FDA Investigational New Drug (IND) Toolkit

Version 1.0_16 Jan 2020 KZT

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Step 1

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STEP 1: Mark "Yes" or "No" for each of the below:

Yes	No	
☐	☐	1. Does the project involve administration of a drug to humans?
☐	☐	2. Is the project a clinical investigation? A clinical investigation is an experiment in which a drug is administered to humans for any use that is not per the marketed use of the drug in the course of medical practice. If use of the drug is subject to a randomization scheme, the project is a clinical investigation.

If only one of the above rows is checked "Yes", stop; the study does not require an IND. Otherwise, proceed.

STEP 2: Mark "Yes" or "No" for each of the below:

☐ ☐ 1. Is this drug investigational, i.e., not currently marketed in the U.S. as a drug?
Explain:

☐ ☐ 2. Is there an intention to submit the data collected in the study to FDA as a well-controlled study in support of a new indication or any other significant change in labeling for the drug?
Explain:

☐ ☐ 3. Is the information collected in the study intended to support any significant change in the advertising of the product?
Explain:

☐ ☐ 4. Does the study involve a route of administration, patient population, dosage or formulation that significantly increases the risks associated with the drug?
Explain:

If any of the above rows is checked "Yes", the study does require an IND.

- For the purposes of this document "drug" includes drugs, biologics, and other compounds other than food that are intended to diagnose, treat, mitigate, cure, or prevent disease, or otherwise affect the structure or function of the body.
- Certain projects may produce information of significant public health import. NIH review may determine that such projects must be conducted under an IND even if IND regulations don't apply.

Adapted from NIH, National Institute of Dental and Craniofacial Research, KZT 08Nov19

Investigator's Checklist for IND Application Submission

☐ ***Cover Letter***
☐ ***Form 1571***
☐ ***Form 1572***
☐ ***Form 3674***
☐ ***Table of Contents***
☐ ***Introductory Statement and General Investigational Plan***
☐ ***Chemistry, Manufacturing, and Control Information***
☐ ***Pharmacology Toxicology Information***
☐ ***Investigator's Brochure***
☐ ***Clinical Protocol(s)***
☐ ***Summary of Previous Human Experience with the Investigational New Drug***
☐ ***Additional Information, if applicable (e.g. drug dependence and abuse potential, pediatric studies, etc.)***
☐ ***Other Relevant Information, if applicable or if requested by FDA***

Notes:

Investigational New Drug (IND) Submission Checklist

1. Cover Letter

- Submission Identifier: "Initial Investigational New Drug Application"
- Brief explanation of the intended investigation (type and title of study)
- Investigational new drug product's name and proposed formulation
- Disease or condition under investigation
- IND manufacturer's name and contact information (if applicable)
- Reference to an existing IND application (if applicable)
- The Cover Letter is typically addressed to the Director of the Review Division in the Office of New Drugs and signed by the sponsor of the IND application.

2. Submit completed Form FDA 1571 as instructed by FDA

- If a study conduct obligations have been contracted to a CRO, indicate that a CRO is contracted rather than listing individual obligations.
- If an investigation involves an exception from informed consent for emergency research, state on the Cover Sheet.

3. Submit completed Form FDA 1572 (Statement of Investigator) as instructed by FDA

Complete for each Investigator participating in the study

4. Submit completed Form FDA 3674 (Certification of Compliance) as instructed by FDA

Requirements for ClinicalTrials.gov Data Bank

5. Table of Contents

6. Introductory Statement and General Investigational Plan *(typically 2-3 pages)*

A brief overview of the general investigational plan for the study. This information is repeated later in the IND, in a concise detail.

- **First section:** must include the name of drug, active ingredients, its pharmacological class, structural formula (if known), formulation of the dosage form(s) to be used, route of administration, and broad objectives and expected duration of the study.
- **Second section:** must include a summary of previous human experience, reference to other INDs, if relevant, and investigational and marketing experience in other countries, if applicable.
- **Third section:** indicate if the drug has been withdrawn from investigation or marketing for any safety or effectiveness reasons, including where and why.
- **Last section:** provide a summarize plans for investigating the drug within the next 12 months, including rationale for the study, indications(s) to be studied, general plan for evaluating the drug, kind of studies planned for the first year (specify if these plans are not yet complete), expected number of patients to be enrolled and anticipated risks based on animal toxicology data.

7. Chemistry, Manufacturing, and Control Information

Drug Substance:

- Description of physical, chemical, or biological characteristics and evidence supporting structure and identity of the active pharmaceutical ingredient(s).
- Name and address of manufacturer.
- Description of the general method of preparation of the drug substance, including a list of the reagents, solvents, and catalysts used →A *detailed flow diagram* is suggested.
- The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug substance, with a brief description of the test methods used. Submission of *certificates of analysis* is suggested.
- Information to support stability of the drug substance during storage in the intended container closure and during the toxicological and clinical studies.

Drug Product:

- A list of all components and composition used in manufacturing process, including reasonable alternatives for inactive compounds used in the manufacture of the investigational drug product. This list is expected to include both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process.
- Summary of quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage.
- Brief general description of the manufacturing process (*flow diagram* is suggested) and packaging procedure, as well as other relevant tests, as appropriate for the product. Final specifications for the drug product intended to be used in toxicological and clinical studies should be included. For injectable products, sterility and pyrogenicity tests, endotoxin levels and particulate matter should be included. Submitting a copy of the certificate of analysis of the clinical batch is also suggested.
- The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug product.
- Information to support stability of the drug product during the planned clinical studies.

Placebo Formulation (if applicable):

- Brief general description of the composition, manufacture, and control of any placebo formulation to be used in the proposed clinical study. The description may be structured similarly to the description of the drug product recommended above.
- ***Note:*** For placebo, the Quality Control test will include the absence of the active pharmaceutical ingredient(s). The physical characteristics of the placebo formulation should be comparable to the actual drug product to enable effective blinding.

Labeling:

- Copies of labeling for the investigational product, when applicable. Investigator's Brochure is considered the current and most up-to-date label of the investigational new drug. IB may be obtained from the IND product's manufacturer or referenced from an existing IND application.

Environmental Assessment:

- Assessment of effects of the investigational product on the environment. Environmental Assessment may be obtained from the IND product manufacturer or referenced from an existing IND application.
- Most products qualify for a categorical exclusion from such an assessment. In general, exclusion is based upon a variety of considerations, including the following:
    - Environment compartment (soil, air, water) into which the material will partition;
    - Degradation of the material and degree;
    - Safety margin between expected environmental concentration and effect level, for materials that slowly degrade.

Granting of a categorical exclusion will also depend upon the size of study population and amount of active moiety manufactured for the study.

8. Toxicology

Include information on the toxicological effects of the drug in animals and in vitro.

Depending on the nature of the drug and the phase of the investigation, the description is expected to include:

- the results of acute, subacute, and chronic toxicity tests;
- the results of tests of the drug's effects on reproduction and the developing fetus;
- any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

For each toxicological study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review is expected. This should consist of line listings of the individual data points, including laboratory data points for each animal along with appropriate summary tabulations.

9. Investigator Brochure *(when applicable)*

May obtain Investigator's Brochure (IB) from IND product's manufacturer. For investigator-initiated IND applications that have a right of reference to an existing manufacturer's IND application, submission of the IB is not required. IB is updated as the development program progresses and new information becomes available. IB is expected to contain the following information:

- Brief description of the drug substance and the formulation, including the structural formula, if known
- Summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans
- Summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans
- Summary of information relating to safety and effectiveness in humans obtained from prior clinical studies

- Description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug. Adverse Events (AEs) described in the IB help determine whether an AE that occurs during a clinical trial is "expected" and, if so, how it will be reported to FDA.

10. Protocol(s)

Phase I

- Include all the elements of the study that are critical to safety (may include all clinical safety assessments, toxicity monitoring, description of toxicity-based stopping rules, dose adjustment rules for individual patients and the overall trial, and adverse event recording and reporting);
- Study enrollment criteria should be written with consideration of the following: (1) background risks associated with the disease or condition studied, (2) previous knowledge of toxicities of the investigational drug observed in animal studies or with human experience, (3) warnings and precautions described in the product's label (when approved products are investigated for other than approved uses);
- It is preferable that toxicity is assessed and graded according to a standardized grading scale relevant to the studied population and that adverse events are collected, recorded, and reported in a consistent manner.

Phase II-III

- All the above described expectations for adequate safety elements also apply to Phase 2-3 trials;
- Detailed protocols describing efficacy and safety should be submitted for Phase 2-3 trials. Clearly stated objectives and purposes of a trial, including description of the observations & measurements to fulfill the objectives of the trial;
- Clear description of trial design, patient selection criteria, clinical procedures, laboratory tests, and all measures to be taken to monitor the effects of the drug;
- Previous experience with the proposed primary endpoints should be discussed with relevant scientific references (including any available data regarding the measurement's validation as relevant to clinical outcomes, biomarkers, or patient reported outcomes);
- All potential deviations from trial design should be built in the protocol from the outset, including when adaptive design is considered;
- Rules for adverse events' collection, recording, and reporting should be thoroughly described;
- Protocols lacking the necessary elements describing the intended investigations may be placed on clinical hold.

Note: Protocols not submitted with the original IND must be submitted in an IND Protocol Amendment.

11. Summary of Previous Human Experience with the Investigational Drug

- If no previous human experience exists, this should be stated here.
- If an investigational drug has been investigated or marketed previously, either in the U.S. or other countries, detailed information about such experience relevant to the safety of the proposed investigation or to the investigation's rationale should be included in this section. A

summary of previous human experience should contain all relevant information about previous investigations or marketing, including clinical trial reports and published material relevant to the product's safety and effectiveness.

- If the product has been marketed outside of the United States, all countries where the product has been marketed or withdrawn from any of those markets (and why) should be listed.
- For an IND application with investigational new drug that is subject to another existing IND application (e.g., an IND application sponsored by the investigational new drug's manufacturer), the investigator-sponsor may obtain a *Letter of Authorization* from the existing IND sponsor with the right of reference to the information contained in the existing IND application, including information related to any previous human experience.
- If an investigational new drug is a combination of drugs previously investigated or marketed, the description of human experience should be provided for each active drug component. However, if any component in such combination is an approved marketed product, submission of a copy of prescribing information leaflet may be sufficient. Additional published material about the approved drug may need to be submitted, if such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

12. Additional Information

When referencing any previously submitted information, refer to it by name, reference number, and volume and page number to assist FDA in finding the reference(s). Examples of other information that can be included: discussion about drug dependency or abuse potential and radioactive dissymmetry information.

13. Material in a Foreign Language

Material in a language other than English (including scientific literature published in a foreign journal) must be included in the IND with a certified accurate and complete English translation.

Investigational New Drug Submission Checklist

IND applicants may choose to reference data from other applications included in the available Chemistry, Manufacturing and Control (CMC) Information.

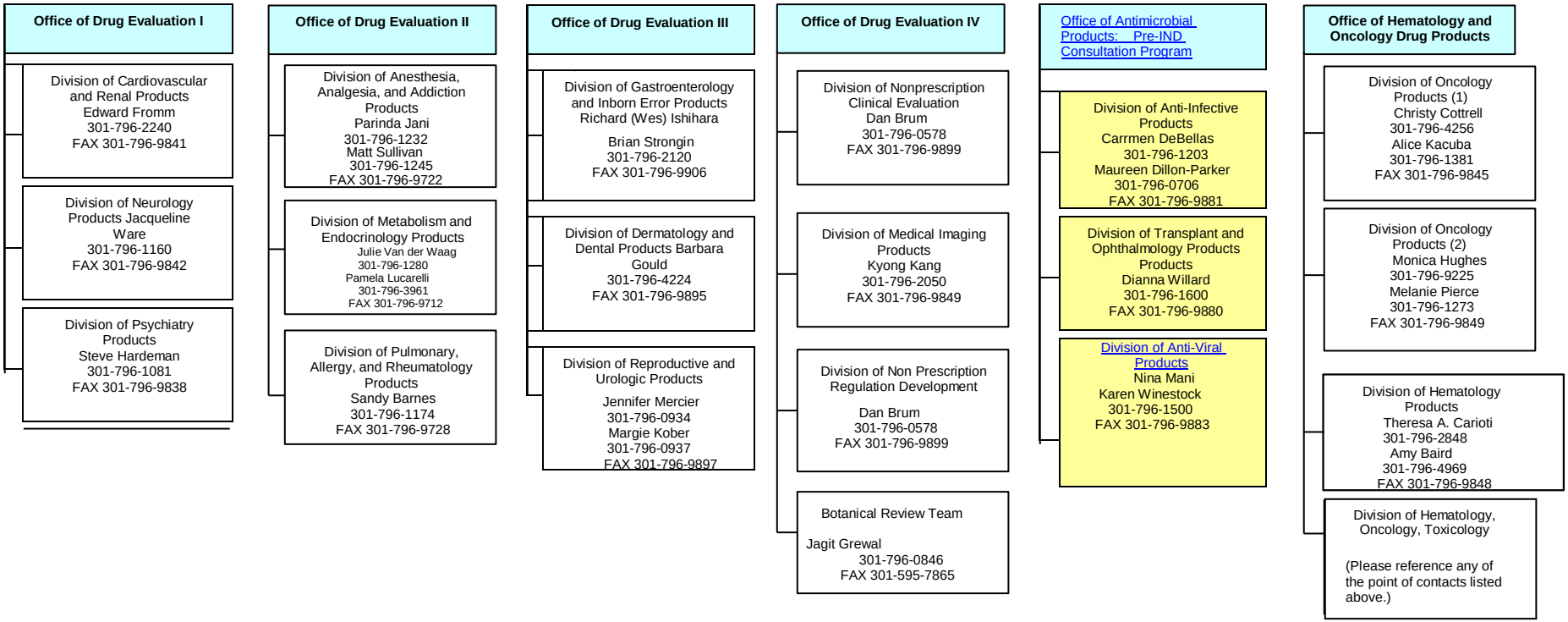
May include (and is not limited to):

Sections 6- Environmental assessment
Section 7- Toxicology
Section 8- Investigator Brochure
Section 10- Summary of previous human experience

OPTION A	***OPTION B***
IND application with an investigational new drug or biological product that is the subject of another existing IND application: In order to refer to the existing information about an investigational drug submitted under another IND application, the investigator-sponsor may obtain a Letter of Authorization from the existing IND application's sponsor (e.g., product's manufacturer). Such Letter of Authorization will grant a right of reference to the existing information which, in essence, will result in two permissions: 1. For the current IND applicant: to refer in their current IND application to the proprietary information about the investigational new drug already submitted to FDA under the previously submitted existing IND application, and 2. For FDA: to review the information already submitted to FDA under the existing IND application and, without disclosing this information to the current IND applicant, to determine whether the referenced information is sufficient to address the needs of the current IND application.	***IND application with an approved marketed drug or biological product:*** With regard to referencing the available information previously submitted and reviewed by FDA as part of a marketing application, two examples may be considered: 1. Applies to both CMC and Pharmacology and Toxicology: The proposed investigation may rely on previous FDA's findings of acceptability of CMC and Pharmacology and Toxicology information for the approved product. If the proposed dose, route, frequency of dosing and duration of therapy do not exceed the approved labeled dosing regimen, the investigator-sponsor may provide the product's labeling information and state in the non-clinical section of the application that they believe their IND application may rely on the previous FDA's acceptance of the CMC and/or Pharmacology and Toxicology information related to the approved marketed drug intended for this investigation. FDA will then determine during the review of the IND application (30 days) whether additional information is needed. 2. Applies to CMC: The proposed investigation may rely partially on the information available from the manufacturer's Drug Master File (DMF). The investigator-sponsor of the IND application may obtain a Letter of Authorization from the current manufacturer of the marketed product permitting to reference the manufacturer's DMF. FDA will then review the referenced DMF and determine whether additional information is needed.

Extracted from FDA site: https://wayback.archive-it.org/7993/20170112060139/http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362273.htm
KZT 13 NOV 2019

CENTER FOR DRUG EVALUATION AND RESEARCH
PRE-IND Consultation Contacts



Updated on 4/12/2017

FDA IND: Background Information

The need: Federal law requires that a drug be the subject of an approved marketing application before it is transported/distributed across state lines

IND provides an exemption from this legal requirement

FDA's Role: Begins when the drug's sponsor, having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic/therapeutic potential in humans

→ 21 Code of Federal Regulations: most regulations pertaining to food & drugs (interprets Federal Food, Drug & Cosmetic Act)

IND Types

1. Investigator IND: Submitted by a physician who initiates & conducts an investigation; under whose immediate direction the investigational drug is administered or dispensed (unapproved drug or new indication or new population)
2. Emergency Use IND: FDA authorized use of an experimental drug in an emergency situation; or patients who do not meet criteria for an existing study protocol; or if approved protocol does not exist
3. Treatment IND: experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions, while final clinical work is conducted/FDA review takes place

IND Categories

Commercial
Research

IND Application- 3 Key Components

Animal pharmacology & toxicology studies (pre-clinical data)
Manufacturing information (composition, manufacturer, stability, controls used)
Clinical protocols & investigator information
(avoiding unnecessary risks to subjects, investigator qualifications, informed consent, IRB review)

Timeline

Investigator must wait 30 calendar days after submission to initiate any trials

https://catalyst.harvard.edu/programs/regulatory/indide.html

FDA GUIDANCE DOCUMENTS & RESOURCE LINKS

General Website	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents
Pre-IND Consultation Program	Early communications between sponsors & drug review divisions to provide guidance on data necessary to warrant IND submission https://www.fda.gov/media/77025/download
IND Regulations for application process; Guidance documents to help prepare INDs; Emergency use of an investigational drug; Manual of policies & procedures	https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application#Introduction Guidance Document https://www.fda.gov/media/71203/download
Forms and Instructions	https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-forms-and-instructions
"Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices
Sponsor-Investigator-IRB Interrelationship	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-investigator-irb-interrelationship
Payment & Reimbursement to Research Subjects	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects
Drug Study Designs	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-study-designs
Form 1572 Statement of Investigator- FAQ	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-statement-investigator-form-fda-1572

https://catalyst.harvard.edu/programs/regulatory/indide.html

Step 2

Initial Submission

Financial Reporting

- Form 3454
- Form 3455

FDA Submission Forms

- Form 1571
- Form 1572
- Form 3674

Initial IND Submission Templates

Investigator Brochure Template

Resource: FDA Guidance Documents

Submission Checklist

A GUIDE TO FINANCIAL DISCLOSURES

DOES MY IND REQUIRE FINANCIAL DISCLOSURE FORMS?

Part 54 applies to studies that will be used in support of a marketing application. The majority of Sponsor-Investigator studies are not intended to support a marketing application. Therefore, it is unlikely that financial disclosures are required for your IND.

The following is the definition of a clinical study covered by 21 CFR Part 54:

Covered clinical study means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

These types of disclosures can be very important when it comes to large Phase III studies where a single investigator can potentially make a significant contribution to the outcome of a study.

In any event, Financial Disclosures are never submitted to INDs. They are to be saved and submitted with an NDA or other marketing application.

WHERE CAN I GET MORE INFORMATION?

You can contact us if you have questions about the relevance of Financial Disclosures in relation to your IND.

- 21 CFR 54, Financial Disclosure by Clinical Investigators

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54

Guidance for Clinical Investigators, Industry, and FDA Staff

Financial Disclosure by Clinical Investigators

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

February 2013

Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators

Additional copies are available from:

Office of Communication, Division of Drug Information, Building 51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Division of Small Manufacturers, International, and Consumer Assistance
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 66, rm. 4621, Silver Spring, MD 20993-0002 U.S.A.
Tel: 1-800-638-2041 or 301-796-7100; Fax: 301-847-8149; E-mail: dsmica@fda.hhs.gov
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
and/or
Office of the Commissioner, Office of Good Clinical Practice
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 32, rm. 5173, Silver Spring, MD 20993-0002 U.S.A.
Tel: 301-796-8340; Fax: 301-847-8640; E-mail: gcp.questions@fda.hhs.gov
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

February 2013

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Industry, and FDA Staff[1] Financial Disclosure by Clinical Investigators

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54. This document is a revision of the *Guidance for Industry: Financial Disclosure by Clinical Investigators* dated March 20, 2001. In order to address issues raised by the Office of the Inspector General (OIG), Department of Health and Human Services, in its report, OEI-05-07-00730, *The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information*[2] as well as questions FDA has received from industry and the public, FDA issued a revised guidance in draft in May 2011 for public comment. Comments were received from 13 individuals and entities, which were considered in preparing this final guidance. FDA encourages applicants and sponsors to contact the agency for advice concerning specific circumstances regarding financial disclosures that may raise concerns as early in the product development process as possible.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Financial Disclosure by Clinical Investigators regulation (21 CFR part 54) requires applicants who submit a marketing application for a drug, biological product or device to submit certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation (see generally the

[1] This revised guidance was prepared by the Office of the Commissioner, with input from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH).

[2] The OIG's report is available at http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf.

purpose of the regulation at 21 CFR § 54.1). The regulation, which became effective on February 2, 1999, applies to clinical studies submitted in a marketing application, including a supplement or amendment to an original application, that the applicant or FDA relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). The regulation requires applicants to certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or to disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR § 54.4(a)). If the applicant does not include certification and/or disclosure, or does not certify that it was unable to obtain the information despite exercising due diligence, the agency may refuse to file the application (21 CFR § 54.4(c)).

III. FINANCIAL DISCLOSURE REQUIREMENTS

Under the applicable regulations,[3] an applicant is required to submit to FDA a list of all clinical investigators who conducted covered clinical studies and to identify those who are full-time or part-time employees of the sponsor of each covered study (21 CFR § 54.4). For each clinical investigator who was not a full-time or part-time employee of a sponsor of the clinical study, the applicant must provide either a certification, using FORM FDA 3454, that none of the financial interests or arrangements described in 21 CFR § 54.4(a)(3) (see Section III.B. below) exists, or completely and accurately disclose, using FORM FDA 3455, the nature of those interests and arrangements to the agency and describe any steps taken to minimize the potential for bias resulting from those interests and arrangements (21 CFR § 54.4(a)). If the applicant acts with due diligence to obtain the required information but is unable to do so, the applicant may certify that it acted with due diligence but was unable to obtain the information and include the reason the information could not be obtained (21 CFR § 54.4).

FDA generally expects that applicants will be able to provide this information. Under 21 CFR §§ 312.53(c), 812.20(b)(5) and 812.43(c), a sponsor is required to obtain clinical investigator financial information before allowing the clinical investigator to participate in a covered clinical study. Under 21 CFR § 54.4(b), each clinical investigator who is not a full-time or part-time employee of the sponsor of the covered clinical study is required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion.

A. Definitions

Clinical Investigator – For purposes of part 54, "clinical investigator" means a "listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects," including the spouse and each dependent child of the investigator or subinvestigator. (See 21 CFR § 54.2(d).) See Section IV.D, Clinical Investigator, for additional information. Clinical investigators are included in the definition even if they did not participate for the entire length of the study. If a clinical investigator did not participate in the entire study,

[3] 21 CFR parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860

information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation.

Covered clinical study – The part 54 regulations define "covered clinical study" to mean "any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols and parallel track protocols." (See 21 CFR § 54.2(e).) This definition includes clinical studies submitted in support of new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), abbreviated new drug applications (ANDAs) under section 505(j) of the FD&C Act, premarket notification submissions under section 510(k) of the FD&C Act, reclassification petitions under section 513 of the FD&C Act, premarket approval applications (PMAs) under section 515 of the FD&C Act, and biologics licensing applications (BLAs) submitted under section 351 of the Public Health Services Act (PHS Act), as well as studies submitted in support of amendments or supplements to any such applications. (See 21 CFR §§ 54.3 and 54.4(a).) Covered clinical studies would generally not include expanded access under section 561 of the FD&C Act. If an applicant is unsure of whether a particular study is included in this definition, it may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements. (21 CFR § 54.2(e).) See Section IV.G, Covered Clinical Study, for additional information.

Applicant – "Applicant" means the party who submits a marketing application to FDA for approval of a drug, device or biologic product or who submits a reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements. (See 21 CFR § 54.2(g).) Note that for purposes of financial disclosure the term "applicant" includes "submitter" and the term "application" includes "510(k) submission." See Section IV.F, Applicant, for additional information.

Sponsor of the covered clinical study – For purposes of part 54, "sponsor of the covered clinical study" means "a party supporting a particular study at the time it was carried out." (See 21 CFR § 54.2(h).) A covered clinical study may have more than one sponsor for whom financial information will need to be collected. For example, if one party designed and conducted the covered clinical study, a second party provided funding, and a third party provided the test product, there would be three sponsors of the covered clinical study. However, if the third party in this example was reimbursed for the test product, it would not be considered a sponsor of the covered clinical study and the study would be considered to have two sponsors. Note also that the definition of "sponsor" for purposes of part 54 is different than the definition of "sponsor" for purposes of investigational new drug applications (INDs) and investigational device exemptions applications (IDEs) (see 21 CFR §§ 312.3(b) and 812.3(n)). See Section IV.E, Sponsor, for additional information.

B. Disclosable Financial Interests and Arrangements

The financial interests, arrangements, and payments that must be disclosed (see 21 CFR § 54.4(a)(3), referred to herein as "disclosable financial interests and arrangements") are described below.[4] Note that the dollar amounts that trigger reporting are the combined financial interests of the investigator, spouse, and dependent children.

1. Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

4. Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

5. Significant payments of other sorts (SPOOS) are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria. See Section IV, Questions C.4, C.5, and C.6 for additional information on SPOOS.

C. Agency Actions

The agency may refuse to file a marketing application that does not contain the financial information required by 21 CFR part 54 or a certification by the applicant that the applicant has

[4] These are the requirements for studies begun on or after the effective date of the part 54 regulations, February 2, 1999. For older studies, the disclosure requirements vary based on the study's status as of the effective date of the regulation. For studies that were completed prior to February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 3 is required. For studies ongoing as of February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 4 is required as well as payments as described in paragraph 5 that were made on or after February 2, 1999. (See *Federal Register*, volume 63, December 31, 1998, page 72172-3.)

acted with due diligence to obtain the information but was unable to do so stating a sufficient reason. (21 CFR § 54.4(c).)

If FDA determines that the financial interests or arrangements of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)) including:

1. Initiating agency audits of the data derived from the clinical investigator in question;

2. Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome;

3. Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

4. Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

IV. QUESTIONS AND ANSWERS

A. GENERAL

A.1. Q: Why did FDA develop the financial disclosure regulations?

A: In June 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report[5] to FDA stating that FDA's failure to have a mechanism for collecting information on "financial conflicts of interest" of clinical investigators who study products that undergo FDA review could constitute a material weakness under the Federal Managers' Financial Integrity Act. As stated in the preamble to the final rule, although FDA determined that a material weakness did not exist, the agency did conclude that there was a need to address this issue through regulation.[6] During the rulemaking process, FDA also learned about potentially problematic financial interests and arrangements through published newspaper articles, Congressional inquiries, and public testimony and comments. Based on the information gathered, FDA determined that it was appropriate to require the submission of certain financial information with marketing applications that, in part, rely on clinical data.

[5] Office of the Inspector General (OIG), Department of Health and Human Services (DHHS), *Management Advisory Report – Financial Involvement of Clinical Investigators with Sponsors of Research Leading to Food and Drug Administration Marketing Approval*, June 1991, OI-HQ-91-003.

[6] The final rule was published in the *Federal Register*, Vol. 63, February 2, 1998, pages 5233-5254. The referenced statement appears on page 5235.

A.2. Q: What is the purpose of FDA's review of clinical investigator financial disclosure information and how can sponsors minimize bias?

A: FDA's review of clinical investigator financial disclosure information alerts FDA staff to financial interests and arrangements that could lead to bias in covered clinical studies. The financial disclosure process also provides FDA with information regarding whether and to what extent the sponsors have taken steps to minimize the risk of bias. An important means of minimizing the potential for bias resulting from such financial interests and arrangements is through proper study design (see 21 CFR § 54.5(b)). For example, using randomization and blinding helps to minimize the potential for bias in assigning subjects to receive the test article or placebo and in assessing study outcomes and analyzing results. Similarly, having someone with no financial interests or arrangements evaluate study endpoints, especially in an unblinded study, can help minimize potential bias in assessing therapy outcomes.

FDA staff consider the financial disclosure information and the methods the sponsor used to minimize bias during the review of marketing applications to assess the reliability of the clinical data (see 21 CFR § 54.1). Additionally, because sponsors of studies conducted under INDs and IDEs are required to collect financial information from clinical investigators prior to study initiation,[7] sponsors can work with FDA to minimize any potential bias. FDA strongly encourages sponsors of studies not conducted under an IND/IDE to collect financial information prior to study initiation for the same reasons.

B. FORMS AND INFORMATION TO BE SUBMITTED

B.1. Q: What financial disclosure information is to be included in a marketing application?

A: The application must contain a list of all clinical investigators who conducted each covered clinical study (21 CFR § 54.4). For purposes of this list, investigators and subinvestigators who meet the definition of "clinical investigator" in 21 CFR § 54.2(d) must be included. Note that the term clinical investigator includes the spouse and each dependent child of a clinical investigator (21 CFR § 54.2(d)). This list must also identify those clinical investigators who are full or part-time employees of the sponsor of the covered study (21 CFR § 54.4). If a spouse or dependent child is an employee of a sponsor, that clinical investigator should be identified as an employee for purposes of financial disclosure. For each clinical investigator who is not identified as an employee of the sponsor, <u>one</u> of the following must be submitted (21 CFR § 54.4(a)):

[7] 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)

1. FORM FDA 3455, Disclosure Statement,[8] for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. The form should include an attachment with detailed information about those financial interests and arrangements (for example, the nature of the contingent payment or the equity holdings of the investigator, or the investigator's spouse or dependent child, that exceeded the threshold) and a description of the steps taken to minimize the potential for bias resulting from the disclosed financial interests and arrangements (21 CFR § 54.4(a)(3)). See Section IV.C for additional information;

2. FORM FDA 3454, Certification, for any clinical investigator who has no disclosable financial interests in or arrangements with any sponsor of the covered clinical study (21 CFR § 54.4(a)(1)); the applicant may append a list of investigator names to a single FORM FDA 3454 for those investigators with no disclosable financial interests or arrangements; or

3. If the applicant was unable to obtain some or all of the financial information needed to disclose or certify for a clinical investigator, the applicant must identify any disclosable financial interests or arrangements of which it is aware, certify that it acted with due diligence to obtain the information (listed as option 3 on FORM FDA 3454), and include an attachment identifying the reason why any missing information could not be obtained (21 CFR § 54.4). FDA expects that in the vast majority of cases, applicants will be able to provide a complete financial Certification or Disclosure Statement and that the need to certify that they acted with due diligence will be rare. See Question B.7 and Question F.2 for additional information on due diligence.

