Good Clinical Practice Training

Introduction:

Welcome to Good Clinical Practice training.

The purpose of this training is to focus on the Principal Investigator's area of responsibility in clinical trials executed in cooperation with Merck Sharp & Dohme, referred to as Merck & Co., Incorporated in the United States. For the duration of this training we will refer to the company as "Merck."

This training is intended to provide you, the principal investigator, with a high-level overview of Good Clinical Practice and Merck's expectations.

Compliance with Good Clinical Practice standards helps to protect the rights, safety, welfare and confidentiality of the clinical trial subjects, and also helps to ensure the quality and integrity of the data that is collected.

Good Clinical Practice Training

Historical Development of good Clinical Practice:

Good Clinical Practice:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. These standards are consistent with the principles that have their origin in the Declaration of Helsinki , one of the best known international reference codes of medical research ethics, first established in 1964.

In 1962, the Drug Amendment Act was approved in the United States. This became the Food and Drug Administration (FDA) Regulations governing clinical research. These regulations became a framework for legislation and guidelines covering the majority of clinical research that are now in place in almost every country in the world.

Guidelines for the conduct of medical research were subsequently developed in a number of European countries during the 1970s and 1980s, with some harmonization occurring in 1990. The Nordic GCP guidelines were also developed during this time. Meanwhile, other regions of the world, Canada, Israel and Japan also developed GCP guidelines and the World Health Organization (WHO) issued their own set of GCP guidelines in 1993. By that time, it was apparent that a global standard for GCP

was required.

Good Clinical Practice (Contd.):

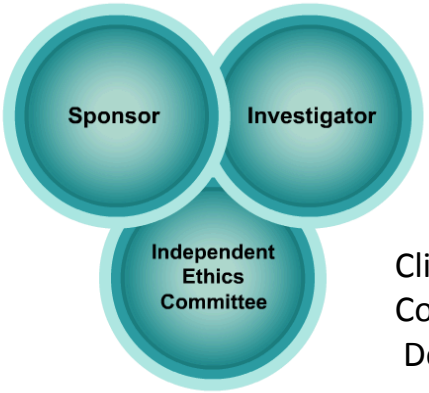
In 1991, the International Conference on Harmonization (ICH) recognized this need and formed an Expert Working Group to draft a guideline on GCP. In May, 1996, this guideline was issued as final and referred to at the " ICH E6 GCP Consolidated Guideline". This guideline was then adopted by the three main ICH regions – Europe, the United States and Japan. In countries and organizations outside the three ICH regions, the ICH GCP guideline quickly became the most widely accepted and followed GCP guideline, with many countries and regions implementing legislation which requires that the ICH GCP guidelines (among other things) be followed.

Click HERE View GCP Guidelines

Good Clinical Practice (Contd.):

A Shared Responsibility…

As a sponsor, Merck is committed to designing, implementing, conducting and reporting the results from our clinical trials in compliance with the highest scientific and ethical standards. This can only be achieved through the dedication and commitment of all contributing parties; that is the sponsor, the investigator, and the Independent Ethics Committee.
This committee is also referred to as the IEC or Institutional Review Board (IRB). For the duration of this module the IRB and IEC will be referred to as the ethics committee.



Click HERE View Code of Conduct Document

Good Clinical Practices (Contd.):

All Merck protocols contain a code of conduct describing our scientific and ethical standards for the design and conduct of our clinical trials. A copy of this code is attached here if you have not already reviewed the code within the protocol. We depend on you, the investigator, to review this code, to uphold its principles and to fully support and embrace these standards of scientific excellence at your study site.

Investigator Responsibility…

Even though the ICH-GCP Guidelines describe the responsibility for the investigator, sponsor and ethics committees, the intent of this presentation is to focus on your responsibilities as the Principal Investigator.

- Medical care of trial subjects
- Communication with ethics committees
- Compliance with the protocol
- Informed consent process
- Handling of clinical supplies
- Data collection & reporting
- Adverse experience assessment & reporting
- Storage of study documents

With the understanding that you may delegate some responsibilities, it is always the Principal Investigator who has the overall responsibility for all clinical trial activities conducted at the study site.

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Investigator Responsibility (Contd.):

Some of the key responsibilities that we will review are:

- Medical care of subjects during the trial
- Required communication with the Ethics Committee
- Protocol compliance
- The need for providing study information to the study subjects and obtaining informed consent
- The handling of clinical supplies, including drug storage and accountability
- Collecting protocol specified data, including the execution of any required protocol procedures
- The evaluation, review and reporting of the results related to the study subjects during the study
- Adverse experience assessment and reporting and finally,
- Maintenance of study documentation related to the clinical trial at the study site

Medical Care of Trial Subjects

A clinical trial involves many tasks and activities. Typically, the Principal Investigator delegates some of these tasks and activities to other individuals. Any delegation of study-related tasks must be to individuals who are qualified by education and/or training. The delegation of all study tasks and procedures must be documented on the Site Signature and Responsibility Log. The format of this form may be different than the one pictured here, however, the intent is always to identify all study staff at your site and their delegated responsibilities.

