Name of Sponsor contact phone, fax]

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the Dartmouth IRB

Since this protocol template is most typically intended for the construction of a protocol to be conducted at Dartmouth, this section specifies the Dartmouth IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or other, including adverse events. The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth IRB requires reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB requires researchers to submit reports of *any incident, experience, or outcome that meets each of the following criteria:*

- ***Unanticipated*** *in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and consent document; and (b) the characteristics of the subject population being studied; and*
- ***Possibly related*** *to participation in the research means there is a reasonable possibility that the incident, experience, or outcome may have been associated with research participation; and*
- *The problem suggests that the research places subjects or others at a* ***greater risk of harm*** *(including physical, psychological, emotional, economic, legal, or social harms) than was previously known or recognized.*

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: "Unanticipated Problem Involving Risks to Subjects or Others (UPR)."

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience, defined as an untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research), that is considered:
  - Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and
  - Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or consent form; and
  - Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research; and
  - Is experienced by a participant in a trial open at a site subject to Dartmouth IRB review
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol deviation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Investigator reporting: Notifying a non-Dartmouth IRB

Investigators who are not Dartmouth faculty or affiliated with a Dartmouth research site are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.3.4 Sponsor reporting: Notifying the FDA

If this protocol is being conducted under an FDA IND, it is the responsibility of the study regulatory sponsor (entity/person responsible for the initiation, management, of the clinical trial --- i.e. the IND holder) to report certain adverse events or unanticipated problems to the FDA. Delete this section if it is not applicable.

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

[Include the FDA Division, contact person, telephone number and fax number here]

8.3.5 Sponsor reporting: Notifying participating investigators

For multi-center clinical trials, in addition to reporting certain unanticipated problems and adverse events noted above to the FDA, it is the responsibility of the study sponsor to report those same adverse events or findings to participating investigators. This section describes that reporting requirement. Delete this section if it is not applicable.

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

8.4 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 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, (i.e. notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

8.5 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. 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.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

An Internal Data and Safety Monitoring Board (DSMB) is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety and oversight to a clinical study. This type of oversight committee can include the sponsor and selected investigators, though must include other members who are independent of the study (can include members from within or external to the sponsor or investigator's institution). The DSMB will look only at blinded data. This section should describe the above noted DSMB attributes. Also include:

- Number of members and roles (e.g. clinicians, biostatisticians, bioethicists, etc.). It is not necessary to list the names or contact information of DSMB members in the protocol. However, the names and contact information of DSMB members should be reported to the EC/IRB and also maintained in the sponsor study file.
- How often the DSMB will meet (and if by phone, face-to-face, or web-assisted conferencing)
- Type of safety information that will be assessed
- How the safety data will be supplied to the DSMB
- Summary of number and type of safety assessments the DSMB will conduct
- How the DSMB will record the summary of its various meetings
- How the DSMB will report it's findings and/or recommendations, and to whom
- Reference the DSMB charter in the Attachments section of the protocol

If there is no internal DSMB, delete this section.

8.6.2 Independent Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety oversight to a clinical study (and at least one biostatistician). This type of oversight differs from a Internal DSMB in that the Independent DSMB is independent of the investigator and sponsor, and is therefore generally also independent of the sponsor's and investigator's institution. Another important difference is that the DSMB can, and most typically does, conduct unblinded analyses. The DSMB should have a charter describing its function as well as an analysis plan for a pre-planned safety analysis(es). This section should describe the above noted DSMB attributes. Also include:

- Number of members and roles (e.g. clinicians, biostatisticians, bioethicists, etc.) Since DSMBs typically review unblinded analyses, in that case, they must be independent of the study. Therefore names and/ or contact information of DSMB members should not be noted in the protocol. However, the names and contact information of DSMB members should be reported to the EC/IRB and also maintained in the sponsor study file.

- How often the DSMB will meet (and if by phone, face-to-face, or web-assisted conferencing)
- Type of safety information that will be analyzed
- How the safety data will be supplied to the DSMB
- Summary of number and type of interim analyses the DSMB will conduct, and who will conduct the actual analyses (including plans/safeguards to keep any unblinded data or DSMB analyses confidential
- How the DSMB will record the summary of its various meetings
- How the DSMB will report it's findings and/or recommendations, and to whom
- Reference the DSMB charter in the Attachments section of the protocol

If there is no Independent DSMB, delete this section.

9 Data Handling and Record Keeping

9.1 Confidentiality

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

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

9.2 Source Documents

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

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

For non-FDA regulated studies, summarize the record retention plan applicable to the study (taking into account any applicable Dartmouth-Hitchcock Department, Division or Research Center requirements, or applicable funding sponsor requirements.)

For FDA-regulated studies the following sample language is appropriate:

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

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in Attachment ___. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and Medical center compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This section should describe how the study will be financed, but should not contain specific dollar amounts (e.g. "This study is financed through a grant from the US National Institute of Health", or "… a grant from the American Heart Association", etc.)

12.2 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.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth-Hitchcock investigators will follow the Dartmouth-Hitchcock conflict of interest policy.

12.3 Subject Stipends or Payments

Describe any subject stipend or payment here. If there is no subject stipend/payment, delete this section.

13 Publication Plan

This section should include the requirements any publication policies of the Medical center, Department, Division or Research Center. If, in addition to the sponsor-investigator, other investigators are involved with the study, identify who holds the primary responsibility for publication of the results of the study. Also define the need to first obtain approval from the primary responsible party before any information can be used or passed on to a third party.

Delete or modify the following sample language:

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

This is the bibliography section for any information cited in the protocol. It should be organized as any standard bibliography.

1. Author, Title of work, periodical and associated information.
2. Author, Title of work, periodical and associated information.

15 Attachments

This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
- Sample Consent Form
- Study Procedures Flowchart/Table
- Core Lab Instructions To Investigators
- Specimen Preparation And Handling (e.g. for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for shipment)
- Drug Conversion Plan (e.g. if there is a special regimen for transitioning a subject from their baseline medication over to study medication)
- Antidote Preparation And Delivery (e.g. special instructions for preparing and delivering any therapy designed to reverse the effects of the study drug, if applicable)

- etc.