FDA encourages applicants to submit financial disclosure information in a format that will ensure all required information is included. For example, applicants should provide the total number of investigators in the study and a table indicating, for each clinical investigator listed who is not identified as an employee, whether they are providing a Certification (FORM FDA 3454), a Disclosure Statement (FORM FDA 3455) or certification that they acted with due diligence but were unable to obtain the information (option 3 on FORM FDA 3454). Applicants should also ensure that all required attachments, as identified above, are included. Applicants with questions about acceptable formats for submitting the financial disclosure information should contact the Center representatives identified in Question K.1.

[8] As an alternative to a separate FORM FDA 3455 for each clinical investigator with information to disclose, applicants may submit a single FORM FDA 3455, with attachments clearly identifying all clinical investigators with information to disclose and, for each investigator, identifying the study, the specific details of their financial interests and arrangements and the steps taken to minimize the potential for bias. Applicants with questions about alternative formats should contact the Center representatives identified in Question K.1.

B.2. Q: May an applicant rely upon the policies and procedures of the clinical investigator's institution for disclosure, review and management of financial conflicts of interest of their employees (including spouse and dependent children)?

A: Each applicant is responsible for disclosing or certifying as required by 21 CFR part 54. Compliance with institutional policies or procedures by an investigator is not a substitute for compliance with part 54.

Although a clinical investigator's institution may take steps to manage a clinical investigator's financial interests and arrangements, in order to minimize study bias, FDA must make its own evaluation of the clinical investigator's financial interests and arrangements (21 CFR § 54.5). When a clinical investigator has disclosable financial interests and arrangements, the disclosure statement submitted to FDA is required to include a description of any steps taken to minimize the potential for bias resulting from any of the disclosed financial interests and arrangements (21 CFR 54.4(a)(3)(v)). A description of the steps taken by the institution to minimize bias should be included with the disclosure statement, if pertinent. See Section IV, Question D.7 for additional information.

B.3. Q: Where in a marketing application for a drug or a biological product should an applicant include the certification or disclosure forms and attachments?

A: Applicants using the format described in FORM FDA 356h (Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use) should include the clinical investigator list and financial certification and/or disclosure forms and attachments as part of item 19 (Financial Information) of the application.[9] Applicants using the Common Technical Document (CTD) format should include this information in Module 1.3.4.[10]

B.4. Q: Where should the information be included in a device marketing application?

A: Applicants should submit the clinical investigator list and financial certification/disclosure forms and attachments according to the format outlined in the appropriate submission guidance.[11]

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[9] Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

[10] The eCTD Backbone Files Specification for Module 1, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf.

[11] For premarket notification submissions, see "Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s," available at www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm.
For premarket approval applications, see "Guidance for Industry and FDA Staff: Premarket Approval Application Filing Review," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089430.htm.

B.5. Q: How should the financial information be submitted?

A: The financial information is required to be submitted using FORMS FDA 3454 and/or 3455 (21 CFR § 54.4(a)), which are available on the Web at the following Internet address: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm (Forms are listed in numerical order).

B.6. Q: Who, specifically, is responsible for signing the financial certification/disclosure forms?

A: The forms are to be signed and dated by the chief financial officer or other responsible corporate official or representative of the applicant. FDA recommends that the "other responsible corporate official or representative" be a senior official who has the authority to ensure the information is collected and reported accurately. Depending on company structure, such an individual could be the person in charge of regulatory or clinical affairs.

B.7. Q: What does FDA mean by the term "due diligence"?

A: "Due diligence" is a measure of activity expected from a reasonable and prudent person under a particular circumstance, in this case, collecting information about financial interests or arrangements. FDA expects that applicants will typically be able to obtain the required information because investigators are required to provide financial disclosure information to sponsors before participating in a clinical study. (21 CFR §§ 54.4, 312.53(c), 812.43(c) and 812.20(b)(5).) In the rare circumstance where applicants are unable to obtain required financial information, applicants must certify that they acted with due diligence and explain why the information was not obtainable (21 CFR § 54.4).

If all of the information required to make a complete certification or disclosure is not available from a sponsor, applicants should make appropriate efforts to obtain the information by other means. That may mean contacting an individual investigator or subinvestigator directly. If an investigator's whereabouts are unknown, for example because the investigator left a study prior to its completion or prior to one year following completion of the study, FDA recommends that sponsors and/or applicants try to locate the clinical investigator. Sponsors and applicants should exercise reasonable judgment regarding the appropriate amount of effort to expend when attempting to contact investigators, which may include consideration of the role of the investigator in the study and the importance of the investigator's data contribution.

In most cases, FDA suggests that more than one attempt at contacting an investigator would be appropriate and that more than one method of contact be attempted. FDA also recommends that each attempt to contact the investigator be documented, for example, by maintaining copies of e-mails and letters and documenting telephone calls and conversation by written memoranda. FDA also suggests that sponsors and applicants consider using a method of contacting investigators that allows verification of receipt, such as certified mail or reliable courier service that provides notice of recipient's receipt

of a letter. When such methods are used, copies of the delivery notice or undeliverable notice should be maintained.

If an investigator is no longer at the institution where the study was conducted, FDA recommends that the sponsor or applicant make a reasonable attempt to locate the investigator, for example, by requesting contact information from the institution where the study was conducted or the institution with which the investigator was affiliated, contacting professional associations the investigator may have been affiliated with, and/or conducting Internet searches.

If a clinical investigator cannot be located or information for some other reason cannot be obtained from the investigator, the sponsor should have access to certain disclosable financial information and arrangements, for example, payments made specifically to the investigator or information related to product sales that may generate royalties due to the investigator. On request from an applicant, sponsors should check their records for such information and, subject to any privacy laws (noting that other countries' laws may differ from United States law), the sponsor should then provide disclosable information to the applicant. In addition, and as necessary, efforts should be made to obtain disclosable financial information from other reasonably available, reliable, public sources of information. For example, information on proprietary interests in the test product, such as patents and trademarks, should be available from publicly available sources.[12] Another possible source of information is the clinical investigator's institution, which may have collected financial information and, if consistent with their policies, may release this information to the applicant upon request. Appropriate certifications, disclosures, and/or explanations should be provided to FDA on the basis of information obtained. See Question F.2 for additional information.

An applicant must exercise due diligence whether a covered study is conducted at foreign or domestic sites. The agency expects that a reasonable and prudent applicant will take affirmative steps at the first opportunity to see that the financial information required for a complete certification or disclosure under part 54 is collected and maintained. This is not only to ensure that the applicant will be able to make a complete submission but also to ensure that the study sponsor will take steps to protect the study against possible bias. See Questions E.3, E.5, and F.3 for additional information.

B.8. Q: Is clinical investigator financial disclosure information required in IND or IDE applications?

A: No, IND/IDE sponsors are not required to submit information regarding clinical investigator financial interests or arrangements in IND or IDE applications. They are, however, required to collect this information before a clinical investigator participates in a clinical study (see 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)(5)), and

[12] Such sources include the Patent and Trademark Office website and, once available, the federal reporting website proposed by the Centers for Medicare & Medicaid Services as required by Section 6002 of the Patient Protection and Affordable Care Act. See the final rule, "Transparency Reports and Reporting of Physician Ownership or Investment Interests," *Federal Register*, Vol. 78, February 8, 2013, page 9458.

clinical investigators are required to disclose financial information to sponsors (see 21 CFR §§ 312.64(d) and 812.110(d)). The information need not be submitted to FDA until a marketing application is submitted containing the results of the covered clinical study (21 CFR § 54.4).

Study sponsors are encouraged to consult with FDA prior to and during clinical studies about the management of specific situations involving potential bias on the part of a clinical investigator. During these consultations, FDA staff should focus on the protection of research subjects and the minimization of bias from all potential sources.

C. FINANCIAL INTERESTS AND ARRANGEMENTS SUBJECT TO DISCLOSURE

C.1. Q: What information about a financial interest or arrangement should be disclosed to the agency? For example, if an investigator owns more than $50,000 of stock in a publicly held company, can the applicant just disclose that there is an interest that exceeds the $50,000 threshold or is it necessary to disclose in written detail the interest or arrangement in question?

A: The applicant must make a complete and accurate disclosure (21 CFR § 54.4(a)(3)). The specific details of the financial interest or arrangement, including its size and nature, should be disclosed as should any steps taken to minimize the potential for study bias resulting from the interest or arrangement. In describing financial interests, for example, the applicant might list: stock valued at $77,000, speaking fees of $7,500, consulting fees of $22,000, and a grant of $125,000 and include a discussion of the specific steps taken to minimize potential bias. Sponsors should request that clinical investigators provide sufficient detail about their financial disclosure information to allow the appropriate disclosures to be made.

C.2. Q: Should a clinical investigator report all fluctuations above and below the $50,000 level during the course of the investigation and one year after completion of the study?

A: In light of the potential volatility of stock prices, FDA recognizes that the dollar value of an investigator's equity holding in a sponsoring company is likely to fluctuate during the course of a study. Clinical investigators should report an equity interest when the investigator becomes aware that the holding has exceeded the threshold and the investigator should use judgment in updating and reporting on fluctuations in equity interests exceeding $50,000. FDA does not expect the investigator to report when an equity interest fluctuates below that threshold. See Question E.4 for additional information.

C.3. Q: Are equity interests in mutual funds and 401(k)s reportable?

A: FDA expects that equity interests held in publicly traded mutual funds will not be reportable in the vast majority of cases. If, however, an investigator would have control

over buying or selling stocks in a mutual fund, equity interests held in such publicly traded mutual funds would be reportable.

If an investigator holds an equity interest in a sponsor over $50,000 in a 401(k) or equivalent account, and has control over whether to buy or sell the interest, the equity interest is reportable.

C.4. Q: How do significant payments of other sorts (SPOOS) relate to the variety of payments the sponsor might make to an individual or institution for various activities?

A: The term "significant payments of other sorts" was intended to capture substantial payments or other support that has a value of more than $25,000 provided to an investigator or institution that could create a sense of obligation to the sponsor.

These payments do not include payments for the cost of conducting the clinical study of the product under consideration or clinical studies of other products, under a contractual arrangement, but do include other payments made directly to the investigator or to an institution for direct support of the investigator.

“Significant payments of other sorts” would include, for example, payments, retainers and honoraria from a sponsor to a clinical investigator for activities such as participating on committees, providing consultation, or serving as a preceptor (21 CFR § 54.2(f)). Grants to fund ongoing research, including laboratory activities and equipment, and compensation in the form of actual equipment for the laboratory/clinic would also be considered significant payments of other sorts. This means that if an investigator were given equipment or money to purchase equipment for use in the laboratory/clinic but not in relation to the conduct of the clinical study, payment would be considered a significant payment of other sorts (21 CFR § 54.4(a)(3)(ii)). If, however, the investigator were provided with computer software or money to buy software needed for use in the clinical study, that payment would not need to be reported.

Payments made to the institution that are not made on behalf of the investigator and are not specifically targeted towards the investigator generally would not need to be reported. Under certain circumstances, however, a grant made to an institution would be considered targeted towards the investigator (and therefore considered reportable); for example, if the grant is worded in such a way that only the investigator could fulfill it.

Finally, payments that meet the criteria for significant payments of other sorts that are made to other researchers at the institution, who are not part of the covered study, do not need to be reported.

C.5. Q: Are payments made to investigators to cover travel expenses (such as transportation, lodgings and meal expenses) reportable as significant payments of other sorts (SPOOS)?

A: Generally, reasonable payments made to investigators to cover reimbursable expenses such as transportation, lodgings and meals do not fall within the definition of SPOOS and, therefore, would not need to be reported. Payment for other expenses that are generally considered outside of normal reimbursable expenditures and not expenses necessary to conduct the study would be considered SPOOS. Such payments would include, for example, entertainment costs, travel costs associated with transporting and/or providing lodgings and meals for family members, and other payments that exceed reasonable expectations (for example, if an investigator was flown to a resort location for an extra week of vacation). These types of expenses are reportable and should be tracked as SPOOS. FDA understands that such payments may be limited or prohibited by industry ethical codes.[13] To the extent such payments are made, they would be SPOOS.

C.6. Q: Is the dollar amount that triggers reporting of significant payments of other sorts (SPOOS) cumulative over the course of the study or is it based on the amount received on an annual basis?

A: The $25,000 threshold amount for reporting SPOOS is based on the cumulative amount of SPOOS received by the clinical investigator (including payments made to the spouse and dependent children) over the course of the study and for one year following completion of the study.

C.7. Q: Does FDA have expectations about how the financial information should be collected? Will FDA consider it acceptable practice for a company to use a questionnaire to collect financial information from investigators rather than constructing an internal system to collect and report this information?

A: FDA regulations do not prescribe a particular method for collecting financial information from investigators. Sponsors/applicants have the flexibility to collect the information in the most efficient and least burdensome manner that will allow for complete and accurate certifications and disclosures. They may use questionnaires completed by the clinical investigators and/or information already available to the sponsor, as appropriate. FDA does not require sponsors to establish elaborate systems to collect and track financial information.

If sponsors intend to use a questionnaire to collect financial information from investigators, FDA recommends that they develop forms suited to that purpose. FORM FDA 3455 was designed for applicants to use to report financial information they collected from clinical investigators to FDA. It does not include the background

[13] Examples of industry ethical codes would be the "Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results" from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the "Code of Ethics on Interactions with Health Care Professionals" from the Advanced Medical Technology Association (AdvaMed).

information needed for clinical investigators to be aware of the financial information to be provided. For example, there is no statement that the reporting requirements apply to the spouse and dependent children as well as to the investigator; no information as to the dollar amounts triggering reporting of equity interests or SPOOS; and no statement that the investigator must report the details of the financial interests and arrangements, not just a statement, for example, of equity interest greater than $50,000. In addition, when there is more than one sponsor for financial disclosure purposes, the investigator should be apprised that the dollar amounts triggering reporting apply separately to each sponsor. This type of explanatory information should be provided to the clinical investigators to ensure that the financial disclosure information collected is as accurate and complete as possible. Please see the Appendix for considerations for collecting financial disclosure information from clinical investigators.

C.8. Q: The regulation requires that investigators provide information on financial interests and arrangements during the course of the study and for one year after completion of the study (see 21 CFR § 54.4(b)). What does "during the course of the study" mean? What does "completion of the study" mean?

A: "During the course of the study" refers to the time from the date the clinical investigator entered into an agreement with the sponsor to conduct the study until the completion of the study. For the purposes of financial disclosure under part 54, completion of the study means that all study subjects have been enrolled and follow-up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol. Many studies have more than one phase (e.g., a study could have a short-term endpoint and a longer term follow-up phase). "Completion of the study" here refers to the part of the study that is being submitted in the application. If there were a subsequent application based on longer term data, completion of the study would be defined using completion of follow-up for the longer term data. An applicant is not required to submit updated financial information to FDA after submission of the application, but applicants must retain complete records (21 CFR § 54.6). Where there is more than one study site, the sponsor may consider completion of the study to occur when the last study site is complete, or may consider each study site individually as it is completed.

C.9. Q: What if the sponsor changes during the course of the study or within one year of completion of the study, for example, through purchase or merger?

A: Agency regulations require that an IND/IDE sponsor collect financial information from all clinical investigators and that clinical investigators promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study (21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Therefore, if the study sponsor changes during the course of the study, the clinical investigators will need to update their financial disclosure information relevant to the new sponsor. The new sponsor is responsible for collecting this information, and to ensure that the new sponsor has complete financial disclosure information, the new sponsor should seek this information from the original sponsor, and the agency encourages the original sponsor to share their records with the new sponsor.

With respect to covered clinical studies conducted outside the United States not pursuant to an IND or IDE (such as studies submitted pursuant to § 312.120 or § 814.15), the agency expects applicants to take affirmative action, at the earliest opportunity, to see that this information is collected and available to make a complete disclosure and/or certification under part 54.

D. CLINICAL INVESTIGATOR

D.1. Q: Who is included in the definition of "clinical investigator"?

A: Under part 54, "clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects" (21 CFR § 54.2(d)). This definition is intended to identify the individuals for whom reporting under this regulation is required. Generally, these individuals are considered to be the investigators and subinvestigators taking responsibility for the study at a given study site. The definition also includes the spouse and each dependent child of such an investigator or subinvestigator.

It should be noted that hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are not meant to be included under the definition of clinical investigator. Additionally, individuals who only collect specimens or perform routine tests (such as blood pressure, EKG, x-ray) are not meant to be included under the definition of clinical investigator for purposes of financial disclosure.

D.2. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?

A: For drugs and biological products, an investigator under 21 CFR part 312 is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." (21 CFR § 312.3(b).)

For purposes of the financial disclosure regulation, a clinical investigator is an investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects (21 CFR § 54.2(d)). Therefore, the term clinical investigator in this context would generally include anyone who fits any of the following criteria: signs the FORM FDA 1572 (Statement of Investigator), is identified as an investigator in initial submissions or protocol amendments under an IND, or is identified as an investigator in the marketing application. This could include individuals identified as subinvestigators

on a FORM FDA 1572.[14] For studies not conducted under an IND, the sponsor will need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455 as appropriate. FDA expects that there will be at least one such person at each clinical site. If other individuals are responsible for a study at a site, those persons should also be included as clinical investigators.

D.3. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?

A: For medical devices, investigator is defined under 21 CFR part 812 as an individual under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments. Where an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. (21 CFR § 812.3(i).)

In general, investigators and subinvestigators sign "investigator agreements" in accordance with 21 CFR § 812.43(c), and it is these individuals whose financial interests and arrangements should be reported as they would fall under the definition at 21 CFR § 54.2(d). For studies not conducted under an FDA-approved IDE (that is, a non-significant risk IDE or an exempt study), the sponsor would need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455, as appropriate. We expect that there will be at least one such person at each clinical site.

D.4. Q: Is it necessary to collect financial information on spouses and dependent children of clinical investigators?

A: Yes. The definition of clinical investigator in 21 CFR part 54 includes the spouse and dependent children of the investigators and subinvestigators who are required to report. Therefore, the financial interests and arrangements of the spouse and each dependent child of each investigator and subinvestigator are to be included in the disclosure (21 CFR § 54.2(d)). The dollar amount that triggers reporting is the total of the financial interests of the investigator, spouse, and dependent children (21 CFR § 54.2(d)). If a spouse or dependent child is an employee of the sponsor, the clinical investigator should be identified as an employee of the sponsor and no further disclosure is required. (See 21 CFR § 54.4.)

D.5. Q: Who is considered a "dependent child"?

A: For purposes of clinical investigator financial disclosure under part 54, a dependent child is the investigator's child (whether by blood or adoption), stepchild or foster child who is unmarried, and for whom the investigator provides more than one-half of the

[14] For guidance on who should be listed as an investigator or subinvestigator on Form FDA 1572, please see FDA's Information Sheet Guidance, "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf.

child's support. This would include a child who, at any time during the course of the study and for one year following completion of the study, is under the age of 19, under the age of 24 if a full-time student, or who is permanently and totally disabled. Such a child would generally have the same principal residence as the investigator.

D.6. Q: What obligations does the clinical investigator have under the financial disclosure regulations?

A: Clinical investigators are to provide sponsors sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements (see 21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Clinical investigators must provide this information to sponsors and also promptly update the information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (see 21 CFR §§ 54.4(b), 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). See also Question C.2.

D.7. Q: May a clinical investigator rely on the information he/she provided to comply with his/her institution's policies and procedures pertaining to financial conflicts of interest to comply with the investigator obligations for financial disclosure under FDA's regulations?

A: The financial information a clinical investigator provides to his/her institution is based on the institution's requirements, which may not be sufficient to meet FDA's regulations. FDA's regulations require the clinical investigator to provide sufficient and accurate financial information to the sponsor to allow the sponsor to submit complete and accurate certification or disclosure statements under FDA's clinical investigator financial disclosure regulations (21 CFR § 54.4(b)). However, if an investigator determines that the financial information he/she provided to his/her institution adequately fulfills the disclosure requirements in FDA's regulations, a clinical investigator could provide the same information to the sponsor. The clinical investigator would still need to commit to promptly updating the financial information if any relevant changes occur during the course of the study and for one year following completion of the study (21 CFR § 54.4(b)).

E. SPONSOR

E.1. Q: How does the definition of "sponsor" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND/IDE regulations (21 CFR parts 312 and 812)?

A: In 21 CFR part 54, the term "sponsor of the covered clinical study" means "the party supporting a particular study at the time it was carried out" (21 CFR § 54.2(h)). FDA interprets "support" to include those who provide material support, for example, monetary support or the test product under study. (See Question E.9 for further explanation of "material support.") This differs from the meaning of "sponsor" in other FDA regulations (such as 21 CFR parts 312 and 812), where the sponsor may be the

person who initiates or takes responsibility for a clinical investigation (21 CFR §§ 312.3(b) and 812.3(n)). While the definition of sponsor under part 54 usually would include the sponsor of an IND/IDE (as defined in 21 CFR parts 312 and 812), it also includes any other individuals who provide material support for the study. Therefore, a covered clinical study may have more than one sponsor for financial disclosure purposes. When there is more than one sponsor, FDA interprets the regulation to mean that the dollar amounts triggering reporting apply separately to each sponsor.

E.2. Q: What obligations do IND and IDE sponsors have regarding information collection prior to study start?

A: The IND and IDE regulations provide that, before permitting an investigator to begin participation in an investigation, the IND/IDE sponsor (that is, the sponsor as defined in 21 CFR parts 312 and 812) must obtain sufficient and accurate financial information that will allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR part 54 (21 CFR §§ 312.53 and 812.43). In order to fulfill these requirements and ensure complete disclosure, the IND/IDE sponsor should identify all "sponsors of the covered clinical study" (as defined in 21 CFR § 54.2(h)) for investigators because the identity of all parties providing support may not be known to investigators.

The sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (21 CFR §§ 312.53 and 812.43). By collecting the information prior to the study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and can take steps to minimize any possibility for bias.

E.3. Q: Why is the IND/IDE sponsor responsible for obtaining financial information from investigators?

A: Although reporting to the FDA is the responsibility of the applicant, the IND/IDE sponsor is required to collect the financial information before permitting an investigator to participate in a clinical study (21 CFR §§ 312.53, 812.20(b)(5), and 812.43). The purpose of this requirement is twofold:

1. to alert the IND/IDE sponsor of the study of any potentially problematic financial interests or arrangements as early in the product development process as possible in order to minimize the potential for study bias, and

2. to facilitate the accurate collection of financial information that may not be submitted until several years later.

The IND/IDE sponsor, who is in contact with the investigator, is best placed to inquire as to the financial interests and arrangements of investigators, and this obligation applies to any IND/IDE sponsor (e.g., commercial, government, or contract research organization

(CRO)). The IND/IDE sponsor is required to maintain complete and accurate records showing any financial interest in, or arrangement with, a sponsor of the covered study, as described in 21 CFR § 54.4(a)(3)(i-iv) (21 CFR §§ 312.57(b) and 812.140(b)(3)). The IND/IDE sponsor is also best situated to ensure that required financial information is collected and made available to the applicant company, so that the information can be included in the marketing application. (Refer to 21 CFR §§ 54.4, 312.53, 312.57(b), 812.43, and 812.140(b)(3).)

IND/IDE sponsors conducting covered clinical studies outside the United States should note that the part 54 regulations do not distinguish between foreign and domestic sites. See Question F.3 for additional information.

E.4. Q: Is the IND/IDE sponsor responsible for obtaining 1-year follow-up financial information from clinical investigators?

A: As noted in response to Question E.2 above, the IND/IDE sponsor is required to obtain financial information from clinical investigators before permitting the investigators to begin participation in an investigation and to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the study and for one year following the completion of the study (21 CFR §§ 312.52 and 812.43). The regulations do not specifically require the IND/IDE sponsor to obtain information from clinical investigators one year following completion of the study. The regulations, however, do require IND/IDE sponsors to maintain complete and accurate records concerning all financial interests and arrangements of clinical investigators subject to part 54 (see 21 CFR §§ 312.57(b) and 812.140(b)(3)) and to secure investigator compliance with the regulations (see 21 CFR §§ 312.56(b) and 812.46(a)). Therefore, an IND/IDE sponsor should take steps to ensure clinical investigator compliance, such as reminding the clinical investigators of the requirement to promptly update their financial information when any relevant changes occur during the study and for one year following completion.

E.5. Q: What if the IND/IDE sponsor is not the party who will be submitting a marketing application?

A: In many cases, the IND/IDE sponsor, the part 54 sponsor, and the applicant will be the same party. However, there may be times when they are not. For example, consider the case when an academic institution serves as the IND/IDE sponsor and a drug company serves as the part 54 sponsor by providing funding or the investigational drug for the study. When a marketing application is submitted, the drug company is likely to be the applicant. If, however, the drug company was sold to another company, the applicant may be neither the IND/IDE sponsor nor a part 54 sponsor.

It should be noted, however, that even if the IND/IDE sponsor will not be submitting the marketing application, the IND/IDE sponsor is still responsible for collecting financial information from the clinical investigators. The responsibility for reporting financial information to FDA falls upon the applicant; that is, part 54 requires the applicant to

submit financial information when the marketing application is submitted to FDA (21 CFR § 54.4(a)).

As stated above and in Question E.3, an IND/IDE sponsor is responsible for collecting financial information from both foreign and domestic clinical investigators. If a sponsor did not collect this information, for example, because the sponsor conducted a foreign study that was not conducted under an IND/IDE and was not originally intended for submission to the FDA, the applicant is expected to contact the sponsor and/or clinical investigators to retrospectively obtain the financial disclosure information. See Questions F.2 and F.3 for additional information.

E.6. Q: If a contract research organization (CRO) is conducting a covered clinical study on behalf of another company, should the CRO collect the financial information from investigators? Is it necessary to collect financial information from investigators who have financial interests in or arrangements with CROs?

A: If a CRO meets the definition of an IND/IDE sponsor or has contracted to collect financial information from clinical investigators on behalf of a sponsor, the CRO must collect financial information on clinical investigators' interests in any sponsors of the covered clinical study. See 21 CFR § 312.52. To satisfy the requirements in part 54, if the CRO provides material support for a covered study, financial information on clinical investigators' financial interests in and arrangements with the CRO is to be collected. If another entity provided material support for the study, and the CRO was responsible for collecting the information, then the CRO also would collect financial information relative to that entity.

E.7. Q: Suppose a public or academic institution conducts a covered clinical study without any support from a commercial sponsor, but the study is later used by an applicant to support its marketing application. In that case, who is the "sponsor" of the study and what information should the applicant submit?

A: In this case, the part 54 sponsor of the study is the public or academic institution. Because such institutions are often not commercial entities, there may not be relevant equity interests to report. However, if the clinical investigator is not a full-time or part-time employee of the public or academic institution, the clinical investigator would need to report any relevant interests under 21 CFR § 54.4, such as any proprietary interest in the tested product, including but not limited to a patent, trademark, copyright or licensing agreement, and reportable financial arrangements with the institution, such as compensation affected by the outcome of studies or significant payments of other sorts. The clinical investigator's financial interests in and arrangements with the applicant would not need to be reported because the company was not a sponsor of the covered clinical study.

If, however, the applicant provided material support for the study (for example, by providing the study product for free), then it would be considered a sponsor for financial disclosure purposes. The academic institution conducting the study would need to collect

information regarding the clinical investigators' financial interests and arrangements with the company.

E.8. Q: If a subsidiary of a larger parent company is conducting a covered clinical study, are the financial interests and arrangements of the clinical investigators with only the subsidiary reported? Or, are the financial interests of the investigators in the parent company to be reported also?

A: If the subsidiary company meets the definition of a sponsor of the covered study as defined in 21 CFR part 54, the IND/IDE sponsor is required to collect clinical investigators' financial information related to the subsidiary company. If the parent company is a 21 CFR part 54 sponsor of the study, the IND/IDE sponsor also must collect financial information related to the parent company. If there are multiple companies providing material support for a covered study, the IND/IDE sponsor is responsible for collecting financial information from clinical investigators related to all companies providing that support (21 CFR §§ 54.4, 312.53 and 812.43). The company that will submit the marketing application is ultimately responsible for submitting to the agency the disclosable financial interests and arrangements of clinical investigators with respect to all the covered study's sponsors, as defined in 21 CFR part 54, at the time the marketing application is submitted (21 CFR § 54.4).

E.9. Q: What is considered "material support" when identifying sponsors of the covered study?

A: Parties that provide "material support" are considered sponsors of the covered clinical study. This would include providing direct funding or other monetary support such as through a grant, or providing services or materials. If a party receives reimbursement for the services and/or materials it is providing, then that party generally would not be considered a sponsor. For example, a CRO paid by a sponsor to perform services would not be considered a sponsor of the covered clinical study. Materials could include the product under study as well as other products and/or equipment that are needed for the conduct of the study, such as ancillary medication and equipment used in testing required by the protocol.

F. APPLICANT

F.1. Q: Do applicant companies need to collect information for a year after completion of the study? Who is responsible for collecting/providing this information?

A: The investigator must promptly provide updated financial information to the sponsor whenever any relevant changes occur during the course of the investigation and for a one-year period following completion of the study (21 CFR §§ 54.4(b), 312.64(d) and 812.110(d)). In addition, sponsors should record SPOOS that are paid to the investigator or the investigator's institution to support activities of the investigator that have a cumulative monetary value of more than $25,000, exclusive of the costs of conducting the covered clinical studies, both during the study and for one year following completion

of the study (21 CFR §§ 54.2(f) and 54.4(a)(3)(ii)). FDA specified the one-year time frame because anticipation of payments or expectation of employment may be as influential as payments already received. Applicants need only report these financial interests and arrangements when the marketing application is submitted, but sponsors and applicants are responsible for keeping updated financial information from the investigators in company files (21 CFR §§ 54.6, 312.57 and 812.140).

F.2. Q: Suppose an applicant has obtained the results of a clinical study conducted by another sponsor and that sponsor certifies it has no financial disclosure information in its files. Is the applicant obligated to use due diligence in attempting to contact the clinical investigators directly to obtain the information? Is the applicant obligated to provide any certification as to proprietary interests? Is the sponsor obligated to provide the applicant with a statement as to outcome payments?

A: The applicant is required to provide financial disclosure information in a marketing application or certify that it acted with due diligence to obtain necessary information but was unable to do so and state the reason (21 CFR § 54.4). (See Question B.7 for a further explanation of "due diligence.") The sponsor should collect financial disclosure information from the clinical investigators, and, regardless of whether it collected all necessary financial information, should have information on any outcome payments (that is, payment that is dependent on the outcome of the study) and/or SPOOS made to the investigators. The applicant should request this information from the sponsor. The applicant should also make reasonable efforts to contact the clinical investigators to obtain disclosable financial information. Information on proprietary interests, such as patents and trademarks, should also be available to the applicant from publicly available sources.

F.3. Q: Do applicants need to provide information on investigators who participate in foreign studies?

A: The applicant has the same financial disclosure obligations (21 CFR part 54) with respect to studies conducted at foreign and domestic sites. An applicant must include a certification or disclosure of information for each investigator participating in a foreign covered study, or, to the extent the applicant is unable to obtain sufficient information to certify or disclose, it must certify that it acted with due diligence but was unable to obtain the information and state the reason why (21 CFR § 54.4).