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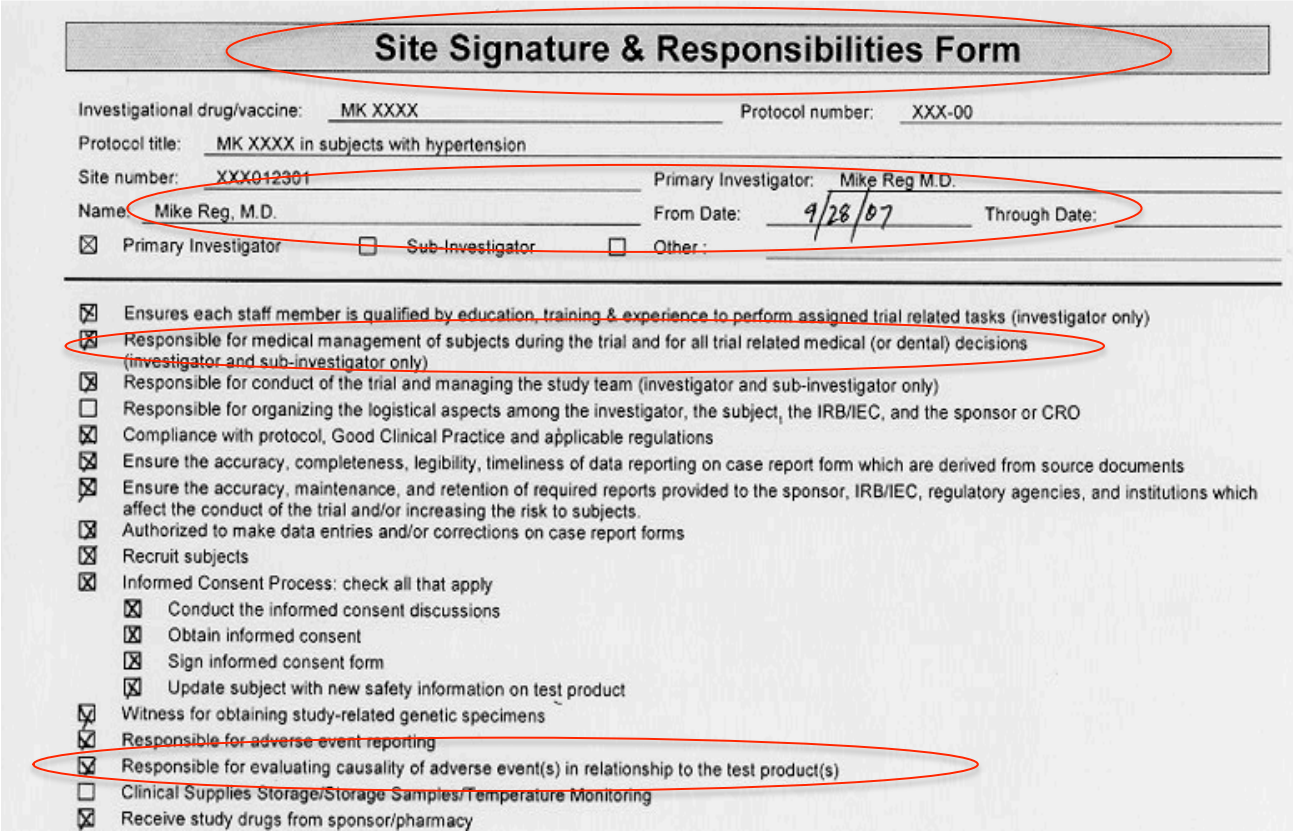
Medical Care of Trial Subjects (Contd.):

When an individual either begins or ends responsibility for a designated activity during the course of a study the start and stop dates should be clearly indicated on the form.



Site Signature & Responsibilities Form

Investigational drug/vaccine: MK XXXX Protocol number: XXX-00

Protocol title: MK XXXX in subjects with hypertension

Site number: XXX012301 Primary Investigator: Mike Reg M.D.

Name: Mike Reg, M.D. From Date: 9/28/07 Through Date:

☒ Primary Investigator ☐ Sub-Investigator ☐ Other :

- ☒ Ensures each staff member is qualified by education, training & experience to perform assigned trial related tasks (investigator only)
- ☒ Responsible for medical management of subjects during the trial and for all trial related medical (or dental) decisions (investigator and sub-investigator only)
- ☒ Responsible for conduct of the trial and managing the study team (investigator and sub-investigator only)
- ☐ Responsible for organizing the logistical aspects among the investigator, the subject, the IRB/IEC, and the sponsor or CRO
- ☒ Compliance with protocol, Good Clinical Practice and applicable regulations
- ☒ Ensure the accuracy, completeness, legibility, timeliness of data reporting on case report form which are derived from source documents
- ☒ Ensure the accuracy, maintenance, and retention of required reports provided to the sponsor, IRB/IEC, regulatory agencies, and institutions which affect the conduct of the trial and/or increasing the risk to subjects.
- ☒ Authorized to make data entries and/or corrections on case report forms
- ☒ Recruit subjects
- ☒ Informed Consent Process: check all that apply
  - ☒ Conduct the informed consent discussions
  - ☒ Obtain informed consent
  - ☒ Sign informed consent form
  - ☒ Update subject with new safety information on test product
- ☒ Witness for obtaining study-related genetic specimens
- ☒ Responsible for adverse event reporting
- ☒ Responsible for evaluating causality of adverse event(s) in relationship to the test product(s)
- ☐ Clinical Supplies Storage/Storage Samples/Temperature Monitoring
- ☒ Receive study drugs from sponsor/pharmacy

It is Merck's expectation based on GCP standards, that all trial-related medical decisions are made by a qualified physician. Therefore, you as the Principal Investigator may not delegate these responsibilities to a Nurse Care Practitioner or Physicians Assistant. Examples of trial-related medical decisions include:

- Review and interpretation of ECGs and laboratory results
- Causality assessment of adverse experiences

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Communicating with the Ethics Committee:

Before initiating a trial, written approval from your local ethics committee must be obtained.

Minimally, your ethics committee must approve: the trial protocol, the patient informed consent form and subject recruitment procedures as well as any other written information that will be provided to the study subjects. As Principle Investigator, you are responsible for ensuring that all ethics committee approvals have been appropriately obtained prior to initiation of the study at your site

- Submission of study and securing document approval
- Reporting deviations from or changes to the protocol
- Reporting serious adverse events that occur at your site

As Principal Investigator you are responsible to report any deviations, changes or revisions to the approved protocol to both Merck and your ethics committee.

Merck requires that you notify your ethics committee of all site-specific serious adverse events in accordance with the ethics committee requirements and/or local regulations.

Ethics committee requirements for these responsibilities vary and should be clearly understood prior to the start of the study. Please discuss any questions you may have with your Clinical Research Associate.

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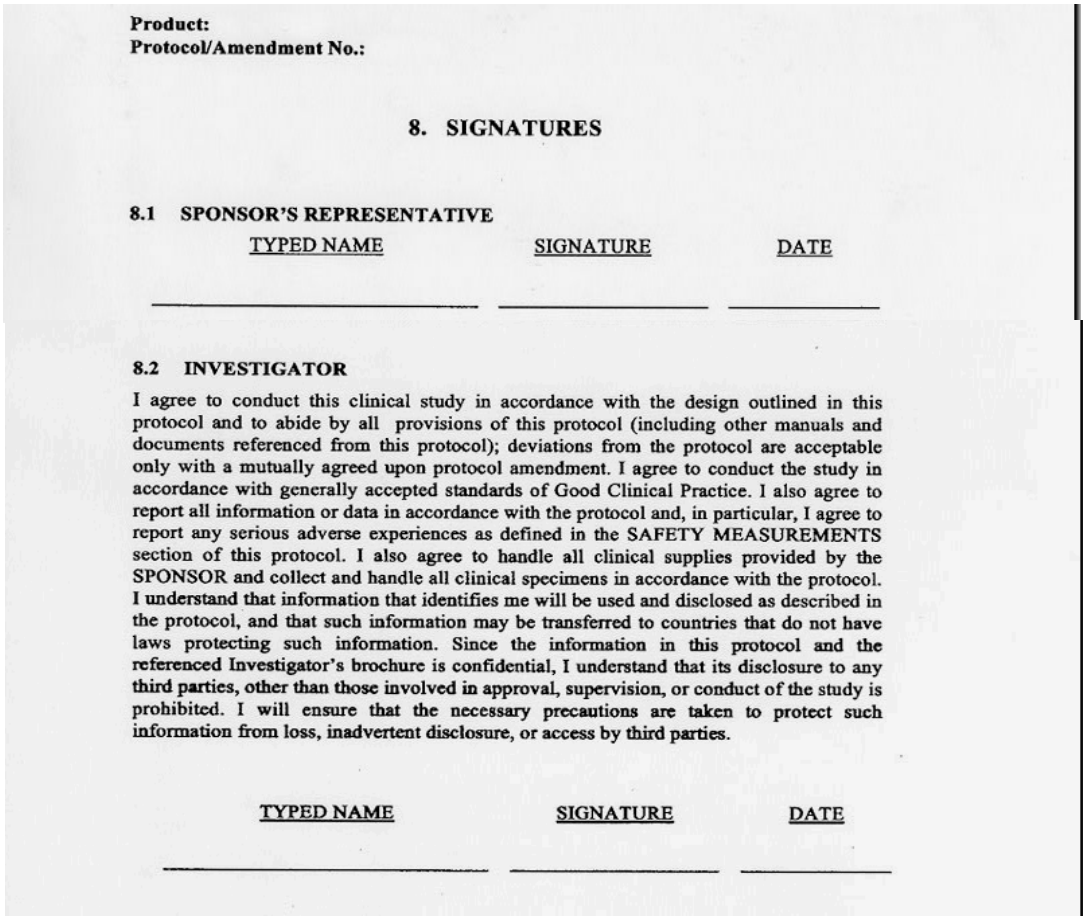
Protocol Compliance:

It is expected that all participating investigators will review the appropriate study documents, including the full protocol and Confidential Investigator's Brochure (CIB).



Product:
Protocol/Amendment No.:

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME SIGNATURE DATE

_____ _____ _____

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME SIGNATURE DATE

_____ _____ _____

By signing a Merck-approved protocol, you, as the Principal Investigator, accept responsibility for adhering to the protocol requirements. Remember, if, a deviation to the protocol occurs at your site, you must report the deviation to Merck and your ethics committee.