Sponsors of foreign covered studies should obtain financial disclosure information from clinical investigators prior to study initiation and provide this information to applicants.[15]

The agency believes that a prudent applicant would take affirmative action at its earliest opportunity to collect financial information relating to a foreign covered study or to ensure that the information is collected by the study sponsor. Where possible, the agency strongly encourages the applicant to arrange for the collection of financial information

[15] If a foreign study is conducted pursuant to an IND or IDE, the sponsor has a legal obligation to comply with applicable rules, including the requirement to collect and maintain financial disclosure information.

prior to study initiation – to ensure that the information is preserved so that a complete submission can be made and to take any steps necessary to minimize potential bias. Where this is not possible, for example, because an applicant is submitting a foreign covered study sponsored by another entity and the applicant did not oversee, support, or direct the study, the applicant should take appropriate steps to obtain financial information from the study sponsor, investigators, or other reasonably available sources. See Question F.2.

G. COVERED CLINICAL STUDY

G.1. Q: Disclosure of financial interests and arrangements is required only for covered clinical studies, specifically, those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). An IND sponsor, acting much earlier, must inquire into investigator financial interests and arrangements before the ultimate role of a study in the application is determined (21 CFR § 312.53). How will the IND sponsor determine which studies will ultimately require certification/disclosure statements?

A: The IND sponsor will need to consider the potential role of a particular study based on study size, design, and other considerations. Almost any controlled effectiveness study could, depending on outcome, become part of a marketing application, but other studies might be critical too, such as a pharmacodynamic study in a population subset or a bioequivalence study supporting a new dosage form. So, for many studies, it would be prudent to collect the information in the event that the study will ultimately require certification and disclosure statements.

G.2. Q: Do the reporting requirements apply to studies that include large numbers of investigators and multiple sites? Will the agency consider a waiver mechanism to exempt applicants from collecting information from clinical investigators conducting these kinds of studies?

A: Large multi-center efficacy studies with many investigators are considered covered clinical studies within the meaning of the regulation (21 CFR § 54.2(e)). Data from investigators having only a small percentage of the total subject population (in a study with large numbers of investigators and multiple sites) could still affect the overall study results depending on the impact of their results on the overall study results. Or, if a sponsor submitted data from a large, multi-center, double-blind study that included several thousand subjects, a single clinical investigator at a large site could be responsible for a significant number of study subjects. In either case, if the investigator fabricated data or otherwise affected the integrity of the data, the results could have been influenced.

By contrast, large open safety studies and treatment protocols that have large numbers of investigators would generally not be considered covered clinical studies. As discussed in the preamble to the final rule,[16] in these large open safety studies and treatment protocols,

[16] See *Federal Register*, volume 63, February 2, 1998, page 5239.

the large number of investigators generally means that no single investigator has a major impact on the data. In addition, important adverse events will generally be apparent because they lead to cessation of therapy and submission of the case report form. Although it is possible that a financial interest could be important in these studies, it is relatively unlikely.

The regulations[17] allow a sponsor to seek a waiver of certain requirements, including financial disclosure requirements. FDA believes it is highly unlikely, however, that a waiver would be justified for studies begun after February 2, 1999, the effective date of the regulation, because the sponsor should already have begun collecting the information on an ongoing basis. FDA will evaluate any request for waiver on a case-by-case basis.

G.3. Q: The definition of a covered clinical study includes "any study in which a single investigator makes a significant contribution to the demonstration of safety." What does this mean?

A: Examples of commonly conducted studies in which a single investigator makes a significant contribution to the demonstration of safety would be studies that are designed to address a particular safety concern. For example, an endoscopy study to evaluate a product's effect on the stomach lining or a study in a subset of patients with a particular pre-existing condition or disease, such as significant cardiovascular risk factors or a history of poor (adverse) response to other treatments. Such studies could have a single investigator, or could involve more than one clinical investigator. If each investigator makes a significant contribution to the study and, therefore, to a demonstration of safety, such studies would be considered covered clinical studies and subject to financial disclosure.

Studies that generally would not be covered studies are large open safety studies (where a large number of clinical investigators enroll subjects) that are designed to look at adverse events in general and do not focus on specific safety concerns.

G.4. Q: Can a literature report be considered a covered clinical study?

A: Yes, a literature report could be considered a covered clinical study if it is being relied upon by the applicant or FDA to establish that the product is effective (including showing equivalence to an effective product) or where a single investigator makes a significant contribution to the demonstration of safety.[18] When an applicant relies on a literature report in this manner, clinical investigator financial disclosure is required. The author(s) and clinical investigators in the study should be contacted for this information to allow the applicant to submit the certification and/or disclosure forms or, if the applicant is unable to obtain the information, certification that the applicant acted with due diligence to obtain the information. Because the financial interests and arrangements

[17] See 21 CFR §§ 312.10, 812.10, 314.90 and 814.20.

[18] Applicants should be aware that additional information may be needed in order for the agency to be able to use published literature reports in support of a marketing application. For example, details about study methodology, the actual products studied, specifics about the patient population, patient accounting, etc. may be needed.

to be reported are those relating to the sponsor(s) of the covered clinical study and the product under study, the clinical investigators would not be required to report their financial interests in and arrangements with the applicant unless the applicant was a sponsor of the covered study.

G.5. Q: Does the regulation include abbreviated new drug applications (ANDAs)? Does the regulation include 510(k)s that include clinical data? What about biosimilars?

A: The regulation requires an applicant whose submission relies in part on clinical data to disclose certain financial interest and arrangements. A "covered clinical study" means any study of a drug (including a biological product) or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product), or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and expanded access protocols. (21 CFR §§ 54.2 and 54.3.) ANDAs are subject to 21 CFR part 54 (21 CFR § 314.94(a)(13)), as are 510(k)s (21 CFR § 807.87(i)). In addition, applications for biological products, including applications submitted under 351(k) of the Public Health Services Act, are also subject to the regulation.

G.6. Q: Does the regulation apply to studies in support of labeling changes?

A: The regulation applies to studies submitted in a supplement when those studies meet the definition of a covered clinical study. The definition includes studies to support safety labeling changes where individual investigators make a significant contribution to the safety information. Studies to support the effectiveness of a new claimed indication are also included. (21 CFR §§ 54.2 and 54.3.)

G.7. Q: Do actual use and labeling comprehension studies conducted to support a request to switch a drug product from prescription to over-the-counter (OTC) status fit the definition of covered clinical study?

A: Applicants who file supplements requesting that FDA approve a switch of a prescription drug to OTC status or who file a new drug application for OTC use often conduct actual use and labeling comprehension studies. These may be intended to demonstrate that the product is safe and effective when used without the supervision of a licensed practitioner; in other cases, they may test labeling comprehension or other aspects of treatment by consumers. Actual use studies performed to support these applications are considered covered clinical studies if they are used to demonstrate effectiveness in the OTC setting or if they represent a safety study where any investigator makes a significant contribution (21 CFR §§ 54.2 and 54.3). Labeling comprehension studies would not be considered covered studies.

G.8. Q: Are clinical investigators of in vitro diagnostics (IVDs) covered under this regulation?

A: Yes. Applicants who submit marketing applications for IVDs that include covered clinical studies must provide the appropriate financial certification or disclosure information (21 CFR § 54.3). Although IVD studies may only involve specimens, under 21 CFR § 812.3(p), "subject" is defined as a "human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control." Under 21 CFR § 812.3(h), an "investigation" is defined as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." Thus, if an investigation of an IVD is used to support a marketing application and it meets the definition of a covered clinical study, it would be subject to this regulation (21 CFR § 54.3).

H. FDA REVIEW

H.1. Q: Under what circumstances relating to financial disclosure would FDA refuse to file an application?

A: FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)). In general, if, during the filing review, an FDA reviewer identifies missing information, an attempt will be made to contact the applicant to obtain the missing information; however, applicants should take reasonable steps to ensure that applications are complete upon submission. Applicants are encouraged to discuss their concerns on particular matters about financial information with FDA.

H.2. Q: Who will review a disclosure of the specified financial interests and arrangements when such information is submitted in a marketing application?

A: FDA review staff, which may include project managers, consumer safety officers, medical officers, and/or others with regulatory or scientific expertise or supervisory authority, will evaluate financial disclosure information.

H.3. Q: What will FDA reviewers consider when evaluating the financial disclosure information?

A: FDA reviewers will evaluate the information disclosed about each covered clinical study in an application to determine the impact of any disclosed financial interests or arrangements on the reliability of the data. See 21 CFR § 54.5(a). FDA may consider many factors in making its evaluation (21 CFR §§ 54.5(a) and (b)).

Part 54 does not categorically prohibit financial interests or arrangements, but it does require applicants to submit a list of clinical investigators who are full-time and part-time employees of the sponsor and to disclose or certify with respect to other investigators so that FDA can assess the possibility of bias. The type of financial interest or arrangement disclosed is important because some financial interests and arrangements are of greater concern than others when assessing the reliability of the data. For example, outcome payments (that is, payment that is dependent on the outcome of the study) elicit the highest concerns, followed by proprietary interests in the test article (such as patents, royalties, etc.). With respect to equity interests and/or SPOOS, the amount and nature of the equity interests and payments may be considered.

When a clinical investigator has disclosable financial interests or arrangements, the FDA reviewer will carefully consider the steps taken by the sponsor to minimize bias[19] as described in the attachment to the FORM FDA 3455. These steps may include study design, use of multiple clinical investigators and study sites, and replication of study results. The agency also gives careful scrutiny to data from clinical investigators who are full-time or part-time employees of the sponsor, because of the possibility of significant financial interests in the outcome of studies. (Hereafter, we refer to these investigator types jointly as "disclosing investigators.") Investigators for whom the applicant is not able to disclose or certify, despite exercising due diligence, will be considered on a case by case basis.

The FDA reviewer may consider elements of the study design, including the method of randomization, the level of blinding (double-blind, single-blind), the presence or absence of a control group, whether placebo or active, the nature of the primary and secondary endpoints (objective, subjective), the method of endpoint assessment, the method of evaluation (including whether someone other than the disclosing investigator measured the endpoints), and whether many investigators, most of whom were not disclosing investigators, participated in the study. The FDA reviewer may also consider the total number of investigators and subjects in the study, the number and percentage of subjects enrolled by the disclosing investigator, information obtained from on-site inspections, and the data (including adverse events) of the disclosing investigator compared to other investigators in the study. The reviewer may look at a re-analysis of the data performed either by the applicant or FDA that excludes the disclosing investigator's results, other relevant types of reanalysis, and/or whether the results were replicated over multiple studies.

The reviewer will make a judgment as to whether the financial interests or arrangements disclosed may have affected the interpretation of study results or otherwise require further action. For example, if a disclosing investigator was a participant in a covered clinical study that (1) had randomized assignment of patients to treatment, (2) had a clearly objective endpoint (such as survival) or an endpoint assessed by a blinded observer other than the clinical investigator, (3) had multiple study sites (so that each investigator enrolled a small fraction of the total number of subjects), and (4) had results generally similar to the results of other investigators, then provided there were no other

[19] See Question A.2 for a discussion of methods to minimize bias.

material, countervailing considerations, the reviewer might determine that a financial interest, employment relationship, or lack of certification or disclosure does not raise serious questions about the integrity of the covered study that require further action. On the other hand, if the results of the disclosing investigator are clearly more favorable than results of the other investigators or centers and the disclosing investigator's results could have influenced outcome, the reviewer would generally need to consider further action. (21 CFR § 54.5(c).)

FDA reviewers should consult with their management as needed to determine appropriate actions.

H.4. Q: What actions may FDA take when a clinical investigator is the employee of a sponsor or has disclosable financial interests or arrangements?

A: If FDA determines that an investigator's financial interests raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)). Please see Section III.C of this guidance for actions that may be taken.

H.5. Q: How is the review to be documented?

A: Each FDA Center provides review templates or checklists for their review staff to use that include a section on financial disclosure issues.

In general, the review should document that a list of clinical investigators for each covered clinical study was provided, and that, as applicable, there was either certification or documentation of disclosable financial interests and arrangements for each investigator on the list who is not an employee of the sponsor[20] (21 CFR § 54.4).

When a disclosure of financial interests and arrangements is included (FORM FDA 3455), reviewers should ensure that the details of the disclosable financial interests and arrangements are attached to the forms along with a description of the steps the sponsor has taken to minimize the potential bias of clinical study results by any of the disclosed interests or arrangements (21 CFR § 54.4(a)(3)). The reviewer will address the question of whether these interests and arrangements raise questions about the integrity of the data and describe any actions taken to minimize bias. The reviewer will also describe any actions taken by the agency to address any questions raised by a disclosable financial interest or provide an explanation for why no action was indicated (21 CFR § 54.5). This documentation should be included in the appropriate section of the review template.

When a sponsor certifies that he/she acted with due diligence to obtain information regarding the clinical investigator's financial interests and arrangements but was unable to obtain it, reviewers should ensure that an explanation of the reason why the information could not be obtained and the efforts made to obtain the information is

[20] If the spouse or dependent child of an investigator is an employee of the sponsor, the investigator should be identified as an employee and further financial disclosure under this provision is not required.

attached to the FORM FDA 3454 (21 CFR § 54.4). See Question B.7 for a discussion of due diligence.

H.6. Q: Under what circumstances will FDA publicly discuss financial interests and arrangements disclosed to the agency?

A: As discussed in the preamble to the 1998 final rule,[21] FDA's policy is that certain types of financial information requested under the rule, notably clinical investigators' equity interests, will be protected from public disclosure unless circumstances relating to the public interest clearly outweigh the clinical investigator's identified privacy interest. FDA cited the example of a financial interest or arrangement so affecting the reliability of a study as to warrant its public disclosure during evaluation of the study by an advisory panel. FDA expects that only rarely would an investigator's privacy interest be outweighed by the public interest and thus warrant disclosure of the details of financial interest or arrangement. The agency will carefully evaluate each circumstance on a case-by-case basis.

FDA recognizes, however, that there is increased interest in the financial arrangements between clinical investigators and sponsors of the clinical trials in which the investigators participate. For this reason, FDA intends to provide information about the number of clinical investigators with disclosable financial interests or arrangements in the new product reviews FDA posts for an approval decision. This information would not identify clinical investigators by name but likely would include information such as the number of clinical investigators in the study and the number of investigators, if any, with disclosable financial interests or arrangements.[22]

I. RECORDKEEPING

I.1. Q: What are the recordkeeping requirements for financial disclosure information?

A: The recordkeeping requirements for applicants are described in 21 CFR § 54.6. Applicants must retain certain information on clinical investigators' financial interests and arrangements (21 CFR § 54.6(a)) and permit FDA employees to have access to the information and to copy the records at reasonable times (21 CFR § 54.6(b)(2)). Records are to be maintained for two years after the date of approval of the application (21 CFR § 54.6(b)(1)).

Additionally, IND and IDE sponsors are required to maintain complete and accurate records of financial disclosure information as part of the records for the investigation (21

[21] *Federal Register*, February 2, 1998, 63 *FR* 5233

[22] FDA also recognizes that subjects participating in a clinical trial may be interested in the financial interests/arrangements of the clinical investigator at the site where the subject is considering participation. The Department of Health and Human Services Guidance Document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," which is applicable to FDA regulated research, recommends that consideration be given to providing potential subjects with information about the financial interests and arrangements of the parties involved in the research. This guidance is available at http://www.hhs.gov/ohrp/policy/fguid.pdf.

CFR §§ 312.57(b) and 812.140(b)(3)) and to retain the records pursuant to the required retention periods identified in the IND and IDE regulations (21 CFR §§ 312.57(c) and 812.140(d)).

I.2. Q: What kind of documentation is necessary for applicants to keep in case questions about certification and/or disclosure arise?

A: To the extent that applicants have relied on investigators as the source of information about potentially disclosable financial interests and arrangements, the underlying documentation (e.g., copies of executed questionnaires returned by investigators, correspondence on the subject of financial disclosure, mail receipts, etc.) should be retained. Likewise, to the extent that applicants who did not sponsor a covered clinical study rely on information furnished by the sponsor, the underlying documentation, including all relevant correspondence with and reports from the sponsor, should be retained. To the extent that applicants rely upon information available internally, all appropriate financial documentation regarding the financial interests or arrangements in question should be retained. For example, in the case of significant payments of other sorts, applicants should keep documentation including, but not limited to, records of electronic financial transactions, certified mail delivery receipts, etc. (21 CFR §§ 54.6(a), 312.57(b) and 812.140(b)(3).)

If storage space is a concern, sponsors and applicants may use electronic storage. For example, required records may be scanned as certified copies [23] of the original and stored electronically, as long as the records remain accessible for inspection and copying by FDA (see Question J.1). If electronic records are used, you should consult guidance on electronic storage of clinical trial records under part 11, "Computerized Systems Used in Clinical Investigations,"[24] for further information about maintaining scanned documents.

J. FDA INSPECTIONS

J.1. Q: Will financial disclosure information be reviewed during a bioresearch monitoring program (BIMO) inspection of the sponsor?

A: During a sponsor inspection, it is FDA's policy to review financial disclosure information that clinical investigators provide to the sponsor, although FDA may request access to these records at other reasonable times. FDA has the authority to access and copy documents supporting an applicant's certification or disclosure statement submitted to the agency in a marketing application (21 CFR § 54.6(b)(2)). FDA's regulations require sponsors to establish and maintain records of data obtained during investigational

[23] FDA's guidance on "Computerized Systems Used in Clinical Investigations" defines "certified copy" as a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all the same attributes and information as the original.

[24] This guidance may be accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf.

studies of drugs, biological products, and devices that will enable the agency to evaluate a product's safety and effectiveness.[25]

J.2. Q: Will financial disclosure be part of a BIMO inspection of a clinical site?

A: It is FDA's policy that FDA investigators should ask the clinical investigator if he/she submitted information to the sponsor prior to initiation of the study and updated that information, as needed, for up to one year after completion of the study at the site.

J.3. Q: Are there any instructions for FDA's inspectional staff with respect to reviewing records pertaining to financial disclosure?

A: FDA has provided instructions in the Compliance Program Guidance Manual (CPGM) chapters on clinical investigator inspections[26] and sponsor inspections.[27]

K. CONTACTS

K.1. Q: Who may be contacted in each FDA Center to answer questions regarding this regulation?

A: The following entities may be contacted: Division of Drug Information in the Center for Drug Evaluation and Research, phone 888-463-6332 or 301-796-3400, Division of Small Manufacturers, International and Consumer Assistance in the Center for Devices and Radiological Health, phone 800-638-2041 or 301-796-7100, and the Office of Communication, Outreach and Development in the Center for Biologics Evaluation and Research, phone 800-835-4709 or 301-827-1800.

[25] 21 CFR §§ 54.6, 312.57, 312.58, 812.140 and 812.145.
[26] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm
[27] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

APPENDIX

Considerations for Collecting Financial Disclosure Information from Clinical Investigators

Suggested items to provide to clinical investigators to assist them in complying with financial disclosure reporting requirements:

1) Identify the sponsor(s) of the covered clinical study. **See Section IV.E.**

2) Identify whose financial interests and arrangements need to be reported (e.g., clinical investigators, their spouses and dependent children). **See Section IV.D.**

3) Identify the financial interests and arrangements that must be disclosed in detail. **See Section III.B and Question C.1.**

   NOTE: The threshold amounts apply separately for each sponsor (**see Question E.1**) but are cumulative for the investigator and his/her spouse and dependent children (**see Section III.B**).

   a) Employment by any sponsor. **See Section III and Questions B.1 and D.4.**

   b) Any compensation by any sponsor in which the value of compensation is affected by study outcome. **See Section III.B.1.**

   c) Any proprietary interest in the tested product. **See Section III.B.2.**

   d) Any equity interest in any sponsor of the covered clinical study whose value cannot be readily determined through reference to public prices. **See Section III.B.3.**

   e) Any equity interest in any sponsor of the covered clinical study if that sponsor is a publicly held company and the interest exceeds $50,000. **See Section III.B.4 and Questions C.2 and C.3.**

   f) Significant payments of other sorts (SPOOS) that have a cumulative monetary value of $25,000 or more made to the investigator or the investigator's institution. **See Section III.B.5 and Questions C.4, C.5 and C.6.**

4) Remind investigators of obligation to promptly update their financial disclosure information when relevant changes occur during the study and for one year following study completion. **See Questions C.2 and D.6.**

FDA Form 3454

Certification: Financial Interest and Arrangements of Clinical Investigator

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Click here for FDA Form 3454

FDA Form 3455

Disclosure: Financial Interest and Arrangements of Clinical Investigators

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Click here for FDA Form 3455

FDA Form 1571

Investigational New Drug Application

Click Here for Instructions

Click here for FDA Form 1571

FDA Form 1572

Statement of Investigator

Click here for Instructions

Click here for FDA Form 1572

FDA Form 3674

Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank

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Click Here for Instructions

Click here for FDA Form 3674

FDA Form 3454

Certification: Financial Interest and Arrangements of Clinical Investigator

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Click here for FDA Form 3454

FDA Form 3455

Disclosure: Financial Interest and Arrangements of Clinical Investigators

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Click here for FDA Form 3455

Initial IND Submission Templates

Cover Letters

- Initial IND Submission Cover Letter- Instructions
- Initial IND Submission Cover Letter Template (Clean)
- Initial IND Submission Cover Letter (Montefiore Letter Head)

Protocol Templates

- NIH FDA Protocol Template

Glossary

Sponsor-Investigator Template (Simple)

Sponsor-Investigator Template (Expanded)

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Montefiore Medical Center.

The initial study protocol for use under this IND is entitled "A Phase I Trial of Deoxyribodismutase in Humans". The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (718) 668-xxxx or at jdurham@montefiore.org. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Commented [KL1]: This is ideally the same as your date of submission.

Commented [KL2]: This part can be customized based on your IND. It may go to CBER or CDRH etc.

Commented [KL3]: Address the cover letter to the appropriate FDA Division Director. The FDA CDER and CBER Divisions can be found on FDA's website at the following links:
CDER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm075128.htm
CBER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123224.htm
Please contact our office if you need additional assistance with finding the appropriate division.

Commented [KL4]: Note: The PI does NOT have to be the sponsor but they may be the same.

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Montefiore Medical Center.

The initial study protocol for use under this IND is entitled “A Phase I Trial of Deoxyribodismutase in Humans”. The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (919) 668-xxxx or at jdurham@notes.duke.edu. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Montefiore
THE UNIVERSITY HOSPITAL FOR
ALBERT EINSTEIN COLLEGE OF MEDICINE

[INSERT: DATE]

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: [*Name of the study drug*]
Initial Investigational New Drug Application
Serial Number 0000

Dear Reviewers:

Pursuant to 21 CFR 312, I am submitting an original, Sponsor-Investigator Investigational New Drug (IND) application.

The IND is being submitted to [*INSERT: Supply short description of experimental treatment/drug and protocol*].

[INSERT: If pre-IND meeting was held, then insert text referencing the pre-IND (PIND) number and the date of meeting.]

Enclosed are the original application, the two copies, and three eCopies. The eCopy is an exact duplicate of the paper copy. UC Davis considers the material and data contained in this application to be confidential and not to be publically disclosed.

UC Davis commits to conduct this clinical investigation in accordance with all applicable regulatory requirements. UC Davise will not initiate this clinical study until this IND has become effective and Investigational Review Board (IRB) approval has been received.

If you have any questions about the material included in this IND, please do not hesitate to contact meat [*INSERT: phone number of Sponsor-Investigator*], by email at [*INSERT: email address of Sponsor-Investigator*], or by fax at [*INSERT: Sponsor-Investigator fax*] any time during your review.

[*COMMENT: If there is another person designated to interact with the FDA on behalf of the SponsorInvestigator,then state "{INSERT: name} is authorized to interact with the FDA on my behalf and{INSERT: name"s} contact information is {INSERT: phone, email, and fax}."]*

Thank you in advance for your consideration.

Sincerely,
[*INSERT: Sponsor-Investigator Name]*
[INSERT: Title]
[INSERT: Affiliation]

Department Name Line 1
Department Name Line 2
111 East 210th Street
Bronx, New York 10467
718-000-0000 Office
718-000-0000 Fax

FirstName LastName
Title 1
Title 2
718-000-0000 Office
718-000-0000 Fax
email@montefiore.org

Once the footer text has been updated please view the document in the "Print Preview" mode. This will force the footer to update on any subsequent pages created in this document.

NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template

PREFACE

Remove this **Preface** before finalizing and distributing the clinical trial protocol.

This clinical trial protocol template is a suggested format for Phase 2 and 3 clinical trials funded by the National Institutes of Health (NIH) that are being conducted under a Food and Drug Administration (FDA) Investigational New Drug (IND) or Investigational Device Exemption (IDE) Application. Investigators for such trials are encouraged to use this template when developing protocols for NIH-funded clinical trial(s). This template may also be useful to others developing phase 2 and 3 IND/IDE clinical trials.

The goal of this template is to assist investigators to write a comprehensive clinical trial protocol that meets the standard outlined in the *International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (ICH-E6)*. Its use will also help investigators think through the scientific basis of their assumptions, minimize uncertainty in the interpretation of outcomes, and prevent loss of data. A common protocol structure and organization will facilitate protocol review by oversight entities.

It is important to note that the clinical trial protocol template is just one piece of information required for an IND or IDE submission. For complete details on IND or IDE submissions see 21 CFR Part 312: Investigational New Drug Application or 21 CFR Part 812: Investigational Device Exemptions, respectively.

How To Use This Template

It is important to incorporate all sections of the template into your protocol and to do so in the same order. If a particular section is not applicable to your trial, include it, but indicate that it is not applicable.

This template contains two types of text: instruction/explanatory and example.

> **Instruction/explanatory text** are indicated by *italics* and should deleted. Footnotes to instructional text should also be deleted. This text provides information on the content that should be included. It also notes if a section should be left blank. For example, many headings include the instruction, "*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*"
>
> **Example text** is included to further aid in protocol writing and should either be modified to suit the drug, biologic or device (study intervention), design, and conduct of the planned clinical trial or deleted. Example text is indicated in [regular font]. Within example text, a need for insertion of specific information is notated by <angle brackets>.

Instruction/explanatory text should be deleted. Example text can be incorporated as written or tailored to a particular protocol. If it is not appropriate to the protocol, however, it too should be deleted. The section headers include formatting to generate a table of contents.

Version control is important to track protocol development, revisions, and amendments. It is also necessary to ensure that the correct version of a protocol is used by all staff conducting the study. With each revision, the version number and date located in the footer of each page should be updated. When making changes to an approved and "final" protocol, the protocol amendment history should be maintained (see Section 10.4).

RESOURCES

Remove **Resources** before finalizing and distributing the clinical trial protocol.

Center for Medicare & Medicaid Services (CMS)

- Clinical Laboratory Improvement Amendments

Code of Federal Regulations (CFR)

- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR Part 210: Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs; General
- 21 CFR Part 211: Current Good Manufacturing Practice For Finished Pharmaceuticals
- 21 CFR Part 312: Investigational New Drug Application
- 21 CFR Part 812: Investigational Device Exemptions
- 42 CFR Part 11: Clinical Trial Registration and Results Information Submission
- 45 CFR Part 46: Protection of Human Subjects Research

Food and Drug Administration (FDA)

- Compliance Actions and Activities
- FDA Regulations Relating to Good Clinical Practice and Clinical Trials
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection
- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
- Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
- Guidance for Industry: Electronic Source Data in Clinical Investigations
- Guidance for Industry: Multiple Endpoints in Clinical Trials
- Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Standardized Study Data
- Guidance for Industry: Safety Assessment for IND Safety Reporting

Department of Health and Human Services (HHS)

- The HIPAA Privacy Rule
- HIPAA Privacy Rule: Information for Researchers

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- Guidance for Industry, E6 (R2) Good Clinical Practice: Consolidated Guidance
- Guidance for Industry, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

- Guideline for Industry, E3 Structure and Content of Clinical Reports
- Guidance for Industry, E9 Statistical Principles for Clinical Trials
- Final Concept Paper E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials

International Organization for Standardization (ISO)

- Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice (ISO 14155:2011)

National Institutes of Health (NIH)

- Certificates of Confidentiality (CoC) Kiosk
- Clinical Trials Registration and Results Information Submission
- Financial Conflict of Interest
- Inclusion of Children- Policy Implementation
- Inclusion Of Women And Minorities As Participants In Research Involving Human Subjects-Policy Implementation Page
- NIH Data Sharing Policies and Related Guidance on NIH-Funded Research Resources
- NIH Data Sharing Policy and Implementation Guidance
- NIH Genomic Data Sharing Policy
- NIH Grants Policy Statement, Section 8.2 Availability of Research Results: Publications, Intellectual Property Rights, and Sharing Research Resources
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- NIH Public Access Policy Details
- Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials
- Required Education in the Protection of Human Research Participants

Office for Human Research Protections (OHRP)

- Human Subject Regulations Decision Charts
- Informed Consent Checklist
- Informed Consent Tips
- IRBs and Assurances
- Regulations & Policy Index
- Unanticipated Problems Involving Risks and Adverse Events Guidance
- Vulnerable Populations

Other

- Citing Medicine, 2nd edition: The NLM Style Guide for Authors, Editors, and Publishers
- CONSORT statement
- International Committee of Medical Journal Editors (ICMJE): Recommendations
- Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII

<Title>

The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity and neutrality is the goal. If there is a "short title" (e.g., an abbreviation used to refer to the study title, include here and that can be used throughout this document in place of the full title).

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <Number, if available>

Principal Investigator: < Principal investigator>

<IND/IDE> Sponsor: <Sponsor name, if applicable>

Sponsor means an individual or pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization who takes responsibility for and initiates a clinical investigation.

Funded by: < NIH Institute or Center (IC)>

Version Number: v.<x.x>

<Day Month Year>

All versions should have a version number and a date. Use the international date format (day month year) and write out the month (e.g., 23 June 2015).