As noted previously, it is essential that prior to carrying out any study related procedures at your site, both Merck and the Ethics Committee have reviewed and approved the protocol and associated study documents

Good Clinical Practice Training

Protocol Compliance Scenario Introduction:

During this training module we will go through 3 different learning scenarios, all of which take place in the same office environment. Unit X is a busy research/practice/unit with multiple physicians. There are typically several clinical research studies being conducted simultaneously and the physicians may serve as Principal Investigators or Sub-Investigators depending on the agreed upon delegation of responsibility. The practice employs one full time and one part time clinical study coordinator. The full time study coordinator is a registered nurse and the part time study coordinator is a biologist. Both study coordinators have other responsibilities in the unit beyond their duties associated with the clinical research studies.

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Protocol Compliance Scenario Part 1:

During this first scenario the study staff is discussing a study subject: You will be asked questions about their decisions regarding protocol compliance.

Dr. Mike Reg (Principal Investigator) is sitting at his desk with a phone message in his hand. Dr. Stephanie Compliance, who is also a medically-qualified physician, is one of the new sub-investigators at the site. She and the Study Coordinator, Ms. Terrific, are also sitting at the desk.

Dr. Mike Reg: " Stephanie, as you may recall, we are currently conducting a Merck pediatric double–blind randomized study comparing active drug with placebo in subject 6 to 24 months old. According to the protocol, study drug granules must be mixed with applesauce at room temperature and give to the child each evening.

I've received this phone message from one of the parents whose child is in the study. Her 8 month old had been taking the study drug every evening since being randomized 2 weeks ago and now all of a sudden her child is refusing to eat the applesauce and has missed two evening study doses. If this were your study subject Stephanie, what would you tell the parents to do?"

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Protocol Compliance Scenario Part 1 (Contd.):

Dr. Compliance: " Well Mike, I know that my 10 month old son goes through periods of not liking certain foods and my husband Joe and I often end up with the rejected food on our clothes. What about suggesting to the parents that they mix the study drug with one of the child's favorite food? I would definitely reinforce with the parents that we don't want to miss any more doses of the study drug. This obviously would also need to get captured in the source documents"

QUESTION 1:

Is Dr. Compliance's response appropriate?

☒ Yes
☐ No

*Correct Answers can be found in the appendix

Good Clinical Practice Training

Protocol Compliance Scenario Part 2:

Ms. Terrific: " This is a tough one. Because the protocol specifically states that applesauce at room temperature must be used, we can't suggest refrigerating or heating the applesauce to see if the child would eat the study drug in the applesauce at a different temperature. I know my babies were much more awake in the morning and much more likely to be cooperative, but the protocol states that the study drug must be administered in the evening, I really believe with this one we have to contact our Merck Clinical Research Associate; to discuss the best way to resolve the situation. "

QUESTION 2:

Is Ms. Terrific's response appropriate?

☑ Yes

☒ No

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Conducting the Study:

Informed Consent

The Informed Consent process is one of the most important aspects of a clinical research study. It is imperative that the Informed Consent form is approved by Merck, the ethics committee and where necessary the Regulatory Authorities prior to providing the consent to a potential study subject.

The Informed consent process includes the open exchange of information that occurs between you, the investigator and the potential study subject of a clinical trial. During this discussion you will review the subject's responsibilities, their rights as well as the risks and benefits of their potential participation in the clinical trial. The subject also needs to be provided with the opportunity to ask you any questions they may have, and to have these questions answered to their complete satisfaction. Although this process begins at the start of a clinical trial, the responsibility for the process continues throughout the study to ensure that all study subjects remain informed of any updated findings or new information concerning the study drug, study protocol, and their willingness to continue with their participation in the study.

Only when the subject has willingly signed the approved informed consent form, may study-related procedures be initiated. This includes changes to the subject's current medication, diet or a study required medication washout period.

We have just reviewed a few key points about the informed consent process. Merck has a dedicated training module that covers the informed consent process in more detail that you will need to complete if you have not already done so.

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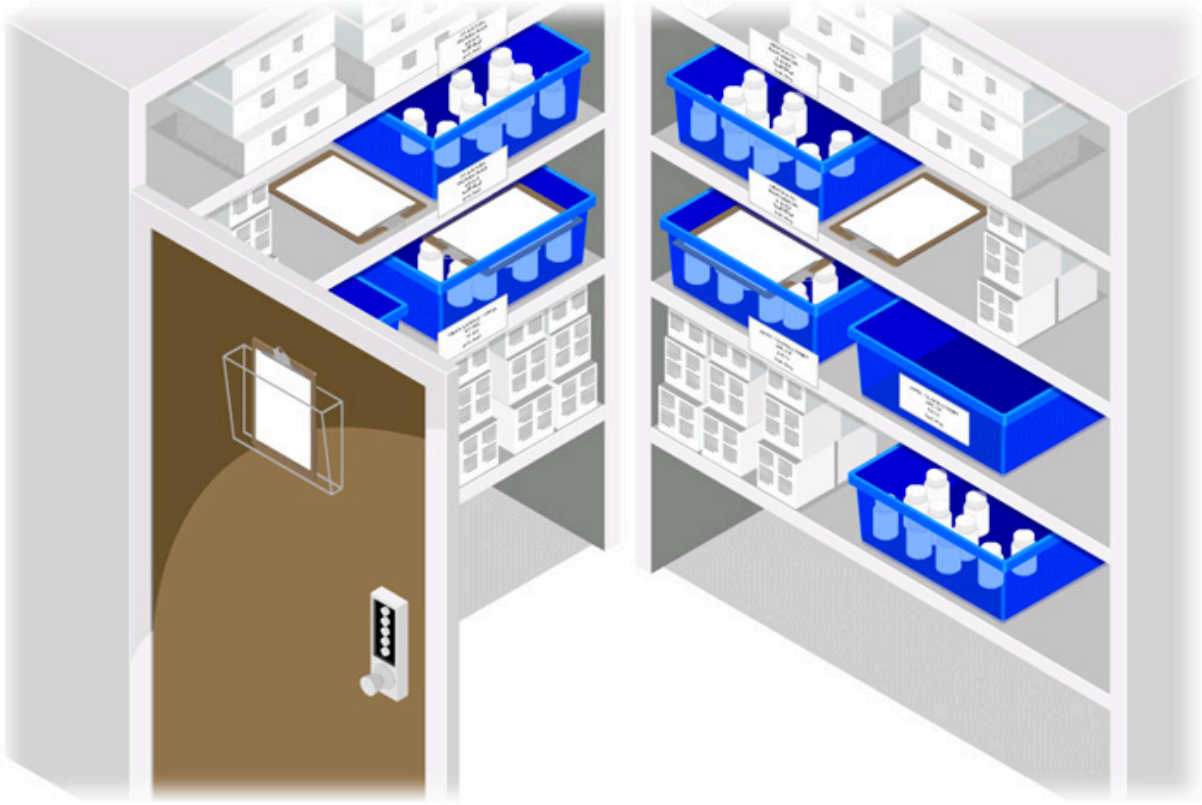
Handling and Storage of Investigational Product:



Now let's look at the requirements for the storage and handling of investigational product. It is important that investigational products are maintained in a secure area with access only to appropriate study personnel.

If the investigational product is to be physically moved between facilities during the course of the trial, as the investigator you must provide adequate documentation to describe the processes followed to ensure the investigational product is securely and properly stored and accounted for at all times. As the investigator you are required to document receipt of investigational products from Merck. In addition, you must carefully and accurately document the distribution to and return of investigational product from the study subjects, and then finally, you must document the return of the used and unused investigational product to Merck.

Good Clinical Practice Training

Handling and Storage of Investigational Product (Contd.):

Temperature Log for Drug Room — Site:
Refrigerator/Freezer: Serial # N/A — Model # N/A
Month/Year March 2007 — Acceptable Range -20-25 (C°) or F°
(for test article/specimen stored) (circle One)

DAILY TEMPERATURE - DIGITAL MIN-MAX THERMOMETER

DAY	If temp not recorded, enter code W=Weekend H=Holiday C=Closed ND=Not Done	Current TIME 24 hour clock	Current TEMP. Record in C° or F° (circle one)	MIN. TEMP.* 24 hour surveillance record in C° or F° (circle one)	MAX. TEMP.* 24 hour surveillance record in C° or F° (circle one)	Min-Max thermometer re-set? ✓=Yes N=No	Temperature remained within acceptable range? ✓=Yes N=No **If no, record reason from legend	STAFF INITIALS
1			22	21	22	✓	✓	
2			22	21	22	✓	✓	
3	W							
4	W							
5		06:50	25	21	25	✓	✓	
6		06:32	22	22	25	✓	✓	
7		06:50	22	21	22	✓	✓	
8		0714	22	21	22	✓	✓	
9		0708	22	21	22	✓	✓	
10	W							
11	W							
12		0716	25	21	25	✓	✓	
13		0710	22	22	25	✓	✓	

The investigational product must be stored under the specific conditions outlined in the protocol. For example, the investigational product may need to be protected from direct light. It must also be stored in a location where the temperature range is maintained according to the protocol required specifications. To verify compliance with these requirements, a temperature log must be maintained, documenting the appropriate temperature of the investigational product storage location.

In accordance with ICH-GCP, it is your responsibility to follow the randomization procedures according to the protocol. You must also retain the sponsor-provided masked randomization codes or IVRS authorization code in a secure location for use in the event of a medical emergency.

Now let's look at a few typical storage

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Investigational Product Storage Scenario:

The Merck Clinical Research Associate, Scott is conducting a routine on site monitoring visit at Dr. Reg's office. Enrollment for the Merck hypertension study that is utilizing the Interactive Voice Response System has ended but the treatment period is continuing for another 5 months. One subject who was a screen failure from the protocol did not return their run-in study drug.

The next few pages will highlight each scenario and ask that you mark the correct answer on the clipboard whether each highlighted area is “Compliant” on “Non-Compliant”.