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below:

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

OR

(2) [The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

1 PROTOCOL SUMMARY

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

1.1 SYNOPSIS

Title:	<Full title>
Study Description:	*Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length. A detailed schematic describing all visits and a schedule of assessments should be included in the* ***Schema and Schedule of Activities, Sections 1.2 and 1.3,*** *respectively.*
Objectives:	*Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol. These align with Primary Purpose in clinicaltrials.gov*[1]*.* <Primary Objective: Secondary Objectives: >
Endpoints:	*Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol. These align with Outcome Measures in clinicaltrials.gov.* <Primary Endpoint: Secondary Endpoints: >
Study Population:	*Specify the sample size, gender, age, demographic group, general health status, and geographic location.*
Phase:	<2 or 3 or N/A> *Phase applies to drugs and biologics*[2].
Description of Sites/Facilities Enrolling Participants:	*Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites only and if the study is intended to include sites outside of the United States.*
Description of Study Intervention:	*Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices, provide a description of each important component, ingredient, property and the principle of operation of the device.*
Study Duration:	*Estimated time (in months) from when the study opens to enrollment until completion of data analyses.*
Participant Duration:	*Time (e.g., in months) it will take for each individual participant to complete all participant visits.*

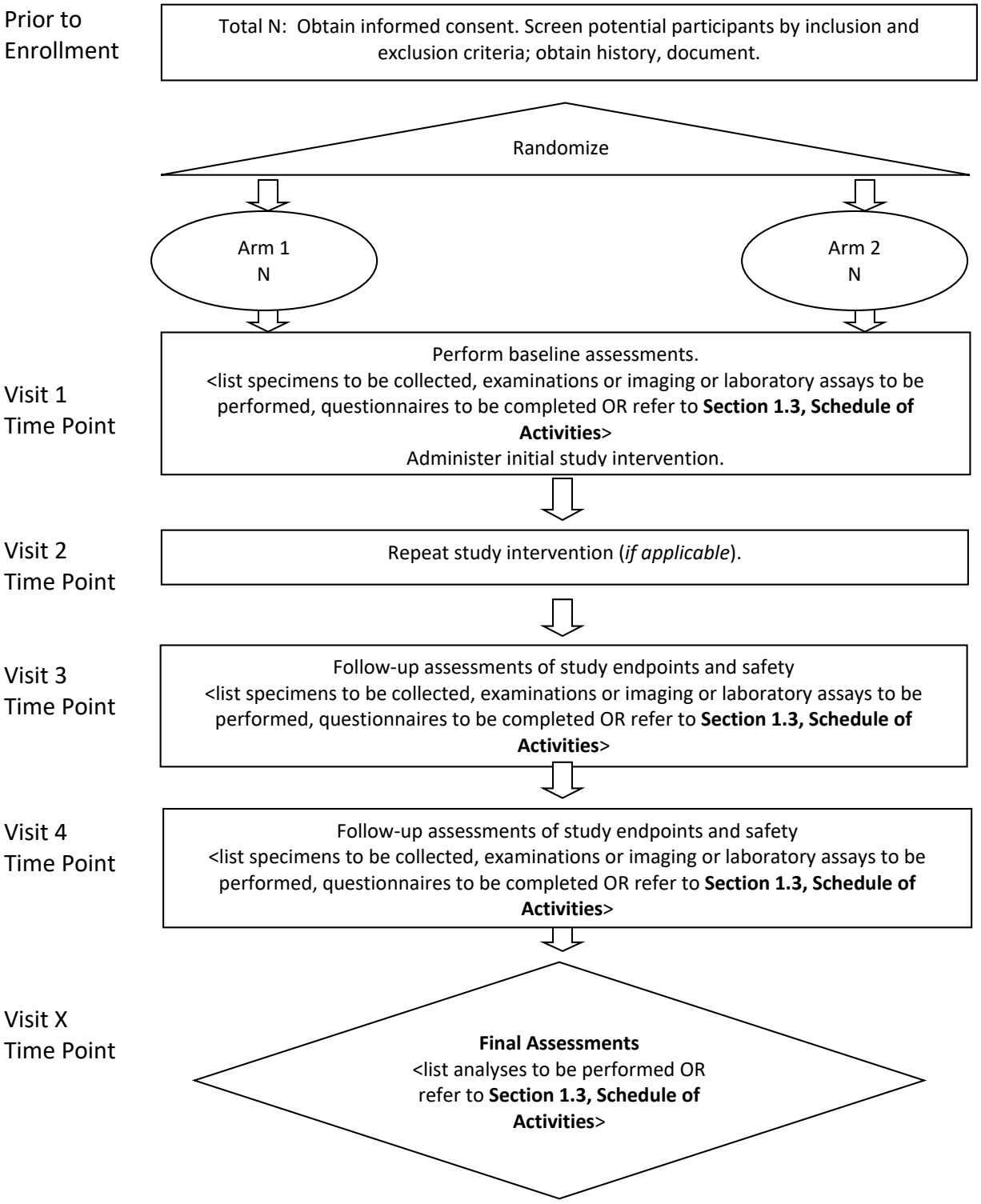
[1] From ClinicalTrials.gov Protocol Data Element Definitions available at: *https://prsinfo.clinicaltrials.gov/definitions.html*. Accessed March 2017.

[2] From 21 CFR 312.21 "Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects… Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects."

1.2 SCHEMA

This section should include a diagram that provides a quick "snapshot" of the study and ideally be limited to 1 page. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Depending on the nature of your study, one example may be more appropriate than another. Regardless, the examples included here are intended to guide the development of a schematic that is appropriate to the planned study design and will need to be customized for the protocol. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). The time point(s) indicated in the schematic should correspond to the time point(s) in ***Section 1.3, Schedule of Activities****, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.*

Example #1 Flow diagram *(e.g., randomized controlled trial)*



Example #2 provided as a guide, customize as needed: Process diagram *(e.g., randomized controlled trial)*

Week/Day (Insert time) Screening

- Total n=x
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Week/Day (Insert time) Randomization

- Intervention Group 1 (n=y)
- Placebo (n=z)

Week/Day (Insert time) Follow-up assessments of study endpoints and safety
Baseline assessments/ Study Intervention

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>
- Administer initial dose of study intervention

Week/Day (Insert time)

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Week/Day (Insert time) Follow-up assessments of study endpoints and safety

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

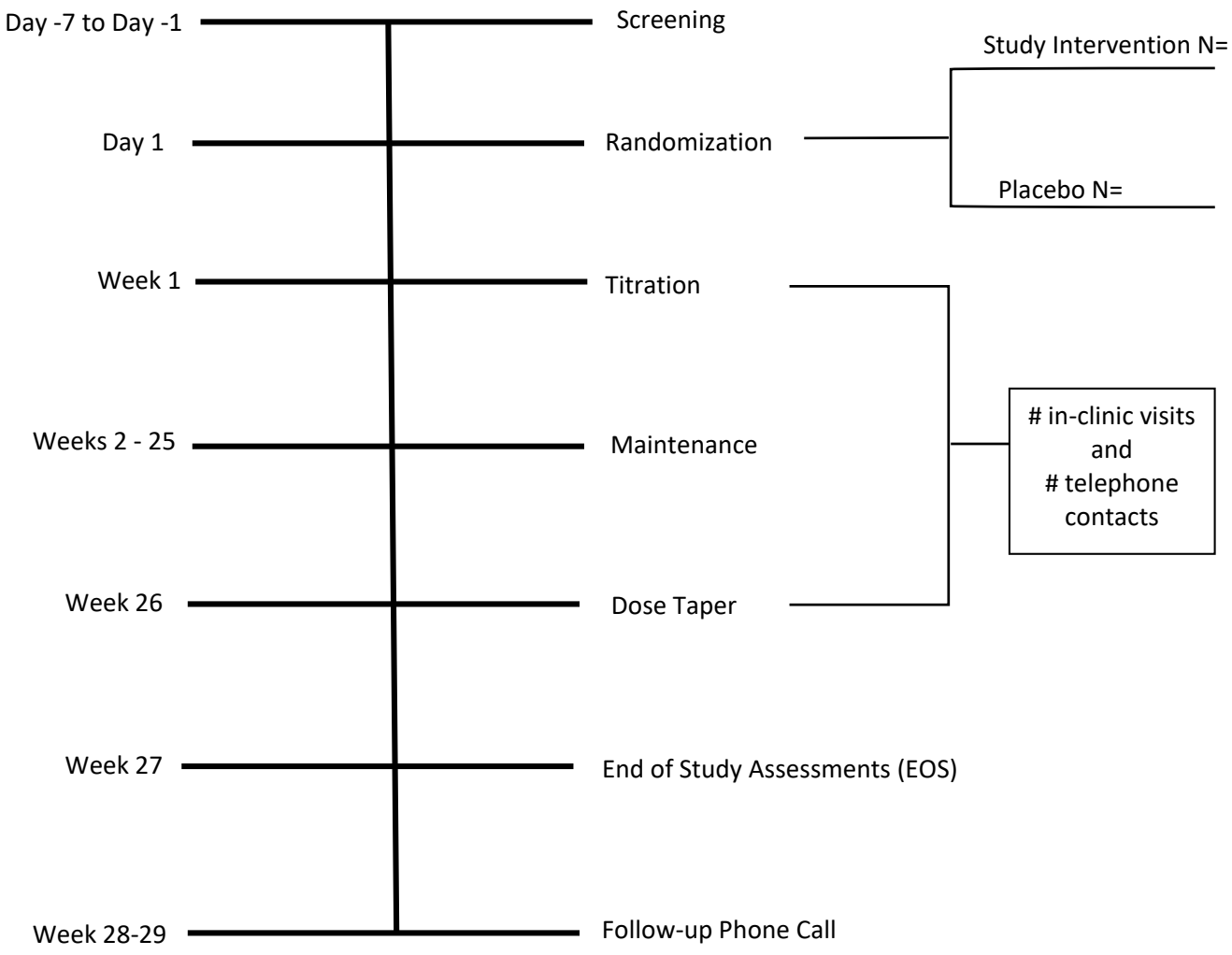
Week/Day (Insert time) End of Study Assessments

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Week/Day (Insert time) Follow-up Telephone Call

- <List questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Example #3 provided as a guide, customize as needed: Timeline diagram *(e.g., randomized controlled trial)*



1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is provided as an example and should be modified as appropriate.

The schedule of activities must capture the procedures that will be accomplished at each study visit, and all contact, with study participants e.g., telephone contacts. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility and study objectives and endpoints. Other procedures should be done sparingly and with consideration, as they may add unnecessary complexity and detract from recruitment.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints (e.g., pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).

Procedures	Screening Day -7 to -1	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 Day 7 +/-1 day	Study Visit 3 Day 14 +/- 1 day	Study Visit 4 Day 21 +/-1 day	Study Visit 5 Day 28 +/-1 day	Study Visit 6 Day 35 +/-1 day	Study Visit 7 Day 42 +/-1 day	Study Visit 8 Day 49 +/-1 day	Study Visit 9 Day 56 +/-1 day	Study Visit 10 Day 63 +/-1 day	Study Visit 11 Day 70 +/- 1 day	Study Visit 12 Day 77 +/-1day	Final Study Visit 13 Day 84 +/-1 day
Informed consent	X													
Demographics	X													
Medical history	X													
Randomization	X													
Administer study intervention		X			X			X			X			
Concomitant medication review	X	X----------												X
Physical exam (including height and weight)	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [b]	X													
EKG (as indicated)	X													
Adverse event review and evaluation	X	X----------												X
Radiologic/Imaging assessment	X				X				X					X
Other assessments (e.g., immunology assays, pharmacokinetic)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.
b: Serum pregnancy test (women of childbearing potential).

<Insert table>

2 INTRODUCTION

No text is to be entered in this section; rather, it should be included under the relevant subheadings below.

The following subsections should include relevant background information and rationale for the clinical trial. This should be a brief overview (e.g., approximately 3-7 pages). Referring to the Investigator's Brochure (IB) for more detail is also appropriate.

2.1 STUDY RATIONALE

State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial

<Insert text>

2.2 BACKGROUND

This section should include:

- *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance*
- *A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies*
- *Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in **Section 11, References**)*
- *Applicable clinical, epidemiological, or public health background or context of the clinical trial*
- *Importance of the clinical trial and any relevant treatment issues or controversies*

<Insert text>

2.3 RISK/BENEFIT ASSESSMENT

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should include a discussion of known risks and benefits, if any, to human participants.

2.3.1 KNOWN POTENTIAL RISKS

Include a discussion of known potential risks from either clinical or nonclinical studies. If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of risk information. If the product is investigational, the IB should be the primary source of the risk information. In addition, relevant published literature can also provide relevant risk information. If the risk profile cannot be described from the package insert, device labeling, or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately.

Describe any physical, psychological, social, legal, economic, or any other risks to participants by participating in the study that the Principal Investigator (PI) foresees, addressing each of the following:

- *Immediate risks*

- *Long-range risks*
- *If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered and explain why alternative procedures are not included*

<Insert text>

2.3.2 KNOWN POTENTIAL BENEFITS

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

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

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

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

<Insert text>

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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

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

<Insert text>

3 OBJECTIVES AND ENDPOINTS

For purposes of registration and reporting to ClinicalTrials.gov, the terms Objectives and Endpoints as used in this template align with the terms Primary Purpose and Outcome Measures in ClinicalTrials.gov, respectively. Provide a description of the study objectives and endpoints, as well as a justification for selecting the particular endpoints, in the table format included below. This will provide clear articulation of how the selected primary and secondary endpoint(s) are linked to achieving the primary and secondary objectives and an explanation of why endpoint(s) were chosen. Data points collected in the study should support an objective or have a regulatory purpose. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study's objectives.

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

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

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

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).	*The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective (e.g., "the study wins"). Often Phase 2 and 3 trials include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold. However, this is not always the case. For example, in many trials of medical devices there are primary endpoints for both safety and effectiveness.* *In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful*	*Briefly explain why the endpoint(s) were chosen.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	therapeutic effect or should have demonstrated ability to predict clinical benefit.	
Secondary		
The secondary objective(s) are goals that will provide further information on the use of the intervention.	*Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention's effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases.*	*Briefly explain why the endpoint(s) were chosen.*
Tertiary/Exploratory		
Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.	*Exploratory endpoints should be specified. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.* *Endpoints that are not listed in an alpha conserving plan will be considered exploratory.*	*Briefly explain why the endpoint(s) were chosen.*

4 STUDY DESIGN

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

4.1 OVERALL DESIGN

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should be consistent with the ***Protocol Synopsis (section 1.1) and Protocol Schema (section 1.2)*** *and include:*

- *A statement of the hypothesis*
- *Phase of the trial*
- *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design)*
- *A description of methods to be used to minimize bias*
- *Dose escalation or dose-ranging details should be contained in* ***Section 6.1.2, Dosing and Administration***
- *The number of study groups/arms and study intervention duration*
- *Indicate if single site or multi-site*
- *Name of study intervention(s)*
- *Note if interim analysis is planned and refer to details in* ***Section 9.4.6, Planned Interim Analysis***
- *Note if the study includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details* ***in Section 9.4.7, Sub-Group Analyses***
- *Name of sub-studies, if any, included in this protocol*

<Insert text>

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Describe the rationale for the type and selection of control (e.g. placebo, active drug, dose-response, historical) and study design (e.g., non-inferiority as opposed to superiority). Discuss known or potential problems associated with the control group chosen in light of the specific disease and intervention(s) being studied.

<Insert text>

4.3 JUSTIFICATION FOR DOSE

Provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the study intervention(s) and control product(s).

<Insert text>

4.4 END OF STUDY DEFINITION

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

Example text provided as a guide, customize as needed:

[A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

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

<Insert text>

5 STUDY POPULATION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should include a description of the study population and participant recruitment. The study population should be appropriate for clinical trial phase and the development stage of the study intervention. Given the continuing challenges in achieving clinically relevant demographic inclusion in clinical trials, it is important to focus on clinically relevant potential participants at the earliest stages of protocol development. Therefore, it is essential that the population's characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities).

Use the following guidelines when developing participant eligibility criteria to be listed in ***Sections 5.1 Inclusion Criteria and 5.2 Exclusion Criteria****:*

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

5.1 INCLUSION CRITERIA

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

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

Example text provided as a guide, customize as needed:

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

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

<Insert text>

5.2 EXCLUSION CRITERIA

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

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

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

Example text provided as a guide, customize as needed (including adding a statement about equitable selection):

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

1. Current use of < specify disallowed concomitant medications>
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Febrile illness within <specify time frame>
6. Treatment with another investigational drug or other intervention within <specify time frame>
7. Current smoker or tobacco use within <specify timeframe>
8. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>]

<Insert text>

5.3 LIFESTYLE CONSIDERATIONS

Include content in this section if applicable, otherwise note as not-applicable.

Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, timing of meals relative to dosing, intake of caffeine, alcohol, or tobacco, or limits on activity), and considerations for household contacts. Describe what action will be taken if prohibited medications, treatments or procedures are indicated for care (e.g., early withdrawal).

Example text provided as a guide, customize as needed:

[During this study, participants are asked to:

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from [X days] before the start of <study intervention> until after the final dose.
- Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for [x hours] before the start of each dosing session until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
- Abstain from strenuous exercise for [x hours] before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Minimize interactions with household contacts who may be immunocompromised.]

<Insert text>

5.4 SCREEN FAILURES

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

Example text provided as a guide, customize as needed:

[Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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

<Insert text>

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Identify general strategies for participant recruitment and retention. This section may refer to a separate detailed recruitment and retention plan in the manual of procedures (MOP) and site specific plans could be included in a site-specific standard operating procedure (SOP). Consider inclusion of the information below either in this section or the MOP.

- *Target study sample size by gender, race and ethnicity, and age; identify anticipated number to be screened including women and minorities in order to reach the target enrollment (should be consistent with information contained in **Section 9.2, Sample Size Determination**)*
- *Anticipated accrual rate*
- *Anticipated number of sites and participants to be enrolled from the U.S. and outside the U.S.*
- *Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public)*
- *Recruitment venues*
- *How potential participants will be identified and approached*
- *Types of recruitment strategies planned (e.g. patient advocacy groups, national newspaper, local flyers; social media, specific names of where advertisements may be planned are not needed)*
- *If the study requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).*
- *Specific strategies that will be used to recruit and retain historically under-represented populations in order to meet target sample size and conform with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects. Include the number of women and minorities expected to be recruited, or provide justification on those rare occasions where women and/or minorities will not be recruited.*

In addition, this section should address:

- *If appropriate, include justification for inclusion of vulnerable participants and recruitment strategy. Vulnerable participants include, but are not limited to pregnant women, those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, children, and employee volunteers. Include safeguards for protecting vulnerable populations. Please refer to OHRP guidelines when choosing the study population. Note that these regulations apply if any participants are members of the designated population, even if it is not the target population (e.g., if a participant becomes a prisoner during the study).*
- *If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation, describe amount, form and timing of such compensation in relation to study activities (include financial and non-financial incentives). Describe who will receive incentives (if not the participant). For example, if minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.*

<Insert text>

6 STUDY INTERVENTION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should describe the study intervention that is being tested for safety and effectiveness in the clinical trial, and any control product being used in the trial. The study intervention may be a drug (including a biological product), imaging intervention, or device subject to regulation under the Federal Food, Drug, and Cosmetic Act that is intended for administration to humans or use in humans, and that has been or has not yet been approved by the Food and Drug Administration (FDA). This also includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, when used for an unapproved indication or when used to gain further information about an approved use.

If multiple study interventions are to be evaluated in the trial, ***Section 6.1 Study Intervention(s) Administration*** *and* ***Section 6.2 Preparation/Handling/Storage/Accountability*** *and their accompanying subsections, should clearly differentiate between each product. Address placebo or control product within each part of* ***Section 6.1*** *and* ***Section 6.2****. If the control product is handled differently than the study intervention, be sure to state how they are each handled, separately. If the control product is handled the same as the study intervention, state as such.* ***In addition, all sections may not be relevant for the trial. If not relevant, note as not applicable in that section.***

6.1 STUDY INTERVENTION(S) ADMINISTRATION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.1.1 STUDY INTERVENTION DESCRIPTION

Describe the study intervention(s) and control product. Product information can usually be obtained from the:

- *IB for an investigational drug or biologic*

- *Package insert for a licensed or approved drug or biologic or device labeling for a licensed device*
- *Proposed labeling and/or material safety data sheet (MSDS) for an investigational device*
- *Final labeling for a marketed device*

In addition:

- *If a device study is being conducted under an IDE, and is determined to be non-significant risk, such that only abbreviated IDE requirements apply, provide justification here.*
- *Indicate if the study intervention is commercially available and is being used in accordance with approved labeling. For a device, note if any modifications have been performed for the study.*
- *If conducting a study with a device, the following information should be included:*
    - *Device size(s)*
    - *Device model(s)*
    - *Description of each component*
    - *Device settings and programming (if applicable)*
    - *Duration of implant or exposure (if applicable)*
    - *Frequency of exposure (if applicable)*
    - *If a device has not been approved or cleared for the indications the protocol is designed to investigate, then a summary/report of test validation studies should accompany this protocol*

<Insert text>

6.1.2 DOSING AND ADMINISTRATION

Describe the procedures for selecting each participant's dose of study intervention and control product. For drugs, that includes the timing of dosing (e.g., time of day, interval), the duration (e.g., the length of time study participants will be administered the study intervention), the planned route of administration (e.g., oral, nasal, intramuscular), and the relation of dosing to meals.

State the starting dose and schedule of the study intervention and control product, including the maximum and minimum duration for those participants who continue in the study. For example, in some oncology trials for participants with no available therapeutic alternatives, intervention continues even after disease progression. In this instance, consider alternative designs that enable participants to rollover to a continued treatment arm and include appropriate instructions to guide this implementation.

If applicable, describe the dose escalation scheme and dose regimen (using exact dose, rather than percentages). State any minimum period required before a participant's dose might be raised to the next higher dose or dose range. If applicable, the protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy). Address dose modifications for specific abnormal laboratory values of concern or other adverse events (AEs) that are known to be associated with the planned study intervention. The protocol must state explicitly the dose-limiting effects that are anticipated. Provide criteria that will be used to determine dose escalations. If a participant is responding positively to the intervention, the protocol should specify whether study intervention administration would progress to still higher doses. If appropriate, provide a dose de-escalation schema with intervention modifications. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.

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

While much of the above section is specific to drugs, similar considerations apply to certain devices. For example, some devices have adjustable settings including those related to energy delivery to participants. Other devices must be sized correctly for individual participants. Similar to the discussion above for dosage of drugs, such considerations should be described for devices, as applicable.

<Insert text>

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.2.1 ACQUISITION AND ACCOUNTABILITY

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product. Detailed information may be provided in a MOP or a separate SOP.

<Insert text>

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

<Insert text>

6.2.3 PRODUCT STORAGE AND STABILITY

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

<Insert text>

6.2.4 PREPARATION

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section, as appropriate, or within a MOP or SOP. For devices, include any relevant assembly or use instructions.

<Insert text>

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated). If adaptive randomization or other methods of covariate balancing/minimization are employed, include a cross link to the methods of analysis in ***Section 9, Statistical Considerations****. In addition, details regarding the implementation of procedures to minimize bias should be included in this section. DO NOT include details that might compromise these strategies. Design techniques to avoid bias can be found in the ICH Guidance for Industry E9 Statistical Principles for Clinical Trials.*

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

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

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

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

<Insert text>

6.4 STUDY INTERVENTION COMPLIANCE

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries). Include a discussion of what documents are mandatory to complete (e.g., participant drug log) and what source documents/records will be used to calculate study intervention compliance.

<Insert text>

6.5 CONCOMITANT THERAPY

Include content in this section if applicable, otherwise note as not-applicable.

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe the data that will be recorded related to permitted concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. Include details about when the information will be collected (e.g., screening, all study visits). Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints) and how the independent effects of concomitant and study interventions could be ascertained.

Example text provided as a guide, customize as needed:

[For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.]

<Insert text>

6.5.1 RESCUE MEDICINE

Include content in this section if applicable, otherwise note as not-applicable.

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions about administration of rescue medications.

Example text provided as a guide, customize as needed:

[The study site <will/will not> supply <specify type> rescue medication that will be <provided by the sponsor/obtained locally>. The following rescue medications may be used <specify name(s)>.

Although the use of rescue medications is allowable <at any time during the study>, the use of rescue medications should be delayed, if possible, for at least <insert timeframe> following the administration of <study intervention>. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.]

<Insert text>

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. This section should state which adverse events would result in discontinuation of study intervention or participant discontinuation/withdrawal. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Consider requiring separate documentation for study intervention

discontinuation and participant discontinuation/withdrawal from the study. In addition, a dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

7.1 DISCONTINUATION OF STUDY INTERVENTION

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or rechallenging with study intervention.

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems (UPs).

Example text provided as a guide, customize as needed:

[Discontinuation from <study intervention> does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- <Describe the procedures and data to be collected, as well as any follow-up evaluations>]

<Insert text>

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Provide a list of reasons participation may be discontinued. It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also, note that participants may withdraw voluntarily from the study or discontinue the study intervention at any time. But, investigators should seek to minimize participant discontinuation/withdrawal from study except for safety reasons.

*In studies of implantable devices, a discussion should be included of any pertinent information that will be provided to withdrawn or discontinued participants (e.g., whether and how the device can be removed, how to replace batteries, how to obtain replacement parts, who to contact). In addition, it is important to capture the reason for withdrawal or discontinuation, as this may impact inclusion of participant data in the analysis of results (see **Section 9, Statistical Analyses**).*

*This section should include a discussion of replacement of participants who withdraw or discontinue early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in the **Section 9, Statistical Analyses.***

Example text provided as a guide, customize as needed:

[Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive <study intervention> for [x] days/weeks.]

The reason for participant discontinuation or withdrawal from the study will be recorded on the <specify> Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, <will> *or* <will not> be replaced.]

<Insert text>

7.3 LOST TO FOLLOW-UP

The protocol should describe the nature and duration of study follow-up. Validity of the study is a potential issue when participants are lost to follow-up, as information that is important to the endpoint evaluation is then lost. Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures. Describe the plans to minimize loss to follow-up and missing data.

Example text provided as a guide, customize as needed:

[A participant will be considered lost to follow-up if he or she fails to return for <specify number of visits> scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit <specify time frame> and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

<Insert text>

8 STUDY ASSESSMENTS AND PROCEDURES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.1 EFFICACY ASSESSMENTS

List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy, as per the primary and secondary objectives outlined in this protocol. Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrollment). If a separate screening protocol is developed, describe how the screening protocol will be used to identify participants for this study. In addition, discuss any special conditions that must be achieved during the enrollment and/or initial administration of study intervention. Include the procedures for administering the study intervention and follow-up procedures after administration (e.g., assessment of vital signs), as well as any specifics about subsequent follow-up visits, and unscheduled visits. Also, note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Include any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

For participants that may discontinue or withdraw early, it is important to capture the rationale during the final visit. See ***Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal****, for details.*

Note that the protocol should provide a high-level discussion of all procedures and detailed information can be further provided in a MOP or SOP. Provide justification for any sensitive procedures (e.g., provocative testing, deception). In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in ***Section 1.3, Schedule of Activities (****SoA) and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.*

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

- ***Physical examination*** *(e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
- ***Radiographic or other imaging assessments****. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study's MOP or a separate SOP.*
- ***Biological specimen collection and laboratory evaluations****. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If*

more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study's MOP.

- ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study's MOP.*
- ***Administration of questionnaires or other instruments*** *for patient-reported outcomes, such as a daily diary.*
- ***Procedures that will be completed during the study as part of regular standard of clinical care****.*

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

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

<Insert text>

8.2 SAFETY AND OTHER ASSESSMENTS

List and describe all study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention's safety or that are done for other purposes (e.g., screening, eligibility, enrollment).

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

Note that the protocol should provide a high-level discussion of all procedures and detailed information can be further provided in a MOP or SOP. In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in ***Section 1.3, Schedule of Activities***

(SoA) *and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.*

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

- ***Physical examination*** *(e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
- ***Vital signs*** *(e.g., temperature, pulse, respirations, blood pressure). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.*
- ***Electrocardiograms (EKGs)****: specify if the EKG is for screening purposes only. Include any specific instructions for the collection and interpretation of the EKG (e.g., time points relative to dosing with study intervention or other evaluations). If EKGs will be analyzed at a central laboratory, instructions for the collection (e.g., equipment), transmission and archiving of the EKG data should be summarized in this protocol, and further outlined in the MOP. If the EKG will be read locally, indicate how these will be handled and in what format (e.g., digital or paper), as well as instructions with respect to local review.*
- ***Radiographic or other imaging assessments.*** *State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study's MOP or a separate SOP.*
- ***Biological specimen collection and laboratory evaluations****. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens may be briefly explained in this section; detailed discussion should be included in the study's MOP.*
- ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study's MOP.*
- ***Counseling procedures, including any dietary or activity considerations*** *that need to be adhered to during study participation.*
- ***Assessment of study intervention adherence*** *or see Study Intervention Compliance, section 6.4*
- ***Administration of questionnaires or other instruments*** *for patient-reported outcomes, such as a daily diary.*
- ***Assessment of adverse events.*** *Describe provisions for follow-up of ongoing AEs/SAEs.*

Include in this section a discussion of the results of any study specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).

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

<Insert text>

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections are intended to highlight the specific assessments related to safety and the aspects of the study which are proposed to ensure the safety of trial participants. Consider developing this section in consultation with the study Medical Monitor. Consider the risks of the study intervention and other study procedures and the characteristics of the study population (e.g., vulnerable populations such as children). This section should be tailored for specific study characteristics, including but not limited to the following:

- *The study involves an investigational new drug or investigational device*
- *The study involves washout from current medication regimen*
- *The study involves the use of placebo in a population with a diagnosed disease*
- *The study requires selection of an appropriate toxicity grading scale*
- *The study involves risks to individuals other than research participants (e.g., household or intimate contacts or communities, study clinicians, pharmacists or interventionists, etc.)*
- *Reporting of certain events (e.g., suspected child abuse or substance abuse) is mandatory because of the study population or study design characteristics*
- *The study is conducted at multiple sites, and will require centralized safety oversight*

In developing this section, consider the risks of the study intervention. Review and reference the applicable sources of information, such as the IB, package insert, device labeling, literature and other sources that describe the study intervention.

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Provide the definition of an AE being used for the clinical trial. The FDA definition of an AE is used in this template since this template is for phase 2 or 3 IND and IDE studies. For some studies, definitions from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events; or ICH GCP definition may be more appropriate. However, it is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, regardless of the definition of AE used in the protocol.

Example text provided as a guide, customize as needed:

[Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).]

<Insert text>

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Provide the definition of an SAE being used for the clinical trial. The FDA definition of an SAE is used in this template since this template is for phase 2 or 3 IND and IDE studies. It is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, regardless of the definition of SAE used in the protocol. Note that the example text provided is from the drug regulations (21 CFR 312.32 (a)). There is no definition for SAE in the device regulations. Therefore, investigators should develop an appropriate definition for their study. This definition could include an unanticipated adverse device effect, but an SAE is broader than that definition. According to 21 CFR 812.3(s), an "unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

Example text provided as a guide, customize as needed:

[An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.]

<Insert text>

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections will include a discussion of how AEs will be classified.

8.3.3.1 SEVERITY OF EVENT

All AEs will be assessed by the study clinician using a protocol defined grading system. Describe the method of grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs. Selection of a toxicity table or severity scale should be made in consultation with the study Medical Monitor.

Example text provided as a guide, customize as needed:

[For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

<Insert text>

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs will have their relationship to study intervention or study participation assessed with a level of specificity appropriate to the study design. The clinician's assessment of an AE's relationship to study intervention (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. Describe the method of determining the relationship of an AE to a study intervention. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. Some protocols may use a binary assessment (related/not related); others may have a scale of relatedness. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. In a clinical trial, the study intervention must always be suspect.

Example text provided as a guide, customize as needed:

[All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the

study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

<Insert text>

8.3.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Identify the source of the reference safety information used to determine the expectedness of the AE (e.g., IB, approved labeling). Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB or package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB or package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation.

Example text provided as a guide, customize as needed:

[<Insert role> will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.]