*Correct answers can be found in the appendix

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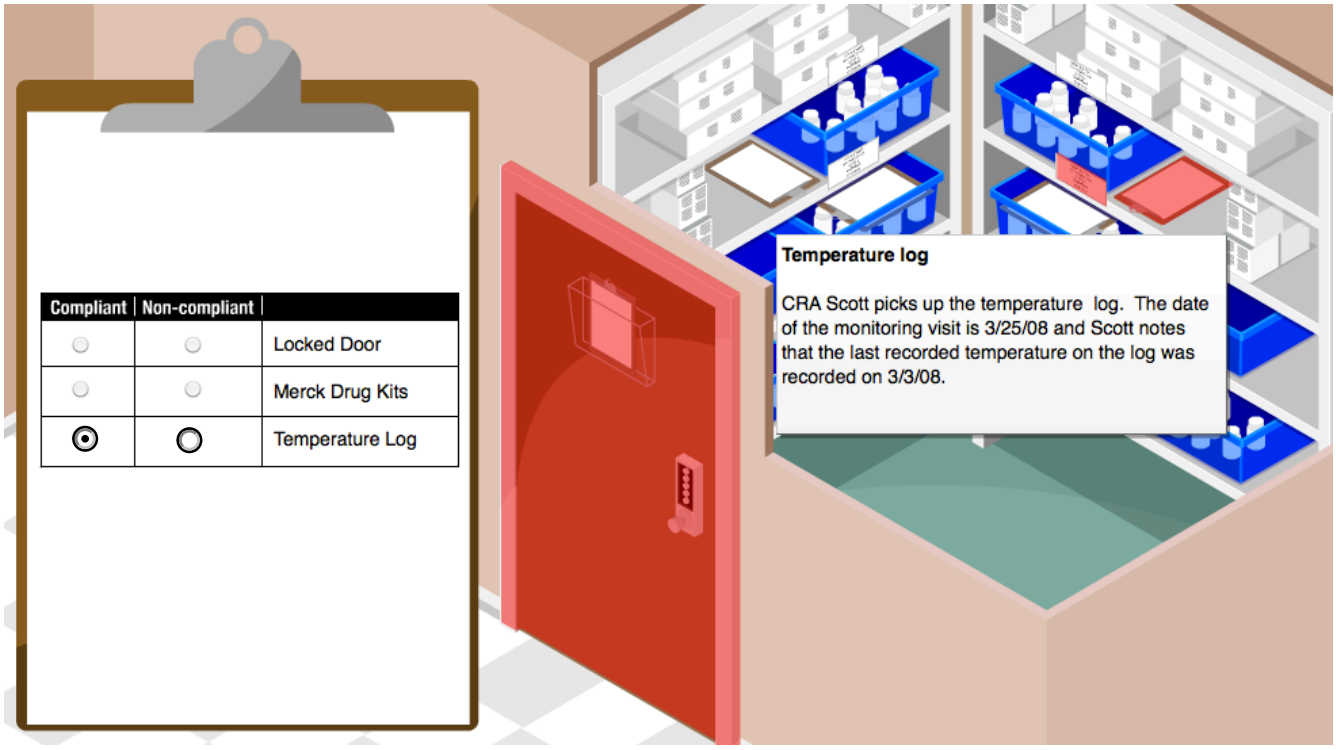
Investigational Product Storage Scenario (Contd.):

Temperature log:

CRA Scott picks up the Temperature log. The date of the monitoring visit is 3/25/08 and Scott notes that in the last recorded temperature on the log was recorded on 3/3/08



*Correct answers can be found in the appendix

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Investigational Product Storage Scenario (Contd.):

Merck study drug kits:
CRA Scott notes that available study drug kits are on the shelves that are clearly labeled and a box is on shelf for returned drug