<Insert text>

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

*Describe how AEs and SAEs will be identified and followed until resolved or considered stable. Specify procedures for recording and follow-up of AEs and SAEs that are consistent with the information contained within **Section 8.2, Safety and Other Assessments** including what assessment tools will be used to monitor AEs. Include duration of follow-up after appearance of events (e.g., 1 week, 2 months).*

An unsolicited AE would occur without any prompting or in response to a general question such as "Have you noticed anything different since you started the study; began the study intervention, etc." A solicited AE is one that is specifically solicited such as "Have you noticed any dry mouth since you started the study medication?"

- *Describe which AEs will be collected as solicited events. Plan the reporting and data collection system to avoid double capture (captured both as an unsolicited and a solicited AE).*
- *Describe how unsolicited events will be captured.*
- *Include time period of collection (e.g., Days 0 -28) and note how long SAEs are collected – usually collected through entire study.*

Example text provided as a guide, customize as needed:

[The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

<Insert role or name> will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of

study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

<Insert text>

8.3.5 ADVERSE EVENT REPORTING

This section addresses responsibilities of investigators for reporting of AEs. However, it is important to recognize that sponsors have additional responsibilities under regulations that are not described in this template and should be incorporated into relevant SOPs.

Describe the AE reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight (e.g., Data and Safety Monitoring Board (DSMB), safety monitoring committee, independent safety monitor) and regulatory groups, and what study staff are responsible for completing and signing off on the AE reports, and who will receive notification of AEs. According to 21 CFR 312.64(b), "…The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol".

In addition, list any disease-related events (DREs) common in the study population (e.g., expected), which will not be reported per the standard process for reporting, as applicable. Describe how these events will be recorded and monitored.

<Insert text>

8.3.6 SERIOUS ADVERSE EVENT REPORTING

This section addresses responsibilities of investigators for reporting of SAEs. However, it is important to recognize that sponsors have additional responsibilities under regulations that are not described in this template and should be incorporated into relevant SOPs.

Describe the SAE reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the SAE reports, and who will receive notification of SAEs.

*Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Section 8.3.2, Definition of Serious Adverse Events** must be submitted on an SAE form to the Data Coordinating Center (DCC) if one exists for the study. Studies overseen by a DSMB or other independent oversight body (e.g., safety monitoring committee, independent safety monitor), may be required to submit expedited notification of all SAEs or only SAEs thought to be related to study intervention.*

According to 21 CFR 312.64(b), "An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal

relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor…"

According to 21 CFR 312.32(c)(1), "the sponsor must notify FDA and all participating investigators…in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting… In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

> *(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);*
> *(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);*
> *(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."*

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

*As noted previously, an unanticipated adverse device effect could be considered an SAE (**Section 8.3.2, Definition of Serious Adverse Events).** For IDE studies, according to 21 CFR 812.150(a)(1), "an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect." In addition, according to 21 CFR 812.150(b)(1), "A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests."*

Example text provided as a guide, customize as needed:

Example 1, applicable for a drug or biologic protocol:

[The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.]

OR

Example 2, applicable for device protocol:

[The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.]

<Insert text>

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Include content in this section if applicable, otherwise note as not-applicable.

Describe how participants will be informed about AEs and SAEs, and study-related results on an individual or aggregate level. In addition, describe plans for detecting and managing incidental findings associated with study procedures.

<Insert text>

8.3.8 EVENTS OF SPECIAL INTEREST

Include content in this section if applicable, otherwise note as not-applicable.

Describe any other events that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies. For example, in oncology trials, secondary malignancies are often captured.

Include any other reportable events not already included in the previous sections, such as cardiovascular and death events, medical device incidents (including malfunctions), laboratory test abnormalities, and study intervention overdose.

<Insert text>

8.3.9 REPORTING OF PREGNANCY

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

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

<Insert text>

8.4 UNANTICIPATED PROBLEMS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The reporting of UPs applies to non-exempt human subjects research conducted or supported by HHS. Provide the definition of an UP being used for this clinical trial. An incident, experience, or outcome that meets the definition of an UP generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
- *Implementation of additional safety monitoring procedures*
- *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
- *Modification of informed consent documents to include a description of newly recognized risks*
- *Provision of additional information about newly recognized risks to previously enrolled participants*.

Example text provided as a guide, customize as needed:

[The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Additional example text, applicable for device protocols:

[This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]

<Insert text>

8.4.2 UNANTICIPATED PROBLEM REPORTING

This section addresses responsibilities of investigators for reporting of UPs. Describe the UP reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight (e.g., DSMB, safety monitoring committee, independent safety monitor) and regulatory groups, and what study staff are responsible for completing and signing off on the UP report forms.

Institutions engaged in human subjects research conducted or supported by Department of Health and Human Services (DHHS) must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)). Furthermore, for research covered by an assurance approved for federal wide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

Example text provided as a guide, customize as needed:

[The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

Additional example text, applicable for device protocol:

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

<Insert text>

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Include content in this section if applicable, otherwise note as not-applicable.

Describe how participants will be informed about UPs on an individual or aggregate level.

<Insert text>

9 STATISTICAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should describe the statistical tests and analysis plans for the protocol. They should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH Guidance for Industry E9 Statistical Principles for Clinical Trials and the CONSORT statement which describes standards for improving the quality of reporting randomized controlled trials.

State whether there will be a formal Statistical Analysis Plan (SAP). A formal SAP should be completed prior to database lock and unblinding of the study data. The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies). If a separate SAP will be developed, subsections below can be summarized.

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

- Primary Efficacy Endpoint(s):

<Insert text>

- Secondary Efficacy Endpoint(s):

<Insert text>

9.2 SAMPLE SIZE DETERMINATION

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants. In particular, specify all of the following:

- *Outcome measure used for calculations (almost always the primary variable)*
- *Test statistic*
- *Null and alternative hypotheses*
- *Type I error rate (alpha)*
- *Power level (e.g., 80% power)*
- *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc. on study power (see also **9.4.2 Analysis of the Primary Efficacy Endpoint(s) and 9.4.3 Analysis of the Secondary Endpoint(s)**)*
- *Method for adjusting calculations for planned interim analyses, if any (**Section 9.4.6, Planned Interim Analyses**).*

Further, present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

*Discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term, **Section 9.4.9, Exploratory Analyses**).*

<Insert text>

9.3 POPULATIONS FOR ANALYSES

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:

- *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
- *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data)*
- *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)*

- *Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)*
- *Other Datasets that may be used for sensitivity analyses*

<Insert text>

9.4 STATISTICAL ANALYSES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should include a description of the planned statistical methods.

9.4.1 GENERAL APPROACH

As a guide, the following should be addressed, as appropriate:

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

<Insert text>

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For each primary endpoint:

- *Define the measurement or observation and describe how it is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
- *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*
- *Describe the Populations for which the analysis will be conducted, as discussed in **Section 9.3, Populations for Analyses***

- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
- *Define the measurement or observation and describe how it is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
- *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, ANCOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (LSMEANS) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, and number-needed-to-treat).*
- *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests).*
- *Describe the Populations for which the analysis will be conducted as discussed in* ***Section 9.3, Populations for Analyses.***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up.*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

9.4.4 SAFETY ANALYSES

Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in ***Section 9.4.2, Analysis of the Primary Efficacy Endpoint(s)*** *should be included here. Describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g.,*

severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, expectedness, outcome, and duration). Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within ***Section 8.2, Safety and Other Assessments****.*

<Insert text>

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Include content in this section if applicable, otherwise note as not-applicable.

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

<Insert text>

9.4.6 PLANNED INTERIM ANALYSES

Include content in this section if applicable, otherwise note as not-applicable.

This section should describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing and who reviews the interim analyses. In addition, if the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when evaluating results. Pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data and trial futility. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unblinded and how the blinding will be preserved.

If statistical rules will be used to halt enrollment into all or a portion of the study (e.g., for safety or futility), describe the statistical techniques and their operating characteristics. If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

Describe safety findings that would prompt temporary suspension of enrollment and/or study intervention use until a safety review is convened (either routine or ad hoc). Provide details of the proposed rules for halting study enrollment or study intervention/administration of study product for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study.

State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

*This section should be consistent with **Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal.***

<Insert text>

9.4.7 SUB-GROUP ANALYSES

Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).

Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).

<Insert text>

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

<Insert text>

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses cannot be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.

<Insert text>

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

*The following subsections should include a description of the regulatory and ethical considerations, and context for the conduct of the trial. Of note, the guiding ethical principles being followed by this study are included in the **Statement of Compliance** at the beginning of this protocol. For NIH Intramural Research Program studies only: A statement referencing compliance with NIH Human Research Protections Program policies and procedures is adequate for **Subsection 10.1.1, Informed Consent Process.***

10.1.1 INFORMED CONSENT PROCESS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

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

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

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

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

Example text provided as a guide, customize as needed:

[Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol <insert list>.]

<Insert text>

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English. Describe procedures for obtaining surrogate consent for those unable to consent on their own behalf. This section should be consistent with ***Section 5.5, Strategies for Recruitment and Retention*** *when describing consent plans and special considerations for children or other vulnerable participants. Address re-consent processes for children who become adults or emancipated during a study.*

Example text provided as a guide, customize as needed:

[Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions

prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.]

<Insert text>

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

*When a study is prematurely terminated, refer to Section **7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**, for handling of enrolled study participants.*

Example text provided as a guide, customize as needed:

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

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

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

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

<Insert text>

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

- *Describe whether identifiers will be attached to data/samples, or whether data will be coded or unlinked.*
- *If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.*
- *If research data/samples will be coded, describe how access to the "key" for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.*
- *Include a discussion of the circumstances in which data or samples will be shared with other researchers.*
- *Include a discussion of plans to publish participant's family pedigrees, with a description of measures to minimize the chance of identifying specific families.*
- *Describe any situations in which personally identifiable information will be released to third parties.*
- *State who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access.*
- *Discuss any additional features to protect confidentiality (e.g., use of a certificate of confidentiality).*
- *Approaches to ensure privacy of study participants*

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

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

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

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

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

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

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

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.]

<Insert text>

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

If intended specimens or residual specimens are retained after the study is complete, include the provisions for consent and the options that are available for the participant to agree to the future use of his/her specimens, images, audio or video recordings. Specify the location(s), if other than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens or data (e.g., specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Include a statement that genetic testing will or will not be performed.

*See also **Section 10.1.3, Confidentiality and Privacy** and **Section 10.1.9, Data Handling and Record Keeping**, for further information on future use of study records.*

Example text provided as a guide, customize as needed:

[Data collected for this study will be analyzed and stored at the <specify name of Data Coordinating Center >. After the study is completed, the de-identified, archived data will be transmitted to and stored at the <specify name of Data Repository>, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the <specify name of Biosample Repository> with the same goal as the sharing of data with the <specify name of Data Repository>. These samples could be used to research the causes of <specify condition(s)>, its complications and other conditions for which individuals with < specify condition(s)> are at increased risk, and to improve treatment. The <specify name of Repository> will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the <specify name of Repository>.]

<Insert text>

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
Name, degree, title	*Name, degree, title*
Institution Name	*Institution Name*
Address	*Address*
Phone Number	*Phone Number*
Email	*Email*

In addition, briefly describe any study leadership committees (e.g.: Steering Committee, Executive Committee, Subcommittee) and their roles. Note that it is not necessary to list specific members. Also, describe country-specific administrative requirements or functions that materially affect the conduct of the study. The MOP should include a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.

<Insert text>

10.1.6 SAFETY OVERSIGHT

Appropriate safety oversight should be used for each trial. This could include a Safety Monitoring Committee (SMC)[3], Data Safety Monitoring Board (DSMB)[4], Safety Assessment Committee[5], and/or an Independent Safety Monitor (ISM)[6]. Independent oversight is an important component to ensure human subjects' protection and data integrity and should be considered for each study. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.

Example text provided as a guide, customize as needed:

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

<Insert text>

10.1.7 CLINICAL MONITORING

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of

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[3] A Safety Monitoring Committee (SMC) is a small group of experts with at least two members who are independent of the protocol who review data from a particular study. Generally, independent investigators and biostatisticians should be included. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, intervention, and target population under study.

[4] A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises funding IC(s) and the study investigators. The members of the DSMB provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, intervention, or target population under study.

[5] As noted on page 4 of the FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting, "A group of individuals chosen by the sponsor to review safety information in a development program (i.e., across trials, INDs, and other sources) for IND safety reporting purposes...The safety assessment committee should oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all of the trials in the development program, as well as other available important safety information (e.g., findings from epidemiological studies and from animal or in vitro testing) and performing unblended comparisons of event rates in investigational and control groups, as needed, so the sponsor may meet its obligations under § 312.32(b) and (c). The safety assessment committee's primary role should be to review important safety information on a regular basis, with additional reviews as needed, and make a recommendation to the sponsor to help the sponsor determine whether an event or group of events meets the criteria for IND safety reporting. The safety assessment committee, possibly together with other parties (e.g., steering committees, data monitoring committees [DMCs]), can also participate in decisions about whether the conduct of the study should be revised (e.g., change ineligibility criteria, revision of informed consent).

[6] An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

This section should give a general description of how monitoring of the conduct and progress of the clinical investigation will be conducted (i.e., who will conduct the monitoring, the type, frequency, and extent of monitoring, who will be provided reports of monitoring, if independent audits of the monitoring will be conducted). This section may refer to a separate detailed clinical monitoring plan.

A separate clinical monitoring plan (CMP) should describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A CMP ordinarily should focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the sponsor with the PI, electronic data capture, relative safety of the study intervention, stage of the study, and quantity of data.

If a separate CMP is not used, include all the details noted above in this section of the protocol.

*Example text when a **separate CMP is being used is provided as a guide, customize as needed**:*

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by <insert text>.
- <Insert brief description of type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)>.
- <Insert text> will be provided copies of monitoring reports within <x> days of visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.]

OR

*Example text when a **separate CMP is <u>not</u> being used is provided as a guide, customize as needed**:*

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- <Insert detailed description of who will conduct the monitoring, the type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)), and the distribution of monitoring reports>
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites.]

<Insert text>

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

This section will briefly describe the plans for quality management, the system for assessing the quality of processes within a system. Quality management encompasses quality assurance (QA)[7] and quality control (QC)[8].

Each site, both clinical and laboratory, should have SOPs for quality management that describe:

- *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.*
- *The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*
- *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).*
- *Staff training methods and how such training will be tracked.*
- *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*

*Regular monitoring and an independent audit, if conducted, must be performed according to ICH GCP. See also **Section 10.1.7, Clinical Monitoring**.*

[7] All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with ICH GCP and the applicable regulatory requirement(s) (ICH E6 Section 1.46).
[8] The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 Section 1.47).

Example text provided as a guide, customize as needed:

[Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

<Insert text>

10.1.9 DATA HANDLING AND RECORD KEEPING

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored or NIH-affiliated study, each site will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.

The following subsections should include a description of the data handling and record keeping for the conduct of the trial.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Provide details regarding the type(s) of data capture that will be used for the study and any relevant data standards or common data elements that are being utilized as a part of the trial. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Further details should be provided in the MOP or the data management plan, including detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data

initially recorded in electronic form. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, 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, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

It is not acceptable for the CRF to be the only record of a participant's inclusion in the study. Study participation should be captured in a participant's medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

Describe responsibilities for data handling and record keeping as they specifically relate to the IND/IDE sponsor (if applicable), the award site, clinical site(s), laboratory(ies), and DCC. Information should include the role in data collection, review of data, trial materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes (if applicable).

If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.

Provide a list of planned data standards, formats, terminologies and their versions, used for the collection, tabulation, analysis of study data. Refer to the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Standardized Study Data, Study Data Technical Conformance Guide and FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Example text provided as a guide, customize as needed:

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to

identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.]

<Insert text>

10.1.9.2 STUDY RECORDS RETENTION

Specify the length of time for the investigator to maintain all records pertaining to this study. The investigator should use the most conservative rule for document retention – i.e., retention should follow the rule that has the longest period. For NIH, grantees must retain records for a period of three years from the date of Federal Financial Report (FFR) submission.

Indicate whether permission is required (and from whom) prior to destruction of records. If under an IND/IDE, records should not be destroyed without the IND/IDE sponsor's agreement. Pharmaceutical companies who supply unapproved products should be consulted.

Study intervention records may be described here if not addressed elsewhere in the protocol.

Example text provided as a guide, customize as needed:

[Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.]

<Insert text>

10.1.10 PROTOCOL DEVIATIONS

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

Example text provided as a guide, customize as needed:

[A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

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

<Insert text>

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

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

Example text provided as a guide, customize as needed:

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

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

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

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

nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

<Insert text>

10.1.12 CONFLICT OF INTEREST POLICY

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

Example text provided as a guide, customize as needed:

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

<Insert text>

10.2 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.

<Insert text>

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert, device labeling or investigational brochure***
  Cite date accessed, version number, and source of product information.

Glossary

Adverse Drug Reaction (ADR) Any noxious and unintended response associated with the use of a drug in humans. 1. Post-approval: an adverse event that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. 2. Preapproval: an adverse event that occurs at any dose and where a causal relationship is at least a reasonable possibility.

Adverse Event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. *Synonyms: side effect, adverse experience.*

Biologics Licensing Application (BLA) An application to FDA for a license to market a new biologic product in the United States.

Clinical Hold An order issued by FDA to the Sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation.

Clinical Investigation *See clinical trial.*

Clinical Investigator's Brochure (CIB) *See Investigator's Brochure.*

Clinical Protocol *See protocol.*

Clinical Trial Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one of more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s), and/or to study absorption, distribution, metabolism and excretion of one of more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

Compliance (in relation to clinical trials) Adherence to trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

Consent Form Document used during the informed consent process that is the basis for explaining to potential subjects the risks and potential benefits of a study and the rights and responsibilities of the parties involved. NOTE: The informed consent document provides a summary of a clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives to participation, etc.) and explains an individual's rights as a subject. It is designed to begin the informed consent process, which consists of conversations between the subject and the research team. If the individual then decides to enter the trial, s/he gives her/his official consent by signing the document. *Synonym: informed consent form; see also informed consent.*

Contract Research Organization (CRO) A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Coordinating Investigator An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

Drug 1. Article other than food intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body. Not a device or a component, part, or accessory of a device. 2. Substance recognized by an official pharmacopoeia or formulary.

Effective Date The date an IND becomes effective, which is usually 30 days after the IND submission, unless you are otherwise notified by the FDA.

Ethics Committee *See institutional review board, independent ethics committee.*

Food and Drug Administration (FDA) The United States regulatory authority charged with, among other responsibilities, granting IND and NDA approvals.

Generic Name The drug identifying name to which all branded (proprietary) names for that indication are associated.

Good Clinical Practice (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Informed Consent (IC) An ongoing process that provides the subject with explanations that will help in making educated decisions about whether to begin or continue participating in a trial. Informed consent is an ongoing, interactive process, rather than a onetime information session. NOTE: Under 21 CFR 50.20, no informed consent form may include any "language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."

Institutional Review Board (IRB) An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. *Synonyms: independent review board, independent ethics committee, committee for the protection of human subjects.*

Intervention The drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study: e.g., health-related quality of life, efficacy, safety, pharmacoeconomics. *Synonyms: therapeutic intervention, medical product.*

Investigational New Drug Application (IND) Application of the sponsor to FDA in order to request exception from the pre-marketing approval requirement that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigation of that drug.

Investigational Drug A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigational treatment An intervention under investigation in a clinical trial.

Investigator 1. A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. 2. The individual "under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team".

Investigator's Brochure A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Marketing Application is an application for the marketing of new drug submitted under section 505(b) of the PHS Act or a biologics license application for a biologic product submitted under the PHS Act.

Monitor Person employed by the sponsor or CRO who is responsible for determining that a trial is being conducted in accordance with the protocol and GCP guidance. NOTE: A monitor's duties may include, but are not

limited to, helping to plan and initiate a trial, assessing the conduct of trials, and assisting in data analysis, interpretation, and extrapolation. Monitors work with the clinical research coordinator to check all data and documentation from the trial.

Multicenter Trial Clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

New Drug Application (NDA) An application to FDA for a license to market a new drug in the United States.

Phase Clinical trials are generally categorized into four (sometimes five) phases. A therapeutic intervention may be evaluated in two or more phases simultaneously in different trials, and some trials may overlap two different phases.

Placebo A pharmaceutical preparation that does not contain the investigational agent. In blinded studies, it is generally prepared to be physically indistinguishable from the preparation containing the investigational product.

Preclinical Studies Animal studies that support Phase 1 safety and tolerance studies and must comply with good laboratory practice (GLP). NOTE: Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies or trials).

Protocol A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. NOTE: Present usage can refer to any of three distinct entities: 1) the plan (i.e., content) of a protocol, 2) the protocol document and 3) a series of tests or treatments (as in oncology).

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (serious ADR) Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Serious Adverse Experience Any experience that suggests a significant hazard, contra-indication, side effect or precaution.

Side Effects Any actions or effects of a drug or treatment other than the intended effect. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects. *See also adverse reaction.*

Sponsor 1. An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. 2. A corporation or agency whose employees conduct the investigation is considered a sponsor and the employees are considered investigators.

Sponsor-Investigator An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. NOTE: The term does not include any person other than an individual (i.e., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Sub-Investigator Any member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows)

Unexpected Adverse Drug Reaction An adverse reaction, whose nature, severity, specificity, or outcome is not consistent with the term or description used in the applicable product information.

Abbreviations

ADR – Adverse Drug Reaction
AE – Adverse Event
BLA – Biologics Licensing Application
CBER – Center for Biologics Evaluation and Research
CDER – Center for Drug Evaluation and Research
CDRH – Center for Device and Radiological Health
CF – Consent Form
CIB – Clinical Investigator's Brochure
CMC – Chemistry, Manufacturing and Controls
CRO – Contract Research Organization
FDA – Food and Drug Administration
GCP – Good Clinical Practice
GLP – Good Laboratory Practice
IB – Investigator's Brochure
IC – Informed Consent
ICMJE – International Committee of Medical Journal Editors
IND – Investigational New Drug
IRB – Institutional Review Board
NDA – New Drug Application
PHS Act – Public Health Service Act
SAE – Serious Adverse Event

INITIAL INVESTIGATIONAL NEW DRUG APPLICATION

IND Title (if title is being used)

Serial 000

Name of Sponsor-Investigator, MD
X Professor, Department
MONTEFIORE MEDICAL CENTER

*(**Note to User**: This template is only intended for 'simple' INDs where commercially marketed drugs are being evaluated by sponsor-investigators. Please contact us if you need a more thorough template with CMC, Pharm/Tox etc.)*

Date of Submission

1. FORM FDA 1571

Use this link to access Form FDA 1571:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf

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2. TABLE OF CONTENTS

3. INTRODUCTION

3.1. Introductory Statement

This section is brief; usually two to three pages should be sufficient. The information here is intended to place the use of the drug(s) with this indication into perspective for the FDA. After your introductory statement, use the headings below to ensure you fulfill all of the requirements. This is also easier for the reviewers to follow. ***Maintain all of the headings*** *in this document and if not applicable to your IND, simply state this.*

3.1.1. Name of the Drug and All Active Ingredients

3.1.2. Pharmacological Class of the Drug

3.1.3. Structural Formula of the Drug

This section may not be applicable to biologics. You could describe the protein or complex of proteins instead (e.g. 341 amino acids with a molecular weight of 150 g/mol)

3.1.4. Formulation of the Dosage Forms to be Used

3.1.5. Route of Administration

3.1.6. Objectives and Duration of the Proposed Clinical Investigations

3.2. Summary of Previous Human Experience

A brief summary of previous human experience with the drug, with reference to other INDs if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s). This topic will be written up in detail in Section 9. However, for many sponsor-investigator INDs that use commercially available drugs, Section 3.2 and 9 are often identical.

3.3. Status of Drug in Other Countries

If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal. For a Sponsor-Investigator IND, you may simply state you are not aware of any withdrawals.

3.4. References

List any references for Section 3.

4. GENERAL INVESTIGATIONAL PLAN

4.1. Rationale

The rationale for the drug or research study, including the dose, schedule, and patient population (the science behind why this is a good idea).

4.2. Indication to be Studied

4.3. General Approach for Evaluation of Treatment

4.4. Description of First Year Trial(s)

4.5. Number of Subjects to be Evaluated

4.6. Drug Related Risks

Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug(s) or related drugs.

4.7. References

List any references for Section 4.

5. INVESTIGATOR'S BROCHURE

For sponsor-investigator initiated INDs, there is no requirement to create an Investigator Brochure (IB) if you have a single site study. If no IB is required for your study, you may incorporate the following statement:

In accordance with 21 CFR Part 312.55(a), an Investigator's Brochure is not required for a sponsor-investigator IND.

You can also state that: All investigators will be referred to the latest version of the protocol.

If you are using the marketed approved drug, then it is appropriate here to refer to the product label (also known as the package insert) and provide a URL link to the most current product label. You may find these links useful for finding current product labeling:

- http://dailymed.nlm.nih.gov/dailymed/about.cfm
- http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

If you have a Letter of Authorization (LoA) from another sponsor referencing their FDA submission (IND, NDA, BLA, IDE, DMF, etc), include the LoA in section 5.1. The LoA serves the purpose to allow the FDA reviewer to review their submission on file in relation to your IND application. If part of the document that you are referencing is the IB of the other sponsor, please do not send the actual IB to the FDA. Instead, please state that the company has provided you with the IB and note which version you have received from the sponsor.

However, if you do have a multi-site study being performed under your IND, you will need an IB.

A template for the information included in an IB can be found in the ICH Guideline E6: Good Clinical Practice.

Rather than insert the IB within this document, we recommend that you assemble the IND after separately printing this IND document and the IB. To ensure that the TOC on Page 3 reflects the true number of pages in the IND, format the page number on the Protocol page to reflect the additional pages in the IB.

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6. PROTOCOL

6.1. Study Protocol

Please insert study protocol.

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6.2. Informed Consent

Please insert study Informed Consent.

Rather than insert the Informed Consent within this document, we recommend that you assemble the IND after separately printing this IND document and the Informed Consent. To ensure that the TOC on Page 3 reflects the true number of pages in the IND, format the page number on the Investigator and Facilities Data page to reflect the additional pages in the Informed Consent.

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6.3. Investigator and Facilities Data

Form FDA 1572 and CV of the principal investigator(s).

Rather than insert the Form FDA 1572 and CV within this document, we recommend that you assemble the IND after separately printing this IND document and the Form FDA 1572 and CV. To ensure that the TOC on Page 3 reflects the true number of pages in the IND, format the page number on the following CMC page to reflect the additional pages in the Form FDA 1572 and CV.

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http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM223432.pdf

7. CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION

If the investigational drug has been marketed, this section may be covered by providing the Package Insert of the drug or referencing the label. Please provide a URL link to the most current product label.

If any change to the labeled dosage form, strength, or route of administration is planned, please provide the relevant information such as release and stability data to support the proposed usage. If you are in any way changing the final marketed product, please describe the changes you are making (e.g. – encapsulating, changing the container).

Alternatively, if you are receiving the drug from another party and you refer to their manufacturing information, then you will need a Letter of Authorization (LoA). The LoA should be included as 5.1 and referenced here.

7.1. Environmental Assessment

If no environmental assessment is required, then use this statement:

"We request a claim for categorical exclusion for this proposed clinical trial as provided for in 21 CFR.25.31(e) in that the drug shipped under this notice is intended to be used in clinical trials in which the amount of waste expected to enter the environment may reasonably be expected to be non-toxic."

8. PHARMACOLOGY AND TOXICOLOGY INFORMATION

A section describing the pharmacological effects and mechanism(s) of action of the drug in animal and information on the absorption, distribution, metabolism and excretion of the drug, if known. As was true for Section 7, you may use a package insert or Letter of Authorization or cite the drug label to satisfy much of this section.

9. PREVIOUS HUMAN EXPERIENCE

A summary of previous human experience with the investigational drug, if any, known to the applicant. Simply citing Authorization letters may be appropriate to fulfill this section. If the drug(s) is already marketed in the US, then you may be able to simply refer to the product labeling. If not, the following information is required:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale.

(ii) If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(iii) If the drug is a combination of drugs previously investigated or marketed, the information should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component- component interaction).

(iv) If the drug(s) has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

9.1. References

List any references for Section 9

10. ADDITIONAL INFORMATION

For certain applications, information on special topics may be needed in this section. If you have an IND that requires additional information on drug dependence and abuse potential, radioactive drugs, or pediatric studies, please refer to our full IND template for further guidance.

10.1. Other Information

A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

10.2. Selected References

If you are including reprints with your submission, list them in this section.

*(**Note to User** – For a 'simple' IND, Section 10 is probably not applicable. However, this is a good place to attach 2-3 reprints of articles that might aide the reviewers at FDA. Please do not attach more than this number of reprints.)*

11. BIOSIMILAR USER FEE COVER SHEET (FORM FDA 3792)

Biosimilar biological products are products that are demonstrated to be interchangeable with an FDA-licensed biological product. For sponsor-investigator initiated INDs, this section is probably not applicable due to the fact that the majority of sponsor-investigator initiated INDs are not developing biosimilars. If you are a sponsor-investigator developing a biosimilar biological product, please complete Form FDA 3792 and include it here in section 11.

State Not Applicable *if appropriate, but leave this header in*.

12. CLINICAL TRIALS CERTIFICATION OF COMPLIANCE (FORM FDA 3674)

Include a signed and dated Form FDA 3674.

Use this link to access the Form FDA 3674:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf

Use this link to access instructions for completing Form FDA 3674:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM354618.pdf

INITIAL INVESTIGATIONAL NEW DRUG APPLICATION

IND Title (if title is being used)

Serial 0000

Name of Sponsor-Investigator, MD
X Professor, Department
MONTEFIORE MEDICAL CENTER

Date of Submission

1. FORM FDA 1571

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3.1.2. Pharmacological Class of the Drug

3.1.3. Structural Formula of the Drug

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3.1.4. Formulation of the Dosage Forms to be Used

3.1.5. Route of Administration

3.1.6. Objectives and Duration of the Proposed Clinical Investigation(s)

3.2. Summary of Previous Human Experience

This section is a brief summary of previous human experience with the drug(s), with reference to the literature or other INDs if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s). This topic will be written up in detail in Section 9. However, for many sponsor-investigator INDs that use commercially available drugs, Section 3.2 and 9 are often identical.

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This section is likely not applicable to you. If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal are stated here. For a Sponsor-Investigator IND, you may simply state you are not aware of any withdrawals.

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4.3. General Approach for Evaluation of Treatment

4.4. Description of First Year Trial(s)

4.5. Number of Subjects to be Evaluated

4.6. Drug Related Risks

Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug(s) or related drugs.

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If you are using the marketing approved drugs, then, it is appropriate here to refer to the product label (also known as the package insert) and provide a URL link to the must current product label. You may find these links useful for finding current product labeling:

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Use this link to access instructions for completing Form FDA 1572:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM223432.pdf

7. CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION

If you have Letter of Authorization referencing an IND regarding information that would normally be included in this section, place a copy of the LOA here.

7.1. Introduction

Provide general information about the investigational drug and the study that is proposed under this IND.

7.1.1. Mitigation of Potential Human Risk

What are the potential human risks relating to the method of manufacture or an inherent risk associated with the drug substance (e.g., you have an attenuated viral vector) and what measures were taken to mitigate the potential human risk?

7.2. Drug Substance

7.2.1. Description of Drug Substance

Description of the drug substance including physical, chemical and biological characteristic of the compound. If there is a conformational picture of the drug substance, please paste it in this section.

7.2.2. Manufacturer

Name and address of the manufacturer

7.2.3. Control of Raw Materials

The raw materials used in the manufacture of XY dug substance is listed below

Item Description/Name	Manufacturer	Cat#	Grade	Acceptance Criteria

7.2.4. Control of the Starting Material

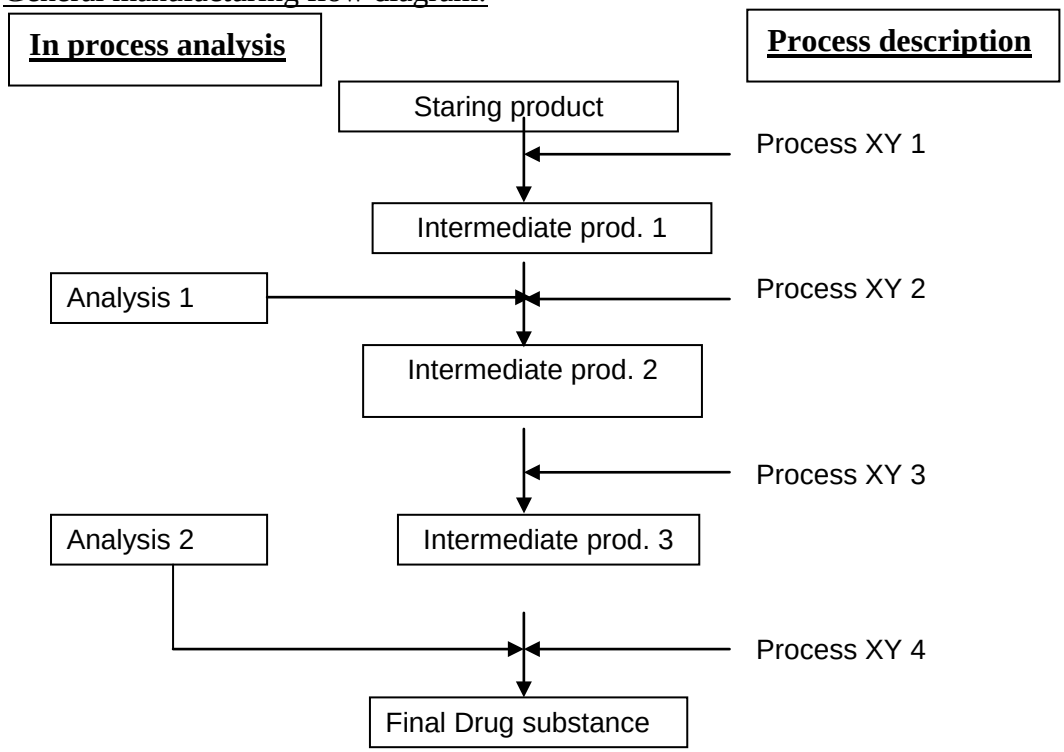
What are the acceptance criteria for each raw material to be used in the production (if differs from the information in the table). For example if plasmid is used in the manufacturing, do you sequence it before use? If yes, please describe the process and

acceptance criteria. If raw material is commercially purchased and accepted based on the CoA or package insert, you can just state it in the table and skip this part.

7.2.5. Manufacturing of the Drug Substance

*Please make a general manufacturing diagram describing how the manufacturing flow looks like. Two **examples** are shown below (flow diagram or table).*

General manufacturing flow diagram:



7.2.6. Manufacturing Process and In-Process Testing

Step	Description	In-process testing	Release testing
1.			
	↓		
2.			
	↓		
3.			
	↓		
4.			
	↓		
5.			

7.2.7. Production Specifics

Every step of the drug substance manufacturing should be described here pointing out if there are any in process testing that will be performed and what are the acceptance criteria of those

1. Process XY 1
Please describe the process No. 1.

2. Process XY 2
Please describe the process No. 2.

3 Process XY 3
Please describe the process No. 3.

4. Process XY 4
Please describe the process No. 4.

7.2.8. Analytical Testing of In-Process Products

Please describe the analytical testing performed on the intermediate drug substance products during the manufacturing.

7.2.9. Analysis of the Drug Substance

Please describe the analytical testing performed on drug substance

7.3. Drug Product

7.3.1. Description and Composition

Please note the difference between drug substance and drug product. Drug substance is the active ingredient. Drug product is the final product configuration that contains drug substance, and it might also contain diluents, vialed in the certain volume etc.

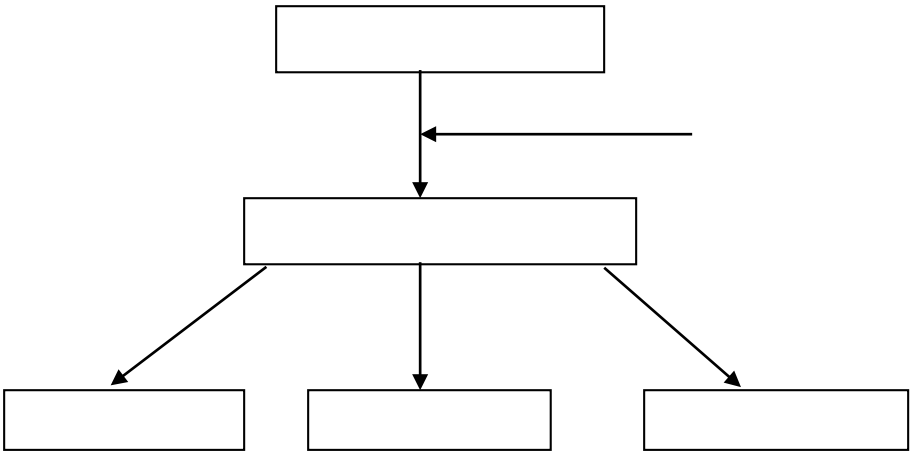
7.3.2. Manufacturer

Name and address of the manufacturer of the final drug product

7.3.3. Manufacturing of the Drug Product

General Manufacturing Flow Diagram

This is just an example, how one diagram that would for example represent the filling and vialing scheme of the final product. You should modify to reflect you manufacturing process. Again, this can be presented as a process flow diagram or cells in a table.



7.3.4. Dosage Preparation and Storage Scheme

7.3.5. Tests and Specifications

As for the manufacturing of drug substance, please list all the in-process testing that might be done during the manufacturing of drug product (if you have any)

7.3.6. Proposed Release Criteria

As for the drug substance, please list what are the released criteria for your final product

7.3.7. Container Closure System

Describe the container closure system

7.3.8. Stability Testing

What is your plan for stability testing? How frequently they will be performed and what are the tests that you will use to evaluate stability? What is the acceptance criteria? Typically, stability testing is performed according to ICH Guidelines Q1A (R2): "STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS". Testing is performed at 0, 3, 6, 9, 12, 18, 24, 36, 48, etc, where the 0 month is data from release testing.

7.4. Placebo

If you are using placebo in your trial, please describe what it is and how do you manufacture it.

As for the drug substance, you need to list the manufacturer of placebo, source of the material, controls used as an acceptance and release criteria etc. Please look through the previous sections.

7.5. Labeling

Include the information in the label as indicated below, listing the font size and the dimensions of the label.

Product Name Date of Manufacture, Lot Number Concentration, Volume, Total units Caution: New Drug – Limited by Federal law to investigational use

Note: Labels must contain the phrase: "Caution: New Drug – Limited by Federal law to investigational use".

7.6. Description of the Manufacturing Facility

7.7. Environmental Assessment

Include the following statement:

We request a claim for categorical exclusion for preparation of an environmental assessment for the drug used in this proposed clinical trial as provided for in 21 CFR Part 25.31(e), Action on an IND.

8. PHARMACOLOGY AND TOXICOLOGY INFORMATION

Please list all the pharmacology & Toxicology information that you might have. If drug product is marketed in the US just refer to its label.

If you have a Letter of Authorization (LOA) referencing an IND regarding information that would normally be included in this section, place a copy of the LOA here.

If this IND will include nonclinical studies that were performed in support of this IND, then the following headings in Section 8 should be used. Otherwise, they can be deleted.

8.1. Introduction

8.1.1. Structural Formula of the Drug

8.1.2. Formulation of the Dosage Forms

8.1.3. Route of Administration

8.1.4. Comparison of Toxicology and Clinical Lots

8.2. Pharmacology

8.2.1. Pharmacological Effects

8.2.2. Mechanism of Action

8.2.3. Absorption, Distribution, Metabolism, and Excretion

8.3. Toxicology

8.3.1. Introduction

8.3.2. Integrated Summary of the Toxicity Studies

Include each toxicology report summary taken from the completed tox study reports.
List the volumes that will contain the full toxicology reports for each summary provided.

8.3.3. Qualification of Individuals Performing Toxicity Study

8.3.4. Testing Facility for the Nonclinical Toxicity Study

8.3.5. Declaration of GLP Compliance

8.4. Other Nonclinical Studies

8.5. References for Item 8

9. PREVIOUS HUMAN EXPERIENCE

A summary of previous human experience with the investigational drug, if any, known to the applicant. Simply citing Authorization letters may be appropriate to fulfill this section. If the drug(s) is already marketed in the US, then you may be able to simply refer to the product labeling. If not, the following information is required:

(i) If the drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale.

(ii) If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(iii) If the drug is a combination of drugs previously investigated or marketed, the information should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component- component interaction).

(iv) If the drug(s) has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

9.1. References

List any references for Section 9

10. ADDITIONAL INFORMATION

For certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as outlined below. If these subsections are not relevant, just delete them, but keep the header "10. ADDITIONAL INFORMATION" and state "Not Applicable"

10.1. Drug Dependence and Abuse Potential

If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

10.2. Radioactive Drugs

If the drug is a radioactive drug, sufficient data from animal or human studies should be provided, to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

10.3. Pediatric Studies

If the investigational drug will be studied in pediatric setting, plans for assessing pediatric safety and effectiveness should be provided.

10.4. Other Information

A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

10.5. Selected References

If you are including reprints with your submission, list them in this section.

11. BIOSIMILAR USER FEE COVER SHEET (FORM FDA 3792)

Biosimilar biological products are products that are demonstrated to be interchangeable with an FDA-licensed biological product. For sponsor-investigator initiated INDs, this section is probably not applicable due to the fact that the majority of sponsor-investigator initiated INDs are not developing biosimilars. If you are a sponsor-investigator developing a biosimilar biological product, please complete Form FDA 3792 and include it here in section 11.

State Not Applicable *if appropriate, but leave this header in*.

12. CLINICAL TRIALS CERTIFICATION OF COMPLIANCE (FORM FDA 3674)

Include a signed and dated Form FDA 3674.

Use this link to access the Form FDA 3674:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf

Use this link to access instructions for completing Form FDA 3674:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM354618.pdf

Name of the Investigational Drug/Biologic Product

Research Number:

Names: *Chemical, Generic (if approved)*

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition: 1

Release Date
Month Date, 20XX

Replaces Previous Edition Number: *N/A (Date: N/A)*

MONTEFIORE MEDICAL CENTER

PI full name and credentials
Department of *Something*
Montefiore Medical Center
Bronx, NY 10467
Phone (718) XXX-YYYY

CONFIDENTIALITY STATEMENT

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC. This section is optional.

1. TABLE OF CONTENTS

2. SUMMARY

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3. INTRODUCTION

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product - please see the subsections listed below.

3.1. Name(s) of Drug Product

Generic Name:
Trade Name: N/A

3.2. Active Ingredients

3.3. Pharmacological Class

3.4. Rationale for Performing Research with the Investigational Product

3.5. Proposed Indication(s)

3.6. General Approach for Evaluating the Investigational Product.

4. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

4.1. Physical, Chemical, and Pharmaceutical Properties

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

4.2. Description of Drug Substances and Formulation

4.3. Storage and Handling

5. NONCLINICAL STUDIES

5.1. Introduction

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- *Species tested*
- *Number and sex of animals in each group*
- *Unit dose (e.g., milligram/kilogram (mg/kg))*
- *Dose interval*
- *Route of administration*
- *Duration of dosing*
- *Information on systemic distribution*
- *Duration of post-exposure follow-up*
- *Results, including the following aspects:*
  - *Nature and frequency of pharmacological or toxic effects*
  - *Severity or intensity of pharmacological or toxic effects*
  - *Time to onset of effects*
  - *Reversibility of effects*
  - *Duration of effects*
  - *Dose response*

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

5.2. Non Clinical Pharmacology

A summary of the pharmacological aspects of the investigational products and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

5.3. Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the

investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

5.4. Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- *Single dose*
- *Repeated dose*
- *Carcinogenicity*
- *Special studies (e.g. irritancy and sensitisation)*
- *Reproductive toxicity*
- *Genotoxicity (mutagenicity)*

6. EFFECTS IN HUMANS

6.1. Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

6.2. Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
− Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
− Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
− Population subgroups (e.g., gender, age, and impaired organ function).
− Interactions (e.g., product-product interactions and effects of food).
− Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

6.3. Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

6.4. Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB

should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

8. REFERENCES

Resource: FDA Guidance Documents

Guidance for submitting INDs to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the FDA.

Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators
Includes the IND review process and general responsibilities of sponsor-investigators related to clinical investigations.

Guidance for Submitting Electronic IND Applications:

Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format-Investigational New Drug Applications (INDs)

Guidance for Developing an Investigator Brochure:

- Environmental Assessment of Human Drug and Biologics Applications

- Guidance for Industry: Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
    - The purpose of this document is to recommend international standards for, and promote harmonization of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

- Toxicology: Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Instructions for Completing FDA Forms:

Form 1571: IND Application
Form 1572: Statement of Investigator

Investigational New Drug (IND) Submission Checklist

1. Cover Letter

- Submission Identifier: "Initial Investigational New Drug Application"
- Brief explanation of the intended investigation (type and title of study)
- Investigational new drug product's name and proposed formulation
- Disease or condition under investigation
- IND manufacturer's name and contact information (if applicable)
- Reference to an existing IND application (if applicable)
- The Cover Letter is typically addressed to the Director of the Review Division in the Office of New Drugs and signed by the sponsor of the IND application.

2. Submit completed Form FDA 1571 as instructed by FDA

- If a study conduct obligations have been contracted to a CRO, indicate that a CRO is contracted rather than listing individual obligations.
- If an investigation involves an exception from informed consent for emergency research, state on the Cover Sheet.

3. Submit completed Form FDA 1572 (Statement of Investigator) as instructed by FDA

Complete for each Investigator participating in the study

4. Submit completed Form FDA 3674 (Certification of Compliance) as instructed by FDA

Requirements for ClinicalTrials.gov Data Bank

5. Table of Contents

6. Introductory Statement and General Investigational Plan *(typically 2-3 pages)*

A brief overview of the general investigational plan for the study. This information is repeated later in the IND, in a concise detail.

- **First section:** must include the name of drug, active ingredients, its pharmacological class, structural formula (if known), formulation of the dosage form(s) to be used, route of administration, and broad objectives and expected duration of the study.
- **Second section:** must include a summary of previous human experience, reference to other INDs, if relevant, and investigational and marketing experience in other countries, if applicable.
- **Third section:** indicate if the drug has been withdrawn from investigation or marketing for any safety or effectiveness reasons, including where and why.
- **Last section:** provide a summarize plans for investigating the drug within the next 12 months, including rationale for the study, indications(s) to be studied, general plan for evaluating the drug, kind of studies planned for the first year (specify if these plans are not yet complete), expected number of patients to be enrolled and anticipated risks based on animal toxicology data.

7. Chemistry, Manufacturing, and Control Information

Drug Substance:

- Description of physical, chemical, or biological characteristics and evidence supporting structure and identity of the active pharmaceutical ingredient(s).
- Name and address of manufacturer.
- Description of the general method of preparation of the drug substance, including a list of the reagents, solvents, and catalysts used →A *detailed flow diagram* is suggested.
- The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug substance, with a brief description of the test methods used. Submission of *certificates of analysis* is suggested.
- Information to support stability of the drug substance during storage in the intended container closure and during the toxicological and clinical studies.

Drug Product:

- A list of all components and composition used in manufacturing process, including reasonable alternatives for inactive compounds used in the manufacture of the investigational drug product. This list is expected to include both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process.
- Summary of quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage.
- Brief general description of the manufacturing process (*flow diagram* is suggested) and packaging procedure, as well as other relevant tests, as appropriate for the product. Final specifications for the drug product intended to be used in toxicological and clinical studies should be included. For injectable products, sterility and pyrogenicity tests, endotoxin levels and particulate matter should be included. Submitting a copy of the certificate of analysis of the clinical batch is also suggested.
- The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug product.
- Information to support stability of the drug product during the planned clinical studies.

Placebo Formulation (if applicable):

- Brief general description of the composition, manufacture, and control of any placebo formulation to be used in the proposed clinical study. The description may be structured similarly to the description of the drug product recommended above.
- ***Note:*** For placebo, the Quality Control test will include the absence of the active pharmaceutical ingredient(s). The physical characteristics of the placebo formulation should be comparable to the actual drug product to enable effective blinding.

Labeling:

- Copies of labeling for the investigational product, when applicable. Investigator's Brochure is considered the current and most up-to-date label of the investigational new drug. IB may be obtained from the IND product's manufacturer or referenced from an existing IND application.

Environmental Assessment:

- Assessment of effects of the investigational product on the environment. Environmental Assessment may be obtained from the IND product manufacturer or referenced from an existing IND application.
- Most products qualify for a categorical exclusion from such an assessment. In general, exclusion is based upon a variety of considerations, including the following:
    - Environment compartment (soil, air, water) into which the material will partition;
    - Degradation of the material and degree;
    - Safety margin between expected environmental concentration and effect level, for materials that slowly degrade.

Granting of a categorical exclusion will also depend upon the size of study population and amount of active moiety manufactured for the study.

8. Toxicology

Include information on the toxicological effects of the drug in animals and in vitro.

Depending on the nature of the drug and the phase of the investigation, the description is expected to include:

- the results of acute, subacute, and chronic toxicity tests;
- the results of tests of the drug's effects on reproduction and the developing fetus;
- any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

For each toxicological study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review is expected. This should consist of line listings of the individual data points, including laboratory data points for each animal along with appropriate summary tabulations.

9. Investigator Brochure *(when applicable)*

May obtain Investigator's Brochure (IB) from IND product's manufacturer. For investigator-initiated IND applications that have a right of reference to an existing manufacturer's IND application, submission of the IB is not required. IB is updated as the development program progresses and new information becomes available. IB is expected to contain the following information:

- Brief description of the drug substance and the formulation, including the structural formula, if known
- Summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans
- Summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans
- Summary of information relating to safety and effectiveness in humans obtained from prior clinical studies

- Description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug. Adverse Events (AEs) described in the IB help determine whether an AE that occurs during a clinical trial is "expected" and, if so, how it will be reported to FDA.

10. Protocol(s)

Phase I

- Include all the elements of the study that are critical to safety (may include all clinical safety assessments, toxicity monitoring, description of toxicity-based stopping rules, dose adjustment rules for individual patients and the overall trial, and adverse event recording and reporting);
- Study enrollment criteria should be written with consideration of the following: (1) background risks associated with the disease or condition studied, (2) previous knowledge of toxicities of the investigational drug observed in animal studies or with human experience, (3) warnings and precautions described in the product's label (when approved products are investigated for other than approved uses);
- It is preferable that toxicity is assessed and graded according to a standardized grading scale relevant to the studied population and that adverse events are collected, recorded, and reported in a consistent manner.

Phase II-III

- All the above described expectations for adequate safety elements also apply to Phase 2-3 trials;
- Detailed protocols describing efficacy and safety should be submitted for Phase 2-3 trials. Clearly stated objectives and purposes of a trial, including description of the observations & measurements to fulfill the objectives of the trial;
- Clear description of trial design, patient selection criteria, clinical procedures, laboratory tests, and all measures to be taken to monitor the effects of the drug;
- Previous experience with the proposed primary endpoints should be discussed with relevant scientific references (including any available data regarding the measurement's validation as relevant to clinical outcomes, biomarkers, or patient reported outcomes);
- All potential deviations from trial design should be built in the protocol from the outset, including when adaptive design is considered;
- Rules for adverse events' collection, recording, and reporting should be thoroughly described;
- Protocols lacking the necessary elements describing the intended investigations may be placed on clinical hold.

Note: Protocols not submitted with the original IND must be submitted in an IND Protocol Amendment.

11. Summary of Previous Human Experience with the Investigational Drug

- If no previous human experience exists, this should be stated here.
- If an investigational drug has been investigated or marketed previously, either in the U.S. or other countries, detailed information about such experience relevant to the safety of the proposed investigation or to the investigation's rationale should be included in this section. A

summary of previous human experience should contain all relevant information about previous investigations or marketing, including clinical trial reports and published material relevant to the product's safety and effectiveness.

- If the product has been marketed outside of the United States, all countries where the product has been marketed or withdrawn from any of those markets (and why) should be listed.
- For an IND application with investigational new drug that is subject to another existing IND application (e.g., an IND application sponsored by the investigational new drug's manufacturer), the investigator-sponsor may obtain a *Letter of Authorization* from the existing IND sponsor with the right of reference to the information contained in the existing IND application, including information related to any previous human experience.
- If an investigational new drug is a combination of drugs previously investigated or marketed, the description of human experience should be provided for each active drug component. However, if any component in such combination is an approved marketed product, submission of a copy of prescribing information leaflet may be sufficient. Additional published material about the approved drug may need to be submitted, if such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

12. Additional Information

When referencing any previously submitted information, refer to it by name, reference number, and volume and page number to assist FDA in finding the reference(s). Examples of other information that can be included: discussion about drug dependency or abuse potential and radioactive dissymmetry information.

13. Material in a Foreign Language

Material in a language other than English (including scientific literature published in a foreign journal) must be included in the IND with a certified accurate and complete English translation.

Initial IND Application
Serial No. 000

Sponsor Name
Date of Submission
Volume 1 of X

IND XXXXXX
Serial No. 001

Sponsor Name
Date of Submission
Volume 1 of X

IND XXXXXX
Serial No. 002

Sponsor Name
Date of Submission
Volume 1 of X

IND XXXXXX
Serial No. 003

Sponsor Name
Date of Submission
Volume 1 of X

Step 3

Safety Reporting

Safety Reporting Guidelines

General Instructions

FDA Submission Forms

- Form 1571
- Form 3500
- Form 3500A

FDA Form 1571

Investigational New Drug Application

Click Here for Instructions

Click here for FDA Form 1571

FDA Form 3500
(MedWatch)

Voluntary
Safety Information and
Adverse Event Reporting

Click Here for Instructions

Click here for FDA Form 3500

FDA Form 3500a
(MedWatch)

Mandatory
Safety Information and
Adverse Event Reporting

Click Here for Instructions

Click here for FDA Form 3500A

GENERAL INSTRUCTIONS – IND SAFETY REPORTS

WHAT TYPE OF SAFETY INFORMATION MUST I REPORT TO THE FDA?

IND regulations require that a narrative or tabular summary of the most frequent and most serious adverse events be reported to the FDA in the annual report. However, serious and unexpected adverse events must be reported quickly in the form of an IND Safety Report. For your convenience the reporting time tables for the FDA and the Duke IRB are listed below.

You must also submit findings from laboratory animal studies that suggest a significant risk for human subjects (this is most relevant to commercial companies developing drugs).

Type of SAE	FDA Timeline	Duke IRB Timeline
Fatal or life-threatening adverse drug experience	7 calendar days	24 hours
Serious and unexpected adverse drug experience	15 calendar days	5 business days
New animal findings that suggest significant risk to human subjects	15 calendar days	5 business days
Follow-up reports	As relevant information is available	As relevant information is available

WHERE DO I SEND MY IND SAFETY REPORT? (To your IND as an Amendment)

*For CBER submissions: Staff names should NOT be placed on the document packaging or envelope address.

For a Drug:
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: [Insert Appropriate Name]

For a Therapeutic Biological Product:
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: [Insert Appropriate Name]

For a Biologic:
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

WHOM DO I ADDRESS IN THE SUBMISSION?

All IND Amendments, including IND Safety Reports are sent to the attention of the person identified by the FDA in your initial notification letter.

IS THERE A FORMAT I SHOULD FOLLOW?

You may use FDA Form 3500A or you may submit in narrative form. We recommend using Form 3500A as it will ensure you provide all the required information. For Foreign events, the 3500A or CIOMS I form may be used. For animal studies, a narrative format is used. Here is a link to Form 3500A:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

WHAT DEFINITIONS SHOULD I UNDERSTAND?

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Life-threatening adverse drug experience: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

WHERE CAN I GET MORE INFORMATION?

- See instructions provided with FDA Form 3500A
  - http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM295636.pdf

- FDA Guidance Documents: Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies:
  - http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm227351.pdf

- FDA Draft Guidance Document: Safety Assessment for IND Safety Reporting Guidance for Industry
  - http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm477584.pdf

- FDA Draft Guidance Document: Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting – Improving Human Subject Protection
  - http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126572.pdf

- 21 CFR 312, Investigational New Drug Application
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

IND Safety Reporting Guidelines

What Needs to be Reported?

Any adverse experience associated with the use of the drug that is both serious and unexpected

OR

Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity

When Are Mandatory Safety Reports Submitted?

Initial Reporting: IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

A) Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to the FDA.
   →Report as soon as possible, no later than within 15 calendar days following sponsor's initial receipt of the information
   →Identified as "IND Safety Report"

B) Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information
   →Report as soon as possible but no later than 7 calendar days from sponsor's initial receipt of the information
   →Identified as "7-day IND Safety Report"

Follow-Up Reporting:

To include any additional information obtained by the sponsor that pertains to a previously submitted IND safety report.

→Submitted without delay as soon as the information is available, but no later than 15 calendar days after the sponsor receives the information

How Do I Report?

1. Complete Form 3500A & Form 1571
2. Submit to the Review division
   Recommended to do so electronically to expedited review

Report to IRB per local guidelines

Further Information: https://www.fda.gov/safety/forms-reporting-fda/instructions-completing-form-fda-3500

KZT 18 Nov 2019
https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports

Safety Reporting Terminology

Adverse event: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse reaction: any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or suspected adverse reaction: an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application.

Serious adverse event or suspected adverse reaction: an event or reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- in-patient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly or birth defect.

Life-threatening adverse event or suspected adverse reaction: considered "life-threatening" if, in the view of the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious.

KZT 18 Nov 2019
https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports

Step 4

Amendments

Types of Amendments

Cover Letter Templates

FDA Form 1571

Amendments

Types of Amendments

Cover Letters

Initial IND Submission Cover Letter – Instructions

Initial IND Submission Cover Letter Template- Clean

Initial IND Submission Cover Letter- Montefiore Letterhead

Form 1571

IND: Amendment Submission

Before implementing an amendment, Sponsor must submit to the FDA for review and submit to Institutional Review Board. Changes can only be executed once approved by the IRB of record.

Types of Amendments:

1. *Protocol Amendment:*
    a. New Protocol

        If conduct of study is not covered under already approved IND application, should include a brief description of the most clinically significant differences between it and the previous protocols.

    b. Change in Protocol

        Must submit if changes to protocol significant affect safety of subjects, scope of the investigation, or scientific quality of the study.
        Should contain brief description of the change and reference (date, number) to the submission containing the original protocol.

        Ex: increase in drug dose, duration of exposure, significant increase in number of subjects under the study; significant change in the design of the protocol (adding or eliminating a control group); addition of new test or procedure intended to improve monitoring or reduce risk of a side effect

    c. New investigator

        Should include: investigator's name, qualifications to conduct the investigation, and any reference to the previously submitted protocol, if relevant.
        Should notify FDA *within 30 days* of the investigator added.

2. *Information Amendment*

    Types: Chemistry/microbiology, pharmacology/toxicology, clinical/safety, statistics, clinical pharmacology

    Should Include: a statement of the nature and purpose of the amendment
        An organized submission of the data in a format appropriate for scientific review.
        A request for FDA comment, if desired.

    Should be submitted as necessary but no more than every 30 days.
    Must identify contents (e.g., "Information Amendment: Chemistry, Manufacturing and Control", or "Information Amendment: Pharmacology-Toxicology", or "Information Amendment: Clinical")

3. *Safety Report*

   Serious and unanticipated Adverse Events associated with the use of the drug; see separate document for further information

4. *Annual report*

   Progress of investigation; See separate document for further information

General Guidelines:

- Include cover letter and IND cover sheet (Form 1571)
  - If the Sponsor desires FDA to comment on a submission, they should submit a request for such comment and the specific questions that FDA's response should address.
- If referencing specific technical information in IND application already submitted, identify the source by name, reference number, volume, page number, and date of submission.
- No 30-day review period
  - Only amendments raising concern will receive a reply
- Follow IND serial numbering system (document and maintain records)

Changes can be implemented once the amendment has been
submitted to FDA & has been IRB approved
EXCEPT when to eliminate a hazard to patients

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Montefiore Medical Center.

The initial study protocol for use under this IND is entitled "A Phase I Trial of Deoxyribodismutase in Humans". The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (718) 668-xxxx or at jdurham@montefiore.org. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Commented [KL1]: This is ideally the same as your date of submission.

Commented [KL2]: This part can be customized based on your IND. It may go to CBER or CDRH etc.

Commented [KL3]: Address the cover letter to the appropriate FDA Division Director. The FDA CDER and CBER Divisions can be found on FDA's website at the following links:
CDER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm075128.htm
CBER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123224.htm
Please contact our office if you need additional assistance with finding the appropriate division.

Commented [KL4]: Note: The PI does NOT have to be the sponsor but they may be the same.

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Montefiore Medical Center.

The initial study protocol for use under this IND is entitled “A Phase I Trial of Deoxyribodismutase in Humans”. The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (919) 668-xxxx or at jdurham@notes.duke.edu. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Montefiore
THE UNIVERSITY HOSPITAL FOR
ALBERT EINSTEIN COLLEGE OF MEDICINE

[INSERT: DATE]

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: [*Name of the study drug*]
Initial Investigational New Drug Application
Serial Number 0000

Dear Reviewers:

Pursuant to 21 CFR 312, I am submitting an original, Sponsor-Investigator Investigational New Drug (IND) application.

The IND is being submitted to [*INSERT: Supply short description of experimental treatment/drug and protocol*].

[INSERT: If pre-IND meeting was held, then insert text referencing the pre-IND (PIND) number and the date of meeting.]

Enclosed are the original application, the two copies, and three eCopies. The eCopy is an exact duplicate of the paper copy. UC Davis considers the material and data contained in this application to be confidential and not to be publically disclosed.

UC Davis commits to conduct this clinical investigation in accordance with all applicable regulatory requirements. UC Davise will not initiate this clinical study until this IND has become effective and Investigational Review Board (IRB) approval has been received.