*Correct answers can be found in the appendix

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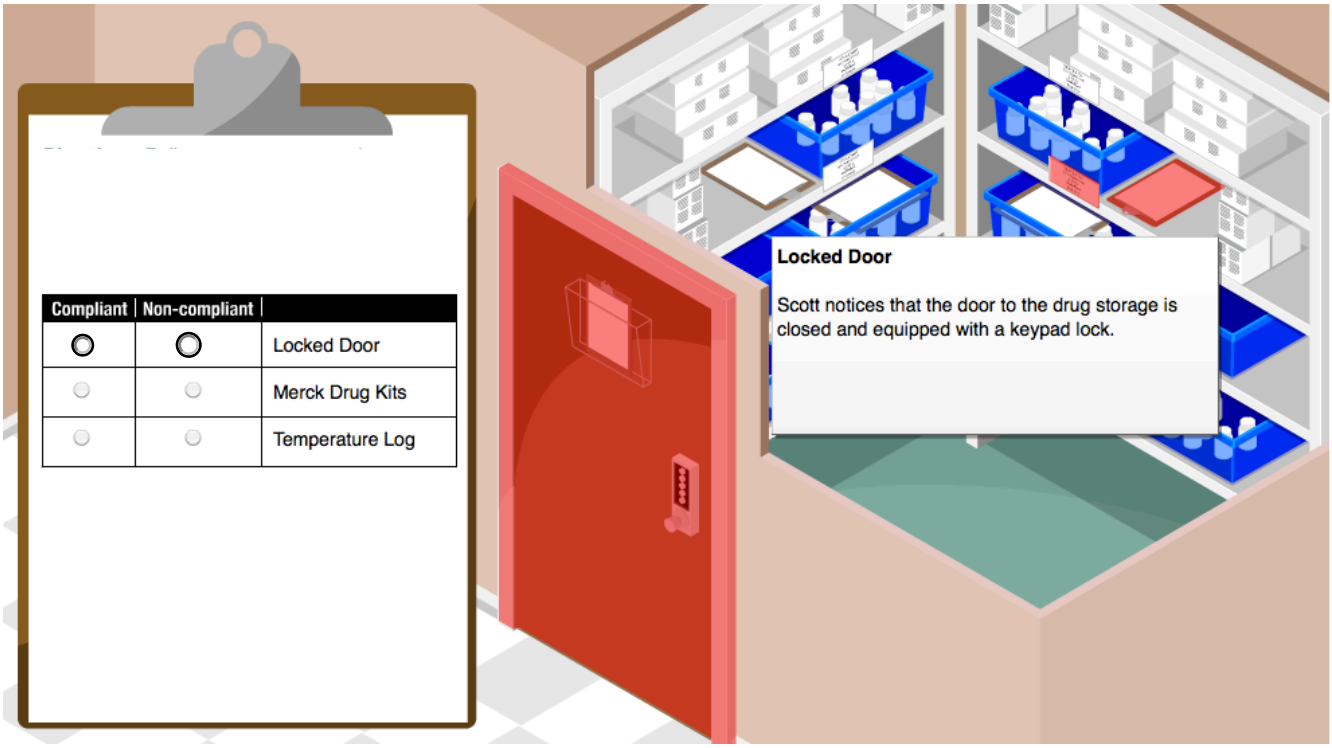
Investigational Product Storage Scenario (Contd.):

Locked Door:
Scott notices that the door to the drug storage is closed and equipped with a keypad lock.



*Correct answers can be found in the appendix

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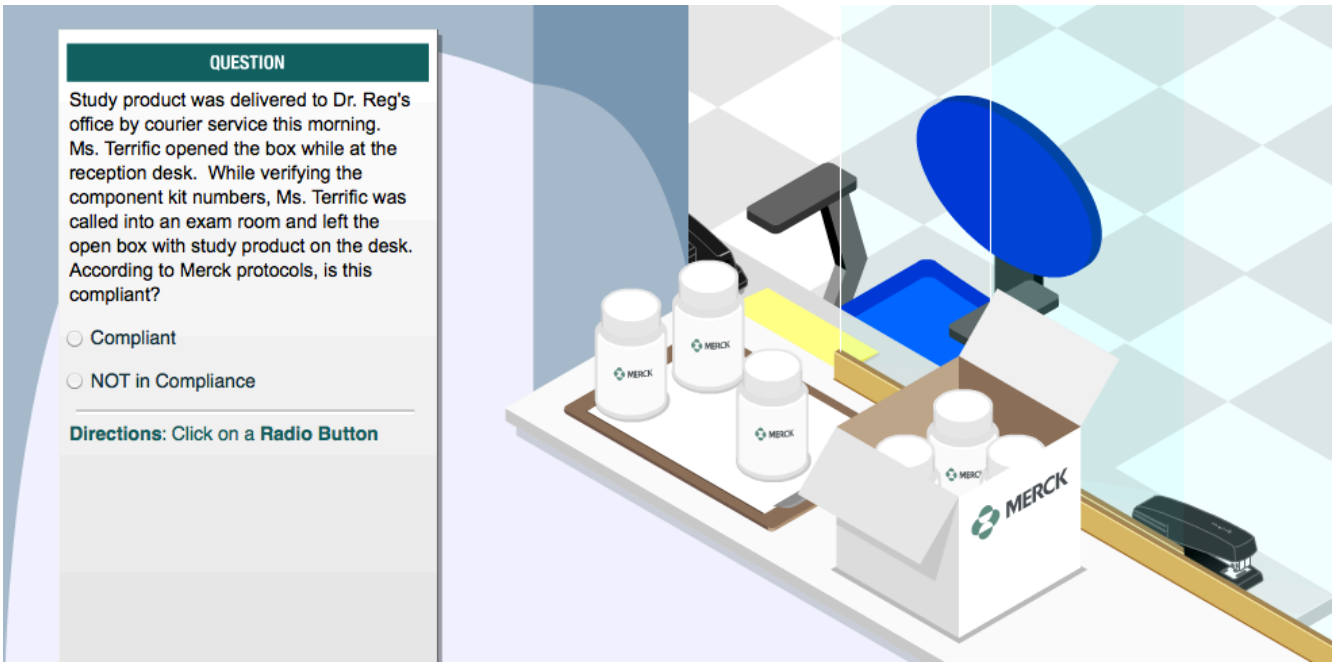
Investigational Product Handling:



QUESTION 3:

Study product was delivered to Dr. Reg's office by courier service in the morning. Ms. Terrific opened the box while at the reception desk. While verifying the component kit numbers, Ms Terrific was called into an exam room and left the open box with the study product on the desk. According to Merck's protocols, is this compliant?