If you have any questions about the material included in this IND, please do not hesitate to contact meat [*INSERT: phone number of Sponsor-Investigator*], by email at [*INSERT: email address of Sponsor-Investigator*], or by fax at [*INSERT: Sponsor-Investigator fax*] any time during your review.

[*COMMENT: If there is another person designated to interact with the FDA on behalf of the SponsorInvestigator,then state "{INSERT: name} is authorized to interact with the FDA on my behalf and{INSERT: name"s} contact information is {INSERT: phone, email, and fax}."]*

Thank you in advance for your consideration.

Sincerely,
[*INSERT: Sponsor-Investigator Name]*
[INSERT: Title]
[INSERT: Affiliation]

Department Name Line 1
Department Name Line 2
111 East 210th Street
Bronx, New York 10467
718-000-0000 Office
718-000-0000 Fax

FirstName LastName
Title 1
Title 2
718-000-0000 Office
718-000-0000 Fax
email@montefiore.org

Once the footer text has been updated please view the document in the "Print Preview" mode. This will force the footer to update on any subsequent pages created in this document.

FDA Form 1571

Investigational New Drug Application

Click Here for Instructions

Click here for FDA Form 1571

Step 5

Annual Reports

Annual Reports

Annual Report Description

Annual Report Instruction Sheet

IND Application Statuses

Cover Letter

- Annual Report Amendment Cover Letter Template Instructions
- Annual Report Amendment Cover Letter Template- Clean
- Form 1571

Annual Reports Templates

- IND Annual Report Template
- IND Annual Report Multi-Study Template

Financial Reporting

- Guide to Financial Disclosure
- Form 3454
- Form 3455

IND Submission: Annual Reports

Submit report within 60 days of the anniversary date that the application went into effect and should include the following information:

FDA Form 1571	
Individual study information	A brief summary of the status of each study in progress and each study completed during the previous year. The summary is expected to include the following information for each study: 1. The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed. 2. The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number of participants who completed the study; and the number who dropped out of the study for any reason. 3. A brief description of any available study results.
Summary information	Information obtained during the previous year's clinical and nonclinical investigations conducted under the IND application, including: 1. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. 2. A summary of all IND safety reports submitted during the past year. 3. A list of subjects who died during participation in the investigation, with the cause of death for each subject. 4. A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related. 5. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, bioavailability, or relevant information from controlled trials. 6. A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings. 7. A summary of any significant manufacturing or microbiological changes made during the past year.

KZT 19 Nov 2019
https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-annual-reports

Update to the General Investigational Plan	A description of the general investigational plan for the coming year to replace that submitted 1 year earlier.
Update to Investigator's Brochure	If the Investigator's Brochure has been revised, a description of the revision and a copy of the new brochure.
Significant protocol updates	A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.
Update on foreign marketing developments	A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.
A log of outstanding business	If desired by the sponsor, a log of any outstanding business with FDA with respect to the IND application for which the sponsor requests or expects a reply, comment, or meeting.

Report to IRB per local guidelines

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-annual-reports

GENERAL INSTRUCTIONS – ANNUAL REPORT

WHEN IS MY ANNUAL REPORT DUE?

- No later than 60 days after your IND "effective date"
- Please register your IND with us and we will send you reminders! Please start early as it takes time to compile this information.

WHERE DO I SEND MY ANNUAL REPORT?

*For CBER submissions: Staff names should NOT be placed on the document packaging or envelope address.

For a Drug:
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: [Insert Appropriate Name]

For a Therapeutic Biological Product:
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: [Insert Appropriate Name]

For a Biologic:
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

TO WHOM DO I ADDRESS THE ANNUAL REPORT?

All IND Amendments, including the Annual Reports are sent to the person identified by the FDA in your initial notification letter.

DO I HAVE TO FOLLOW THIS TEMPLATE EXACTLY?

- Some sections may not be applicable to your IND. However, we recommend that maintain all the headings and state 'not applicable' below.
- **The tables are given as examples. You can use your own versions.**

WHERE CAN I GET MORE INFORMATION?

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.33

IND: Application Status

IND Status	Description
Active (ongoing)	An IND application is in effect and the investigations are ongoing.
On Hold	An active IND application where some or all of the investigations are on Clinical Hold.
Inactive	An IND application may be inactivated upon the IND applicant's request or FDA's request. Inactivation of the IND application may occur if, for example, no subjects entered clinical trial(s) for 2 years or longer, or the IND application is on hold for 1 year or longer. An inactive application may be re-activated if activities under the IND application have restarted.
Withdrawn	An IND application may be withdrawn by the applicant if development of the investigational product has been abandoned for any reason.
Terminated	An IND application may be terminated by FDA if, for example, (1) human subjects are exposed to unreasonable or significant risk, or (2) methods, facilities and controls used for the manufacturing are inadequate to establish and maintain appropriate standards for quality and purity as needed for subject safety. Additional information on the grounds for termination of an IND application may be found in 21 CFR 312.44.

Month DD, 200Y

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
(301) 796-2330

Attn: Patricia Keegan, MD

RE: IND XXXXXX, Annual Report
Serial 00#

Dear Dr. Keegan:

Please find enclosed three copies of the annual report for IND XXXXXX. The sponsor for this IND is Josephine Duke, MD, Montefiore Medical Center.

If there are any questions regarding this submission, please contact myself or Sarah Durham, PhD at (718) 66#-#### or at sdurham@montefiore.org. Dr. Durham can act on my behalf on any issue relating to this IND.

Sincerely,

Josephine Duke, MD
Montefiore Medical Center
Address - Box ####
Address
Bronx, NY 10467
j.duke@montefiore.org

Commented [KL1]: This is ideally the date of your submission.

Commented [KL2]: All submission go first to the Central Document Room. However, you may need to customize for CDER, CBER or CDRH.

Commented [KL3]: All IND amendments, including the annual report, should be sent to the person identified by the FDA in your initial notification letter. This is typically the project manager of the IND.

Commented [KL4]: You can list multiple items here (e.g. New Investigator, New Protocol etc.)

Commented [KL5]: Each submission gets a sequential Serial No.

Month DD, 200Y

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
(301) 796-2330

Attn: Patricia Keegan, MD

RE: IND XXXXXX, Annual Report
Serial 00#

Dear Dr. Keegan:

Please find enclosed three copies of the annual report for IND XXXXXX. The sponsor for this IND is Josephine Duke, MD, Montefiore Medical Center.

If there are any questions regarding this submission, please contact myself or Sarah Durham, PhD at (919) 66#-#### or at sdurham@montefiore.org. Dr. Durham can act on my behalf on any issue relating to this IND.

Sincerely,

Josephine Duke, MD
Montefiore Medical Center
Address - Box ####
Address
Bronx, NY 10467
sdurham@montefiore.org

IND xxxxxx

Title of IND Goes Here

Serial xxx: Annual Report

Reporting Period: mm dd yyyy to mm dd yyyy

xx Month 20xx

Name of Sponsor Investigator, MD
X Professor, Department
MONTEFIORE MEDICAL CENTER

Confidential

Table of Contents

(Table of contents: may be best to recreate when you have completed your document!)

1 STUDY INFORMATION

A brief summary of the status of each study in progress and each study completed during the previous year (duplicate sections below for multiple studies). Specify which 12 months are covered by your report such as "the reporting period for this submission is from June 1, 2010 to May 31, 2011.

General Note: Maintain all headings throughout this document. If a particular section doesn't apply to your IND – state so!

The summary is required to include the following information for each study:

1.1 Title of Study

The title of the study (with appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient populations, and a statement as to whether the study is completed. It may look something like the list below. Also, you can add a table here to list other study sites.

Title of Study: title

Study Design: open label, closed label, randomized etc.

Purpose: This study will…. .

Patient Population: disease state, healthy, age, etc.

Study Status: Open, closed, enrolling, completed etc.

1.2 Enrollment Update

The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. Examples of tables that might be appropriate for your study are below. Use if appropriate or change to suit your needs. There should also be some verbiage summarizing things.

Commented [JCP1]: FDA regulations do not specifically define enrollment, but any subject who signs consent is generally considered enrolled. If you choose to define enrollment differently, such as subjects who pass all screening, make that clear in your written description.

Table 1.2-1 Subject Enrollment by Site

Commented [JCP2]: Please note: for a single center study – you don't need this table – just delete.

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
University of Somewhere			
Somewhere else University			
State Hopsital			
County of Public Health			
Total US sites			
Other country: site			
Other country: site			

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
Total non-US sites			
All Sites			

Table 1.2-2 Subject Demographics

	Female	Male	Both
Ethnic Category	**N**	**N**	**Total**
Hispanic or Latino			0
Not Hispanic or Latino			0
Total	**0**	**0**	**0**
Racial Category (single category per participant)	**N**	**N**	**Total**
White			0
Black or African American			0
Multiracial			0
Other			0
Total	**0**	**0**	**0**
Age at Enrollment Category	**N**	**N**	**Total**
18 − 21 years			0
22 − 29 years			0
30 − 39 years			0
40 − 49 years			0
50 − 59 years			0
60 − 69 years			0
70 − 79 years			0
>80 years			0
Total	**0**	**0**	**0**

Commented [JCP3]: Double click the table to add/edit data. Row/column totals should be automatically calculated. If you have another demographics table you prefer, simply delete this one and use your own.

Table 1.2-3 Status of Enrolled Participants

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment		
Total Terminated Study Early		
Total Completed Study		

Commented [JCP4]: Simple vs. detailed enrollment tables (respectively) are provided as a reference. Choose the approach that works best for your study.

Commented [JCP5]: Total enrollment to date should be equal to the sum of all following main rows – i.e. the sum of participants on study, terminated early, and completed study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment/Follow-Up in Process		
Total Terminated Study Early		
Termination Associated with an Adverse Event		
Termination Due to Subject Death		
Screen Failures		
Other (define based on your situation)		
Total Completed Study		

Commented [JCP6]: Total enrollment to date should be equal to the sum of all following main rows (on study, terminated study early, off study, completed study).

1.3 Brief Description of Study Results

If the study has been completed, or if interim results are known, a brief description of any available study results

2 SUMMARY INFORMATION

Information obtained during the previous year's clinical and nonclinical investigations, including. ***Maintain all headings and if not applicable or none – so state.***

2.1 Adverse Events: Frequent and Serious

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. Examples of reporting tables are below.

Commented [JCP7]: As with all our suggested tables. Use what makes sense for your study. This table is not required – just one of many suggestions to help you.

Body System	N	Incidence
Infections and infestations	27	56.3%
Injury, poisoning and procedural complications	12	25.0%
Investigations	12	25.0%
Nervous system disorders	10	20.8%
Respiratory, thoracic and mediastinal disorders	10	20.8%
Blood and lymphatic system disorders	9	18.8%
Musculoskeletal and connective tissue disorders	9	18.8%
Gastrointestinal disorders	7	14.6%
General disorders and administration site conditions	6	12.5%
Hepatobiliary disorders	5	10.4%
Skin and subcutaneous tissue disorders	4	8.3%
Eye disorders	3	6.3%
Ear and labyrinth disorders	2	4.2%
Psychiatric disorders	2	4.2%
Vascular disorders	2	4.2%
Immune system disorders	1	2.1%
Metabolism and nutrition disorders	1	2.1%
Renal and urinary disorders	1	2.1%

Commented [JCP8]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Reproductive system and breast disorders	1	2.1%
Surgical and medical procedures	1	2.1%

Subject ID	Adverse Event	Expected?	Likely Study Related?
1234	Fever	Yes	No
5678	Tachycardia	Yes	Yes
4321	Hypoxia	No	Yes
8765	Vomiting	No	No

2.2 Summary of IND Safety Reports

*A summary of all IND safety reports submitted (**by you to this IND**) during the past year.*

2.3 Study Subject Deaths

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

2.4 Study Subject Dropouts Resulting from Adverse Drug Experiences

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, and whether or not thought to be drug related. In other words, subjects who withdrew from the study because of intolerable side-effects.

2.5 Understanding of the Drug's Action

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about biovailability.

2.6 List of Preclinical Studies

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

2.7 Summary of Manufacturing or Microbiological Changes

A summary of any significant manufacturing or microbiological changes made during the past year.

3 GENERAL INVESTIGATIONAL PLAN

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigation plan shall contain the information required under Sec. 312.23(a) (3)(iv).

3.1 Brief Description of the Overall Investigational Plan

A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

3.1.1 Rationale

The rationale for the drug or the research study.

3.1.2 Indication(s) to be Studied

The indication(s) to be studied.

3.1.3 General Approach for Evaluation of Treatment

The general approach to be followed in evaluating the drug.

3.1.4 Planned Clinical Trials

The kinds of clinical trials to be conducted in the year following the submission (if plans are not developed for the entire year, the sponsor should indicate so).

3.1.5 Estimated Number of Subjects

The estimated number of patients to be given the drug in planned studies.

3.1.6 Anticipated Risks

Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

4 INVESTIGATOR'S BROCHURE

If the investigator's brochure has been revised, a description of the revision and a copy of the new brochure.

5 PROTOCOL MODIFICATIONS

A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

6 FOREIGN MARKETING DEVELOPMENTS

A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country. This section applies to commercial sponsors – just state:

Not Applicable

7 OUTSTANDING BUSINESS WITH RESPECT TO IND

If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

IND xx,xxx

Title of IND Goes Here

Serial 00XX: Annual Report

Reporting Period: mm dd yyyy to mm dd yyyy

DD Month 20YY

Name of Sponsor Investigator, MD
X Professor, Department
MONTEFIORE MEDICAL CENTER

Confidential

INTRODUCTION

This annual report includes updates on N different studies being run under this IND and covers the period from **month dd, 20yy to month dd, 20yy**. The studies are summarized in the table below. The table is followed by an individual Annual Report for each study.

	Short Title (Study A)	**Short Title (Study B)**	**Short Title (Study C)**	**Short Title (Study D)**
Date of Protocol Submission to IND	mm/dd/yyyy (Serial 0xx)	mm/dd/yyyy (Serial 0xx)	mm/dd/yyyy (Serial 0xx)	mm/dd/yyyy (Serial 0xx)
IRB No.	Pro000yyyyy	Pro000yyyyy	Pro000yyyyy	Pro000yyyyy
DCRU No.	zzzz	zzzz	zzzz	zzzz
Dose				
Other study info.				
Other study info.				
Other study info				
Other study info.				
Other study info.				
Other study info.				

Table of Contents

(Table of contents: may be best to recreate when you have completed your document!)

1. STUDY A

Title

IRB# XXXXXX

1.1 STUDY INFORMATION

A brief summary of the status of each study. Specify which 12 months are covered by your report such as "the reporting period for this submission is from June 1, 2010 to May 31, 2011.

General Note: Maintain all headings throughout this document. If a particular section doesn't apply to your IND – state so!

The summary is required to include the following information for each study:

1.1.1 Title of Study

The title of the study (with appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient populations, and a statement as to whether the study is completed. It may look something like the list below. Also, you can add a table here to list other study sites.

Title of Study: title

Study Design: open label, closed label, randomized etc.

Purpose: This study will…. .

Patient Population: disease state, healthy, age, etc.

Study Status: Open, closed, enrolling, completed etc.

1.1.2 Enrollment Update

The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. Examples of tables that might be appropriate for your study are below. Use if appropriate or change to suit your needs. There should also be some verbiage summarizing things.

Commented [SLG1]: FDA regulations do not specifically define enrollment, but any subject who signs consent is generally considered enrolled. If you choose to define enrollment differently, such as subjects who pass all screening, make that clear in your written description.

Table 1.1.2-1 Subject Enrollment by Site

Commented [SLG2]: Please note: for a single center study – you don't need this table – just delete.

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
University of Somewhere			
Somewhere else University			
State Hopsital			
County of Public Health			
Total US sites			
Other country: site			
Other country: site			
Total non-US sites			

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
All Sites			

Table 1.1.2-2 Subject Demographics

	Female	Male	Both
Ethnic Category	**N**	**N**	**Total**
Hispanic or Latino			0
Not Hispanic or Latino			0
Total	**0**	**0**	**0**
Racial Category (single category per participant)	**N**	**N**	**Total**
White			0
Black or African American			0
Multiracial			0
Other			0
Total	**0**	**0**	**0**
Age at Enrollment Category	**N**	**N**	**Total**
18 – 21 years			0
22 – 29 years			0
30 – 39 years			0
40 – 49 years			0
50 – 59 years			0
60 – 69 years			0
70 – 79 years			0
>80 years			0
Total	**0**	**0**	**0**

Commented [SLG3]: Double click the table to add/edit data. Row/column totals should be automatically calculated. If you have another demographics table you prefer, simply delete this one and use your own.

Table 1.1.2-3 Status of Enrolled Participants

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment		
Total Terminated Study Early		
Total Completed Study		

Commented [SLG4]: Simple vs. detailed enrollment tables (respectively) are provided as a reference. Choose the approach that works best for your study.

Commented [JCP5]: Total enrollment to date should be equal to the sum of all following main rows – i.e. the sum of participants on study, terminated early, and completed study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment/Follow-Up in Process		
Total Terminated Study Early		
Termination Associated with an Adverse Event		
Termination Due to Subject Death		
Screen Failures		
Other (define based on your situation)		
Total Completed Study		

Commented [JCP6]: Total enrollment to date should be equal to the sum of all following main rows (on study, terminated study early, off study, completed study).

1.1.3 Brief Description of Study Results

If the study has been completed, or if interim results are known, a brief description of any available study results

1.2 SUMMARY INFORMATION

Information obtained during the previous year's clinical and nonclinical investigations, including. ***Maintain all headings and if not applicable or none – so state.***

1.2.1 Adverse Events: Frequent and Serious

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. Examples of reporting tables are below.

Commented [SLG7]: As with all our suggested tables. Use what makes sense for your study. This table is not required – just one of many suggestions to help you.

Body System	N	Incidence
Infections and infestations	27	56.3%
Injury, poisoning and procedural complications	12	25.0%
Investigations	12	25.0%
Nervous system disorders	10	20.8%
Respiratory, thoracic and mediastinal disorders	10	20.8%
Blood and lymphatic system disorders	9	18.8%
Musculoskeletal and connective tissue disorders	9	18.8%
Gastrointestinal disorders	7	14.6%
General disorders and administration site conditions	6	12.5%
Hepatobiliary disorders	5	10.4%
Skin and subcutaneous tissue disorders	4	8.3%
Eye disorders	3	6.3%
Ear and labyrinth disorders	2	4.2%
Psychiatric disorders	2	4.2%
Vascular disorders	2	4.2%
Immune system disorders	1	2.1%
Metabolism and nutrition disorders	1	2.1%

Commented [SLG8]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Body System	N	Incidence
Renal and urinary disorders	1	2.1%
Reproductive system and breast disorders	1	2.1%
Surgical and medical procedures	1	2.1%

Commented [SLG8]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Subject ID	Adverse Event	Expected?	Likely Study Related?
1234	Fever	Yes	No
5678	Tachycardia	Yes	Yes
4321	Hypoxia	No	Yes
8765	Vomiting	No	No

1.2.2 Summary of IND Safety Reports

*A summary of all IND safety reports submitted (**by you to this IND**) during the past year.*

1.2.3 Study Subject Deaths

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

1.2.4 Study Subject Dropouts Resulting from Adverse Drug Experiences

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, and whether or not thought to be drug related. In other words, subjects who withdrew from the study because of intolerable side-effects.

1.2.5 Understanding of the Drug's Action

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about biovailability.

1.2.6 List of Preclinical Studies

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

1.2.7 Summary of Manufacturing or Microbiological Changes

A summary of any significant manufacturing or microbiological changes made during the past year.

1.3 GENERAL INVESTIGATIONAL PLAN

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigation plan shall contain the information required under Sec. 312.23(a) (3)(iv).

1.3.1 Brief Description of the Overall Investigational Plan

A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

1.3.1.1 <u>Rationale</u>

The rationale for the drug or the research study.

1.3.1.2 Indication(s) to be Studied
The indication(s) to be studied.

1.3.1.3 General Approach for the Evaluation of Treatment
The general approach to be followed in evaluating the drug.

1.3.1.4 Planned Clinical Trials
The kinds of clinical trials to be conducted in the year following the submission (if plans are not developed for the entire year, the sponsor should indicate so).

1.3.1.5 Estimated Number of Subjects
The estimated number of patients to be given the drug in planned studies.

1.3.1.6 Anticipated Risks
Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

1.4 INVESTIGATOR'S BROCHURE

If the investigator's brochure has been revised, a description of the revision and a copy of the new brochure.

1.5 PROTOCOL MODIFICATIONS

A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

1.6 FOREIGN MARKETING DEVELOPMENTS

A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country. This section applies to commercial sponsors – just state:

Not Applicable

1.7 OUTSTANDING BUSINESS WITH RESPECT TO IND

If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

2. STUDY B

Title

IRB# XXXXXX

2.1 STUDY INFORMATION

A brief summary of the status of each study. Specify which 12 months are covered by your report such as "the reporting period for this submission is from June 1, 2010 to May 31, 2011.

General Note: Maintain all headings throughout this document. If a particular section doesn't apply to your IND – state so!

The summary is required to include the following information for each study:

2.1.1 Title of Study

The title of the study (with appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient populations, and a statement as to whether the study is completed. It may look something like the list below. Also, you can add a table here to list other study sites.

Title of Study: title

Study Design: open label, closed label, randomized etc.

Purpose: This study will…. .

Patient Population: disease state, healthy, age, etc.

Study Status: Open, closed, enrolling, completed etc.

2.1.2 Enrollment Update

The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. Examples of tables that might be appropriate for your study are below. Use if appropriate or change to suit your needs. There should also be some verbiage summarizing things.

Commented [SLG9]: FDA regulations do not specifically define enrollment, but any subject who signs consent is generally considered enrolled. If you choose to define enrollment differently, such as subjects who pass all screening, make that clear in your written description.

Table 1.1.2-1 Subject Enrollment by Site

Commented [SLG10]: Please note: for a single center study – you don't need this table – just delete.

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
University of Somewhere			
Somewhere else University			
State Hopsital			
County of Public Health			
Total US sites			
Other country: site			
Other country: site			
Total non-US sites			

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
All Sites			

Table 1.1.2-2 Subject Demographics

Commented [SLG11]: Double click the table to add/edit data. Row/column totals should be automatically calculated. If you have another demographics table you prefer, simply delete this one and use your own.

	Female	Male	Both
Ethnic Category	**N**	**N**	**Total**
Hispanic or Latino			0
Not Hispanic or Latino			0
Total	**0**	**0**	**0**
Racial Category (single category per participant)	**N**	**N**	**Total**
White			0
Black or African American			0
Multiracial			0
Other			0
Total	**0**	**0**	**0**
Age at Enrollment Category	**N**	**N**	**Total**
18 – 21 years			0
22 – 29 years			0
30 – 39 years			0
40 – 49 years			0
50 – 59 years			0
60 – 69 years			0
70 – 79 years			0
>80 years			0
Total	**0**	**0**	**0**

Table 1.1.2-3 Status of Enrolled Participants

Commented [SLG12]: Simple vs. detailed enrollment tables (respectively) are provided as a reference. Choose the approach that works best for your study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment		
Total Terminated Study Early		
Total Completed Study		

Commented [JCP13]: Total enrollment to date should be equal to the sum of all following main rows – i.e. the sum of participants on study, terminated early, and completed study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment/Follow-Up in Process		
Total Terminated Study Early		
Termination Associated with an Adverse Event		
Termination Due to Subject Death		
Screen Failures		
Other (define based on your situation)		
Total Completed Study		

Commented [JCP14]: Total enrollment to date should be equal to the sum of all following main rows (on study, terminated study early, off study, completed study).

2.1.3 Brief Description of Study Results

If the study has been completed, or if interim results are known, a brief description of any available study results

2.2 SUMMARY INFORMATION

Information obtained during the previous year's clinical and nonclinical investigations, including. ***Maintain all headings and if not applicable or none – so state.***

2.2.1 Adverse Events: Frequent and Serious

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. Examples of reporting tables are below.

Commented [SLG15]: As with all our suggested tables. Use what makes sense for your study. This table is not required – just one of many suggestions to help you.

Body System	N	Incidence
Infections and infestations	27	56.3%
Injury, poisoning and procedural complications	12	25.0%
Investigations	12	25.0%
Nervous system disorders	10	20.8%
Respiratory, thoracic and mediastinal disorders	10	20.8%
Blood and lymphatic system disorders	9	18.8%
Musculoskeletal and connective tissue disorders	9	18.8%
Gastrointestinal disorders	7	14.6%
General disorders and administration site conditions	6	12.5%
Hepatobiliary disorders	5	10.4%
Skin and subcutaneous tissue disorders	4	8.3%
Eye disorders	3	6.3%
Ear and labyrinth disorders	2	4.2%
Psychiatric disorders	2	4.2%
Vascular disorders	2	4.2%
Immune system disorders	1	2.1%
Metabolism and nutrition disorders	1	2.1%

Commented [SLG16]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Body System	N	Incidence
Renal and urinary disorders	1	2.1%
Reproductive system and breast disorders	1	2.1%
Surgical and medical procedures	1	2.1%

Commented [SLG16]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Subject ID	Adverse Event	Expected?	Likely Study Related?
1234	Fever	Yes	No
5678	Tachycardia	Yes	Yes
4321	Hypoxia	No	Yes
8765	Vomiting	No	No

2.2.2 Summary of IND Safety Reports

*A summary of all IND safety reports submitted (**by you to this IND**) during the past year.*

2.2.3 Study Subject Deaths

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

2.2.4 Study Subject Dropouts Resulting from Adverse Drug Experiences

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, and whether or not thought to be drug related. In other words, subjects who withdrew from the study because of intolerable side-effects.

2.2.5 Understanding of the Drug's Action

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about biovailability.

2.2.6 List of Preclinical Studies

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

2.2.7 Summary of Manufacturing or Microbiological Changes

A summary of any significant manufacturing or microbiological changes made during the past year.

2.3 GENERAL INVESTIGATIONAL PLAN

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigation plan shall contain the information required under Sec. 312.23(a) (3)(iv).

2.3.1 Brief Description of the Overall Investigational Plan

A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

2.3.1.1 <u>Rationale</u>

The rationale for the drug or the research study.

2.3.1.2 Indication(s) to be Studied
The indication(s) to be studied.

2.3.1.3 General Approach for the Evaluation of Treatment
The general approach to be followed in evaluating the drug.

2.3.1.4 Planned Clinical Trials
The kinds of clinical trials to be conducted in the year following the submission (if plans are not developed for the entire year, the sponsor should indicate so).

2.3.1.5 Estimated Number of Subjects
The estimated number of patients to be given the drug in planned studies.

2.3.1.6 Anticipated Risks
Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

2.4 INVESTIGATOR'S BROCHURE

If the investigator's brochure has been revised, a description of the revision and a copy of the new brochure.

2.5 PROTOCOL MODIFICATIONS

A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

2.6 FOREIGN MARKETING DEVELOPMENTS

A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country. This section applies to commercial sponsors – just state:

Not Applicable

2.7 OUTSTANDING BUSINESS WITH RESPECT TO IND

If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

3. STUDY C

Title

IRB# XXXXXXX

3.1 STUDY INFORMATION

A brief summary of the status of each study. Specify which 12 months are covered by your report such as "the reporting period for this submission is from June 1, 2010 to May 31, 2011.

General Note: Maintain all headings throughout this document. If a particular section doesn't apply to your IND – state so!

The summary is required to include the following information for each study:

3.1.1 Title of Study

The title of the study (with appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient populations, and a statement as to whether the study is completed. It may look something like the list below. Also, you can add a table here to list other study sites.

Title of Study: title

Study Design: open label, closed label, randomized etc.

Purpose: This study will…. .

Patient Population: disease state, healthy, age, etc.

Study Status: Open, closed, enrolling, completed etc.

3.1.2 Enrollment Update

The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. Examples of tables that might be appropriate for your study are below. Use if appropriate or change to suit your needs. There should also be some verbiage summarizing things.

Commented [SLG17]: FDA regulations do not specifically define enrollment, but any subject who signs consent is generally considered enrolled. If you choose to define enrollment differently, such as subjects who pass all screening, make that clear in your written description.

Table 1.1.2-1 Subject Enrollment by Site

Commented [SLG18]: Please note: for a single center study – you don't need this table – just delete.

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
University of Somewhere			
Somewhere else University			
State Hopsital			
County of Public Health			
Total US sites			
Other country: site			
Other country: site			
Total non-US sites			

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
All Sites			

Table 1.1.2-2 Subject Demographics

Commented [SLG19]: Double click the table to add/edit data. Row/column totals should be automatically calculated. If you have another demographics table you prefer, simply delete this one and use your own.

	Female	Male	Both
Ethnic Category	**N**	**N**	**Total**
Hispanic or Latino			0
Not Hispanic or Latino			0
Total	**0**	**0**	**0**
Racial Category (single category per participant)	**N**	**N**	**Total**
White			0
Black or African American			0
Multiracial			0
Other			0
Total	**0**	**0**	**0**
Age at Enrollment Category	**N**	**N**	**Total**
18 – 21 years			0
22 – 29 years			0
30 – 39 years			0
40 – 49 years			0
50 – 59 years			0
60 – 69 years			0
70 – 79 years			0
>80 years			0
Total	**0**	**0**	**0**

Table 1.1.2-3 Status of Enrolled Participants

Commented [SLG20]: Simple vs. detailed enrollment tables (respectively) are provided as a reference. Choose the approach that works best for your study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment		
Total Terminated Study Early		
Total Completed Study		

Commented [JCP21]: Total enrollment to date should be equal to the sum of all following main rows – i.e. the sum of participants on study, terminated early, and completed study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment/Follow-Up in Process		
Total Terminated Study Early		
Termination Associated with an Adverse Event		
Termination Due to Subject Death		
Screen Failures		
Other (define based on your situation)		
Total Completed Study		

Commented [JCP22]: Total enrollment to date should be equal to the sum of all following main rows (on study, terminated study early, off study, completed study).

3.1.3 Brief Description of Study Results

If the study has been completed, or if interim results are known, a brief description of any available study results

3.2 SUMMARY INFORMATION

Information obtained during the previous year's clinical and nonclinical investigations, including. ***Maintain all headings and if not applicable or none – so state.***

3.2.1 Adverse Events: Frequent and Serious

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. Examples of reporting tables are below.

Commented [SLG23]: As with all our suggested tables. Use what makes sense for your study. This table is not required – just one of many suggestions to help you.

Body System	N	Incidence
Infections and infestations	27	56.3%
Injury, poisoning and procedural complications	12	25.0%
Investigations	12	25.0%
Nervous system disorders	10	20.8%
Respiratory, thoracic and mediastinal disorders	10	20.8%
Blood and lymphatic system disorders	9	18.8%
Musculoskeletal and connective tissue disorders	9	18.8%
Gastrointestinal disorders	7	14.6%
General disorders and administration site conditions	6	12.5%
Hepatobiliary disorders	5	10.4%
Skin and subcutaneous tissue disorders	4	8.3%
Eye disorders	3	6.3%
Ear and labyrinth disorders	2	4.2%
Psychiatric disorders	2	4.2%
Vascular disorders	2	4.2%
Immune system disorders	1	2.1%
Metabolism and nutrition disorders	1	2.1%

Commented [SLG24]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Body System	N	Incidence
Renal and urinary disorders	1	2.1%
Reproductive system and breast disorders	1	2.1%
Surgical and medical procedures	1	2.1%

Commented [SLG24]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Subject ID	Adverse Event	Expected?	Likely Study Related?
1234	Fever	Yes	No
5678	Tachycardia	Yes	Yes
4321	Hypoxia	No	Yes
8765	Vomiting	No	No

3.2.2 Summary of IND Safety Reports

*A summary of all IND safety reports submitted (**by you to this IND**) during the past year.*

3.2.3 Study Subject Deaths

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

3.2.4 Study Subject Dropouts Resulting from Adverse Drug Experiences

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, and whether or not thought to be drug related. In other words, subjects who withdrew from the study because of intolerable side-effects.

3.2.5 Understanding of the Drug's Action

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about biovailability.

3.2.6 List of Preclinical Studies

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

3.2.7 Summary of Manufacturing or Microbiological Changes

A summary of any significant manufacturing or microbiological changes made during the past year.

3.3 GENERAL INVESTIGATIONAL PLAN

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigation plan shall contain the information required under Sec. 312.23(a) (3)(iv).

3.3.1 Brief Description of the Overall Investigational Plan

A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

3.3.1.1 <u>Rationale</u>

The rationale for the drug or the research study.

3.3.1.2 Indication(s) to be Studied
The indication(s) to be studied.

3.3.1.3 General Approach for the Evaluation of Treatment
The general approach to be followed in evaluating the drug.

3.3.1.4 Planned Clinical Trials
The kinds of clinical trials to be conducted in the year following the submission (if plans are not developed for the entire year, the sponsor should indicate so).

3.3.1.5 Estimated Number of Subjects
The estimated number of patients to be given the drug in planned studies.

3.3.1.6 Anticipated Risks
Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

3.4 INVESTIGATOR'S BROCHURE

If the investigator's brochure has been revised, a description of the revision and a copy of the new brochure.

3.5 PROTOCOL MODIFICATIONS

A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

3.6 FOREIGN MARKETING DEVELOPMENTS

A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country. This section applies to commercial sponsors – just state:

Not Applicable

3.7 OUTSTANDING BUSINESS WITH RESPECT TO IND

If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

4. STUDY D

Title

IRB# XXXXXXX

4.1 STUDY INFORMATION

A brief summary of the status of each study. Specify which 12 months are covered by your report such as "the reporting period for this submission is from June 1, 2010 to May 31, 2011.

General Note: Maintain all headings throughout this document. If a particular section doesn't apply to your IND – state so!

The summary is required to include the following information for each study:

4.1.1 Title of Study

The title of the study (with appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient populations, and a statement as to whether the study is completed. It may look something like the list below. Also, you can add a table here to list other study sites.

Title of Study: title

Study Design: open label, closed label, randomized etc.

Purpose: This study will…. .

Patient Population: disease state, healthy, age, etc.

Study Status: Open, closed, enrolling, completed etc.

4.1.2 Enrollment Update

The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. Examples of tables that might be appropriate for your study are below. Use if appropriate or change to suit your needs. There should also be some verbiage summarizing things.

Commented [SLG25]: FDA regulations do not specifically define enrollment, but any subject who signs consent is generally considered enrolled. If you choose to define enrollment differently, such as subjects who pass all screening, make that clear in your written description.

Table 1.1.2-1 Subject Enrollment by Site

Commented [SLG26]: Please note: for a single center study – you don't need this table – just delete.

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
University of Somewhere			
Somewhere else University			
State Hopsital			
County of Public Health			
Total US sites			
Other country: site			
Other country: site			
Total non-US sites			

Site	Total Enrolled	First Enrollment Date	Last Enrollment Date
All Sites			

Table 1.1.2-2 Subject Demographics

	Female	Male	Both
Ethnic Category	**N**	**N**	**Total**
Hispanic or Latino			0
Not Hispanic or Latino			0
Total	**0**	**0**	**0**
Racial Category (single category per participant)	**N**	**N**	**Total**
White			0
Black or African American			0
Multiracial			0
Other			0
Total	**0**	**0**	**0**
Age at Enrollment Category	**N**	**N**	**Total**
18 – 21 years			0
22 – 29 years			0
30 – 39 years			0
40 – 49 years			0
50 – 59 years			0
60 – 69 years			0
70 – 79 years			0
>80 years			0
Total	**0**	**0**	**0**

Commented [SLG27]: Double click the table to add/edit data. Row/column totals should be automatically calculated. If you have another demographics table you prefer, simply delete this one and use your own.

Table 1.1.2-3 Status of Enrolled Participants

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment		
Total Terminated Study Early		
Total Completed Study		

Commented [SLG28]: Simple vs. detailed enrollment tables (respectively) are provided as a reference. Choose the approach that works best for your study.

Commented [JCP29]: Total enrollment to date should be equal to the sum of all following main rows – i.e. the sum of participants on study, terminated early, and completed study.

	Current Reporting Period	Overall
Total Planned for Enrollment		
Total Enrollment To Date		
Total On Study		
On Treatment		
Completed Treatment/Follow-Up in Process		
Total Terminated Study Early		
Termination Associated with an Adverse Event		
Termination Due to Subject Death		
Screen Failures		
Other (define based on your situation)		
Total Completed Study		

Commented [JCP30]: Total enrollment to date should be equal to the sum of all following main rows (on study, terminated study early, off study, completed study).

4.1.3 Brief Description of Study Results

If the study has been completed, or if interim results are known, a brief description of any available study results

4.2 SUMMARY INFORMATION

Information obtained during the previous year's clinical and nonclinical investigations, including. ***Maintain all headings and if not applicable or none – so state.***

4.2.1 Adverse Events: Frequent and Serious

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system. Examples of reporting tables are below.

Commented [SLG31]: As with all our suggested tables. Use what makes sense for your study. This table is not required – just one of many suggestions to help you.

Body System	N	Incidence
Infections and infestations	27	56.3%
Injury, poisoning and procedural complications	12	25.0%
Investigations	12	25.0%
Nervous system disorders	10	20.8%
Respiratory, thoracic and mediastinal disorders	10	20.8%
Blood and lymphatic system disorders	9	18.8%
Musculoskeletal and connective tissue disorders	9	18.8%
Gastrointestinal disorders	7	14.6%
General disorders and administration site conditions	6	12.5%
Hepatobiliary disorders	5	10.4%
Skin and subcutaneous tissue disorders	4	8.3%
Eye disorders	3	6.3%
Ear and labyrinth disorders	2	4.2%
Psychiatric disorders	2	4.2%
Vascular disorders	2	4.2%
Immune system disorders	1	2.1%
Metabolism and nutrition disorders	1	2.1%

Commented [SLG32]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Body System	N	Incidence
Renal and urinary disorders	1	2.1%
Reproductive system and breast disorders	1	2.1%
Surgical and medical procedures	1	2.1%

Commented [SLG32]: Assessment of body system isn't always easy to make (if you're not a clinician). For some Annual Reports, it's OK to simply list the AE (ex. nausea) and provide a Y/N assessment regarding whether the AE is related to the study product and if the AE is unexpected (see example below).

Subject ID	Adverse Event	Expected?	Likely Study Related?
1234	Fever	Yes	No
5678	Tachycardia	Yes	Yes
4321	Hypoxia	No	Yes
8765	Vomiting	No	No

4.2.2 Summary of IND Safety Reports

*A summary of all IND safety reports submitted (**by you to this IND**) during the past year.*

4.2.3 Study Subject Deaths

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

4.2.4 Study Subject Dropouts Resulting from Adverse Drug Experiences

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, and whether or not thought to be drug related. In other words, subjects who withdrew from the study because of intolerable side-effects.

4.2.5 Understanding of the Drug's Action

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about biovailability.

4.2.6 List of Preclinical Studies

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

4.2.7 Summary of Manufacturing or Microbiological Changes

A summary of any significant manufacturing or microbiological changes made during the past year.

4.3 GENERAL INVESTIGATIONAL PLAN

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigation plan shall contain the information required under Sec. 312.23(a) (3)(iv).

4.3.1 Brief Description of the Overall Investigational Plan

A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

4.3.1.1 Rationale

The rationale for the drug or the research study.

4.3.1.2 Indication(s) to be Studied
The indication(s) to be studied.

4.3.1.3 General Approach for the Evaluation of Treatment
The general approach to be followed in evaluating the drug.

4.3.1.4 Planned Clinical Trials
The kinds of clinical trials to be conducted in the year following the submission (if plans are not developed for the entire year, the sponsor should indicate so).

4.3.1.5 Estimated Number of Subjects
The estimated number of patients to be given the drug in planned studies.

4.3.1.6 Anticipated Risks
Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

4.4 INVESTIGATOR'S BROCHURE

If the investigator's brochure has been revised, a description of the revision and a copy of the new brochure.

4.5 PROTOCOL MODIFICATIONS

A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

4.6 FOREIGN MARKETING DEVELOPMENTS

A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country. This section applies to commercial sponsors – just state:

Not Applicable

4.7 OUTSTANDING BUSINESS WITH RESPECT TO IND

If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

A GUIDE TO FINANCIAL DISCLOSURES

DOES MY IND REQUIRE FINANCIAL DISCLOSURE FORMS?

Part 54 applies to studies that will be used in support of a marketing application. The majority of Sponsor-Investigator studies are not intended to support a marketing application. Therefore, it is unlikely that financial disclosures are required for your IND.

The following is the definition of a clinical study covered by 21 CFR Part 54:

Covered clinical study means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

These types of disclosures can be very important when it comes to large Phase III studies where a single investigator can potentially make a significant contribution to the outcome of a study.

In any event, Financial Disclosures are never submitted to INDs. They are to be saved and submitted with an NDA or other marketing application.

WHERE CAN I GET MORE INFORMATION?

You can contact us if you have questions about the relevance of Financial Disclosures in relation to your IND.

- 21 CFR 54, Financial Disclosure by Clinical Investigators

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54

FDA Form 3454

Certification: Financial Interest and Arrangements of Clinical Investigator

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Click here for FDA Form 3454

FDA Form 3455

Disclosure: Financial Interest and Arrangements of Clinical Investigators

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Click here for FDA Form 3455

Step 6

Final Report

Guideline

Cover Letter Templates

Financial Reporting

Final Report

IND Final Report Guideline

IND Application Statuses

Cover Letters

- Submission Cover Letter Template – Instructions
- Submission Cover Letter Template – Clean
- Submission Cover Letter – Montefiore Letterhead

Financial Reporting

- Guide to Financial Disclosure
- Form 3454
- Form 3455

FDA IND: Final Report and Study Closure

1. **Cover Letter & Form 1571**

2. **Individual Study Information**
   - Brief summary of the status of each study in progress and each study completed during the previous year.
     - Title of study w/ identifiers, purpose, statement if study is completed.
     - Summary of enrollment:
       - Total # of subjects initially planned for inclusion in the study
       - Number of subjects entered to date
       - Demographics table by age group, gender, and race
       - Number of subjects who completed study
       - Number of subjects who dropped out for any reason
     - Brief description of any available study results

3. **Summary Information**

   Should include information obtained during the previous year's clinical & nonclinical investigations conducted under the IND application, including:
   - Narrative or tabular summary showing most frequent and most serious adverse experiences (by body system)
   - Summary of all IND safety reports submitted during the past year
   - A list of subjects who died during participation, incl. cause of death
   - List of subjects who dropped out of study in association with any adverse experience, whether or not thought to be drug related.
   - Brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions (ex: info. about dose response, bioavailability, or relevant info. from controlled trials)
   - List of preclinical studies (incl. animal studies) completed or in progress during the past year & summary of major findings
   - Summary of any significant manufacturing or microbiological changes made during the past year

4. **Update to the General Investigational Plan**

   Description of plan for the coming year.

5. **Update to Investigator's Brochure** (if applicable)

   Description of the revision and copy of new brochure

6. **Significant Protocol Updates** (if applicable)

   Description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND as protocol amendment

7. **Update on Foreign Marketing Developments (**if applicable)

   Brief summary of significant foreign marketing developments in the past year, such as approval, withdrawal or suspension of marking in any country.

8. **Log of Outstanding Business** (if desired by Sponsor)

   Log of outstanding business with FDA with respect to IND application for which the sponsor requests or expects a reply, comment or meeting.

9. **Financial Disclosure Reporting**

   Updated throughout investigation and for 1 year after completion of study.

10. **Record Retention**

    2 years after marketing application is approved **OR**
    2 years after investigation discontinued & FDA notified

Report to IRB per local guidelines

IND: Application Status

IND Status	Description
Active (ongoing)	An IND application is in effect and the investigations are ongoing.
On Hold	An active IND application where some or all of the investigations are on Clinical Hold.
Inactive	An IND application may be inactivated upon the IND applicant's request or FDA's request. Inactivation of the IND application may occur if, for example, no subjects entered clinical trial(s) for 2 years or longer, or the IND application is on hold for 1 year or longer. An inactive application may be re-activated if activities under the IND application have restarted.
Withdrawn	An IND application may be withdrawn by the applicant if development of the investigational product has been abandoned for any reason.
Terminated	An IND application may be terminated by FDA if, for example, (1) human subjects are exposed to unreasonable or significant risk, or (2) methods, facilities and controls used for the manufacturing are inadequate to establish and maintain appropriate standards for quality and purity as needed for subject safety. Additional information on the grounds for termination of an IND application may be found in 21 CFR 312.44.

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Montefiore Medical Center.

The initial study protocol for use under this IND is entitled "A Phase I Trial of Deoxyribodismutase in Humans". The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (718) 668-xxxx or at jdurham@montefiore.org. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Commented [KL1]: This is ideally the same as your date of submission.

Commented [KL2]: This part can be customized based on your IND. It may go to CBER or CDRH etc.

Commented [KL3]: Address the cover letter to the appropriate FDA Division Director. The FDA CDER and CBER Divisions can be found on FDA's website at the following links:
CDER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm075128.htm
CBER:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123224.htm
Please contact our office if you need additional assistance with finding the appropriate division.

Commented [KL4]: Note: The PI does NOT have to be the sponsor but they may be the same.

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 000

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The initial study protocol for use under this IND is entitled “A Phase I Trial of Deoxyribodismutase in Humans”. The Principal Investigator for this study will be Josephine Einstein, MD.

If there are any questions regarding this submission, please contact myself or Jacob Albert, at (919) 668-xxxx or at jdurham@notes.duke.edu. Mr. Albert can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Montefiore Medical Center
Address, Box xxxx
Bronx, NY 10467
(718) 68x-xxxx phone
(718) 66x-xxxx fax
jduke@montefiore.org

Montefiore
THE UNIVERSITY HOSPITAL FOR
ALBERT EINSTEIN COLLEGE OF MEDICINE

[INSERT: DATE]

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: [*Name of the study drug*]
Initial Investigational New Drug Application
Serial Number 0000

Dear Reviewers:

Pursuant to 21 CFR 312, I am submitting an original, Sponsor-Investigator Investigational New Drug (IND) application.

The IND is being submitted to [*INSERT: Supply short description of experimental treatment/drug and protocol*].

[INSERT: If pre-IND meeting was held, then insert text referencing the pre-IND (PIND) number and the date of meeting.]

Enclosed are the original application, the two copies, and three eCopies. The eCopy is an exact duplicate of the paper copy. UC Davis considers the material and data contained in this application to be confidential and not to be publically disclosed.

UC Davis commits to conduct this clinical investigation in accordance with all applicable regulatory requirements. UC Davise will not initiate this clinical study until this IND has become effective and Investigational Review Board (IRB) approval has been received.

If you have any questions about the material included in this IND, please do not hesitate to contact meat [*INSERT: phone number of Sponsor-Investigator*], by email at [*INSERT: email address of Sponsor-Investigator*], or by fax at [*INSERT: Sponsor-Investigator fax*] any time during your review.

[*COMMENT: If there is another person designated to interact with the FDA on behalf of the SponsorInvestigator,then state "{INSERT: name} is authorized to interact with the FDA on my behalf and{INSERT: name"s} contact information is {INSERT: phone, email, and fax}."]*

Thank you in advance for your consideration.

Sincerely,
[*INSERT: Sponsor-Investigator Name]*
[INSERT: Title]
[INSERT: Affiliation]

Department Name Line 1
Department Name Line 2
111 East 210th Street
Bronx, New York 10467
718-000-0000 Office
718-000-0000 Fax

FirstName LastName
Title 1
Title 2
718-000-0000 Office
718-000-0000 Fax
email@montefiore.org

Once the footer text has been updated please view the document in the "Print Preview" mode. This will force the footer to update on any subsequent pages created in this document.

A GUIDE TO FINANCIAL DISCLOSURES

DOES MY IND REQUIRE FINANCIAL DISCLOSURE FORMS?

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http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54

FDA Form 3454

Certification: Financial Interest and Arrangements of Clinical Investigator

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Click here for FDA Form 3454

FDA Form 3455

Disclosure: Financial Interest and Arrangements of Clinical Investigators

---

Click here for FDA Form 3455

Step 7

Record Keeping

Requirements

Regulatory File Checklist

Drug Accountability Log Templates

Financial Reporting

Record Keeping

Record Keeping Requirements

Regulatory File Checklist

Drug Accountability Log Templates

- Investigational Product Accountability Log: Stock Record
- Investigational Product Accountability Log: Subject Record

Financial Reporting

IND Record Keeping Requirements

1. **Disposition of drug**

An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under Sec. 312.59.

2. **Case histories**

An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

3. **Record retention**

An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

KZT 18 Nov 2019
https://www.fda.gov/drugs/investigational-new-drug-ind-application/federal-regulations-clinical-investigators

REGULATORY FILES CHECKLIST

STATEMENT OF INVESTIGATOR AND CURRICULUM VITAE

This section should contain the following:

- Copy of Signed Form FDA 1572 for the Investigator
- Copy of Signed Revised Form FDA 1572 (if applicable)
- Current Curriculum Vitae for the Investigator and for each Sub-Investigator
- Copy of Medical License for the Investigator and for each Sub-Investigator

INVESTIGATIONAL NEW DRUG FILING/INVESTIGATION DEVICE EXEMPTION *(If Investigator-Initiated IND/IDE Trial)*

This section should contain the following:

- Investigational New Drug (IND) Application/Investigational Device Exemption (IDE)

FOOD AND DRUG ADMINISTRATION CORRESPONDENCE

(If Investigator-Initiated IND/IDE Trial)

This section should contain the following:

- All Correspondence between the Food and Drug Administration (FDA), the Sponsor, and/or the Site

FOOD AND DRUG ADMINISTRATION ANNUAL REPORTS

(If Investigator-Initiated IND/IDE Trial)

This section should contain the following:

- All FDA Annual Reports and Related Correspondence

INVESTIGATOR'S BROCHURE/DEVICE MANUAL

This section should contain the following:

- Investigator's Brochure or Package Insert
- Revised Investigator's Brochure(s) or Package Insert (If Applicable)

PROTOCOL and AMENDMENTS

This section should contain the following:

- Copy of Final Protocol and Signed Protocol Signature Page
- Copy of all Protocol Amendments and Signed Protocol Amendment Signature Pages (If Applicable)

APPROVED INFORMED CONSENT DOCUMENT AND INFORMATION GIVEN TO SUBJECTS

This section should contain the following:

- Blank Copy of Institutional Review Board (IRB)-Approved Informed Consent Document (ICF), any other Written Information given to Subjects (If Applicable), and Advertisement for Subject Recruitment (If Applicable)
- Blank Copy of IRB-Approved Revised ICF, any other Written Information given to Subjects, and Advertisement for Subject Recruitment (If Applicable)
- Blank Copy of IRB-Approved Authorization for Use and Disclosure of Protected Health Information (If Separate from ICF)

SCIENTIFIC RESEARCH REVIEW COMMITTEE

This section should contain the following:

- Scientific Research Review Committee approvals and correspondence

INSTITUTIONAL REVIEW BOARD COMMITTEE DOCUMENTATION

This section should contain the following:

- Institutional Review Board Membership List covering the Entire Interval of the Study (or Regulatory Agency Registry Number)
- IRB Correspondence, Including the Following:
    - IRB Approval of Protocol, Informed Consent Document (ICF), Any other Written Information given to Subjects (If Applicable), and Advertisement for Subject Recruitment (If Applicable)
    - IRB Approval of Amendments to Protocol, ICF, Any other Written Information given to Subjects, and Advertisements for Subject Recruitment (If Applicable)
    - IRB Approval of Authorization for Use and Disclosure of Protected Health Information (If Separate from the ICF)
    - Investigator Annual Report to IRB
    - IRB Approval of Protocol for Study Continuation
    - Notification to IRB of Serious Adverse Events, as Documented in Tab 11, Safety Information (If Applicable)
    - Notification to IRB of Unanticipated Problems Involving Risks to Subjects and Others (If Applicable)
    - Notification to IRB of Study Completion and Site Final Study Report

SAFETY INFORMATION

This section should contain the following:

- Copy of Serious Adverse Event (SAE) Reports (If Applicable) and any Safety Information
- All Correspondence Between the Sponsor/CRO and the Sites that Concerns SAE Reports and any Safety Information (If Applicable)
- All Correspondence with Regulatory Agencies Regarding Safety Information (If Applicable)

SAFETY AND DATA MONITORING COMMITTEE

This section should contain the following:

- Safety and Data Monitoring Committee (SDMC) Reports and Correspondence

CLINICAL TRIAL MATERIAL DOCUMENTATION

This section should contain the following:

- Records of Receipt of Clinical Trial Material (CTM) and Trial-Related Materials (If Applicable)
- CTM Dispensing/Accountability Records (If Dispensing/Accountability Records are Filed in the Pharmacy, Photocopies of these Records should be made at Study Completion and Inserted in the Regulatory Binder. Please State the Location of Original Records.)
- Documentation of CTM destruction if performed at the site

BIOLOGICAL SAMPLES DOCUMENTATION

This section should contain the following:

- Copies of Biological Sample Transmittal Forms that Accompanied the Shipment to the External Laboratory (If Applicable). (If not kept within the Regulatory Binder, Please State the Location.)
- Correspondence Regarding Biological Samples
- Record of Retained Body Fluids/Tissue Samples (If Applicable)

LABORATORY DOCUMENTATION

This section should contain the following:

- Laboratory Certification (Including Updates Throughout the Study Duration)
- Laboratory Normal Reference Range (Including Updates Throughout the Study Duration)
- Central Laboratory Information (If Applicable)

STUDY PROCEDURE MANUAL

This section should contain the following:

- Study Procedures Manual and Nay Revisions (If Applicable). (If not kept within the Regulatory Binder, Please State the Location). If No Study Procedure Manual was used for the Study, Please Note This.

SOURCE DOCUMENTATION

This section should contain the following:

- Source Document Template and any Revisions
- Completed Source Documents for each Subject. (If not kept in the Regulatory Binder, Please State the Location)

BLANK CASE REPORT FORM

This section should contain the following:

- Blank Case Report Form including any Amended Page(s) (If Applicable). Please Note If Electronic Data Capture is used for this Study.

SUBJECT ACCOUNTABILITY RECORDS

This section should contain the following:

- Subject Screening and Enrollment Logs (List of Subjects Screened for Entry as well as Enrolled in the Study)
- Medical Exception Forms
- Subject Identification Code List (List of Subjects Enrolled in the Study and Identified by a Unique Number) NOTE: This is a Confidential List and should be Maintained only at the Site.
- Signed Institutional Review Board-Approved Informed Consent Document and Authorization for Use and Disclosure of Protected Health Information for each Subject Screened for Entry into the Study. (If not kept in the Regulatory Binder, Please State the Location)
- Copy of Completed Case Report Forms (CRFs) for each Subject with any Related Data Clarification Requests (If Applicable). (If not kept in the Regulatory Binder, Please State the Location)

- Copy of Completed CRF Transmittal Forms (If Applicable). If not kept within the Regulatory Binder, Please State the Location.
- Copy of Completed CRF Edit Logs (If Applicable). If not kept within the Regulatory Binder, Please State the Location.

STUDY STAFF INFORMATION

This section should contain the following:

- Study Staff Responsibilities and Signature Form
- Study-Specific Training Records (If Applicable)

MONITORING ACTIVITIES

This section should contain the following:

- Monitoring Log
- Monitor Correspondence (Site Visit Confirmation and Follow-Up Correspondence)
- Site Initiation Visit Report

INVESTIGATOR AND INSTITUTION AGREEMENT(S), FINANCIAL INFORMATION, AND INSURANCE INFORMATION

This section should contain the following:

- Financial Disclosure/Certification for all investigators (if applicable). If not kept with the Regulatory Binder, Please State the Location.
- Clinical Study Agreement (CSA) (If Applicable)
- Insurance or Indemnification Statement (If Separate from CSA) (If Applicable)
- Data Use Agreement (If Separate from CSA)

GENERAL CORRESPONDENCE

This section should contain the following:

- All Correspondence Between the Sponsor/CRO and the Site Concerning the Study (Except Correspondence Concerning Serious Adverse Events and Safety Information that should be Filed Behind Tab 11, Safety Information; and Monitor Correspondence that should be Filed behind Tab 21, Monitoring Activities)
- Site-Generated Telephone Contact Reports or Logs

CLINICAL STUDY REPORT

This section should contain the following:

- Clinical Study Report (If Applicable)

NOTES TO FILE AND OTHER INFORMATION

This section should contain the following information:

- Notes to File (If Applicable)
- Other Information Felt Necessary to Retain but not Filed Elsewhere in the Regulatory Binder

National Center for Complementary and Integrative Health

Tool Summary Sheet

Tool: Investigational Product Accountability Log: Stock Record

Purpose: To document all study product disposition and accountability on the site level.

Audience/User: Study Coordinators, Principal Investigators (PIs), pharmacy staff, other site staff, clinical monitor.

Details: This tracking log should provide a comprehensive list of all study product dispositions on the site level. It is required for interventional clinical studies using a study product for research.

The set of columns are suggestions and can be customized to meet the needs of the study.

Best Practice Recommendations:

- Complete the log as study product is dispensed and/or received, to ensure completeness and accuracy of the data. A new line should be completed each time study product is dispensed and/or received.
- The "Stock Record" may be used to record overall bulk study product supplies and accountability. The associated "Subject Record" is a separate tool that may be used to record dispensing and return of study product on the subject level.
- In the "Quantity Dispensed and/or Received" column, use a "+" before the number when receiving product; use a "-" before the number when dispensing product. See the example provided within the log.
- In the "Balance Forward" column, use the diagonal line across the box to record the previous balance forward / the resulting balance (e.g., 500 / 600). See the example provided within the log.
- The log recorder should initial the line item as the information is entered.
- Create additional lines and pages as needed.
- For clinical studies that are not blinded, maintain this log in the Essential Documents Binder, behind the "Study Product Records" tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File [ISF], and Study File.)
- For blinded clinical studies, it is recommended that study product accountability records be filed in a separate location (e.g., the research pharmacy), to maintain the blind.
- Number each page and store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.
- Remove this Tool Summary Sheet before use of the log.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	24Apr2013	First approved version of Stock Record log as a separate tool

Investigational Product Accountability Log: Stock Record

Name of Institution:	**Product Name:**
Investigator Name:	**Manufacturer:**
Protocol No.:	**Dose Form and Strength:**
Protocol Title:	**Dispensing Area:**

Line No.	Date	Dispensed To / Received From	Dose	Quantity Dispensed and/or Received	Balance Forward / Balance	Lot No.	Recorder's Initials
Ex.	*15Feb2012*	*Manufacturer*	*10 mg*	*+ 100 tabs*	*500* / *600*	*98765*	*JAD*
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							

Check if final page of log: ☐

National Center for Complementary and Integrative Health

Tool Summary Sheet

Tool: Investigational Product Accountability Log: Subject Record

Purpose: To document all study product disposition and accountability on the subject level.

Audience/User: Study Coordinators, Principal Investigators (PIs), pharmacy staff, other site staff, clinical monitor.

Details: This tracking log should provide a comprehensive list of all study product dispositions on the subject level. It is required for interventional clinical studies using a study product for research.

The set of columns are suggestions and can be customized to meet the needs of the study.

Best Practice Recommendations:

- Complete the log as study product is dispensed and/or received, to ensure completeness and accuracy of the data. A new line should be completed each time study product is dispensed and/or received.
- The “Subject Record” may be used to record dispensing and return of study product on the subject level. The associated “Stock Record” is a separate tool that may be used to record overall bulk study product supplies and accountability.
- In the "Quantity Dispensed and/or Received" column, use a “+“ before the number when receiving product; use a “-“ before the number when dispensing product. See the example provided within the log.
- In the “Balance Forward” column, use the diagonal line across the box to record the previous balance forward / the resulting balance (e.g., 600 / 500). See the example provided within the log.
- The log recorder should initial the line item as the information is entered.
- Create additional lines and pages as needed.
- For clinical studies that are not blinded, maintain this log in the Essential Documents Binder, behind the “Study Product Records” tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File (ISF), and Study File.)
- For blinded clinical studies, it is recommended that study product accountability records be filed in a separate location (e.g., the research pharmacy), to maintain the blind.
- Number each page and store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
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- Remove this Tool Summary Sheet before use of the log.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	24Apr2013	First approved version

Investigational Product Accountability Log: Subject Record

Name of Institution:	**Product Name:**
Investigator Name:	**Manufacturer:**
Protocol No.:	**Dose Form and Strength:**
Protocol Title:	**Dispensing Area:**

Line No.	Date	Subject ID Number	Subject's Initials	Dose	Quantity Dispensed and/or Received	Balance Forward / Balance	Lot No.	Recorder's Initials
Ex.	*15Feb2012*	*12345*	*ABC*	*10 mg*	*- 100 tabs*	*600* / *500*	*98765*	*JAD*
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								

Check if final page of log: ☐

A GUIDE TO FINANCIAL DISCLOSURES

DOES MY IND REQUIRE FINANCIAL DISCLOSURE FORMS?

Part 54 applies to studies that will be used in support of a marketing application. The majority of Sponsor-Investigator studies are not intended to support a marketing application. Therefore, it is unlikely that financial disclosures are required for your IND.

The following is the definition of a clinical study covered by 21 CFR Part 54:

Covered clinical study means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

These types of disclosures can be very important when it comes to large Phase III studies where a single investigator can potentially make a significant contribution to the outcome of a study.

In any event, Financial Disclosures are never submitted to INDs. They are to be saved and submitted with an NDA or other marketing application.

WHERE CAN I GET MORE INFORMATION?

You can contact us if you have questions about the relevance of Financial Disclosures in relation to your IND.

- 21 CFR 54, Financial Disclosure by Clinical Investigators

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54

FDA Form 3454

Certification: Financial Interest and Arrangements of Clinical Investigator

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Click here for FDA Form 3454

FDA Form 3455

Disclosure: Financial Interest and Arrangements of Clinical Investigators

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Click here for FDA Form 3455