☐ Compliant

☑ Not in Compliance

*Correct Answers can be found in the appendix

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Investigational Product Documentation, Part 1:

CRA Scott and Ms. Terrific are in the monitoring room reviewing the Administrative Binder, also referred to as the Investigator Study File

Click on the highlighted binder tabs to review forms under each tab. ICH GCP guidelines will be referenced. Please click on the guidelines tab to review the relevant guideline. You will be asked a question about each document, so review them carefully. Start at the top with the "Shipping Invoices" tab.

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Investigational Product Documentation, Part 1:

QUESTION 4:

Does the shipping invoice appear to be compliant with ICH Guidelines?

☐ Compliant

☑ NOT Compliant

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Investigational Product Documentation, Part 1:

QUESTION 5:

Do the drug accountability forms appear to be compliant with ICH Guidelines?

☐ Compliant

☑ NOT Compliant

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Investigational Product Documentation, Part 1:

Dr. Reg has delegated responsibility for handling study drug to Ms. Terrific. These responsibilities include study drug receipt, storage, and dispensing as well as drug accountability, temperature monitoring and required documentation. Please review the Site Signature & Responsibility Log to ensure this delegation is appropriately captured.

QUESTION 6:

Are these tasks delegated appropriately on the Site Signature and Responsibility log?

☑ Yes

☐ No

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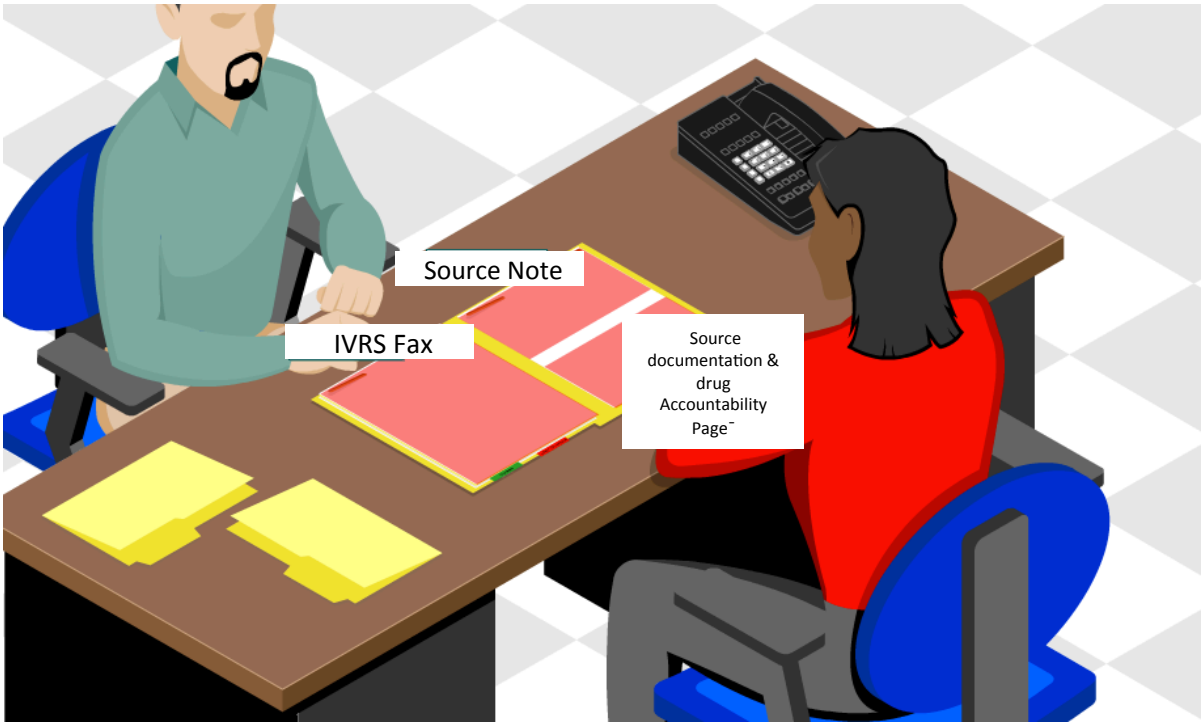
Investigational Product Documentation, Part 2:



CRA Scott and Ms. Terrific are reviewing the study chart for BN 001. This subject was a screen failure because she did not meet the inclusion laboratory value criteria. When she was notified that she did not qualify for the study, CRA Ms. Terrific instructed the subject to return the study medication to the clinic. Ms. Terrific made several follow up phone calls to the subject in an attempt to have study drug returned, however, BN001 was never returned to the site.

Even though the subject was a screen failure, her study records must be retained by the site with the other study documents.

Let's review a couple of the documents filed for this subject to determine if they help to fulfill the requirements of the ICH Guidelines. Again you will be asked a question about each document so review them carefully.

Begin with Clicking on the IVRS Fax document on the desk.

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Investigational Product Documentation, Part 2:

QUESTION 7:

Select the items contained in the fax confirmation that provide supporting documentation for ICH Guideline 4.6.3

- ☐ Product delivery to trial site
- ☑ Inventory at the site
- ☐ Unique code number of investigation product assigned to trial subject
- ☐ Expiration date of investigational product

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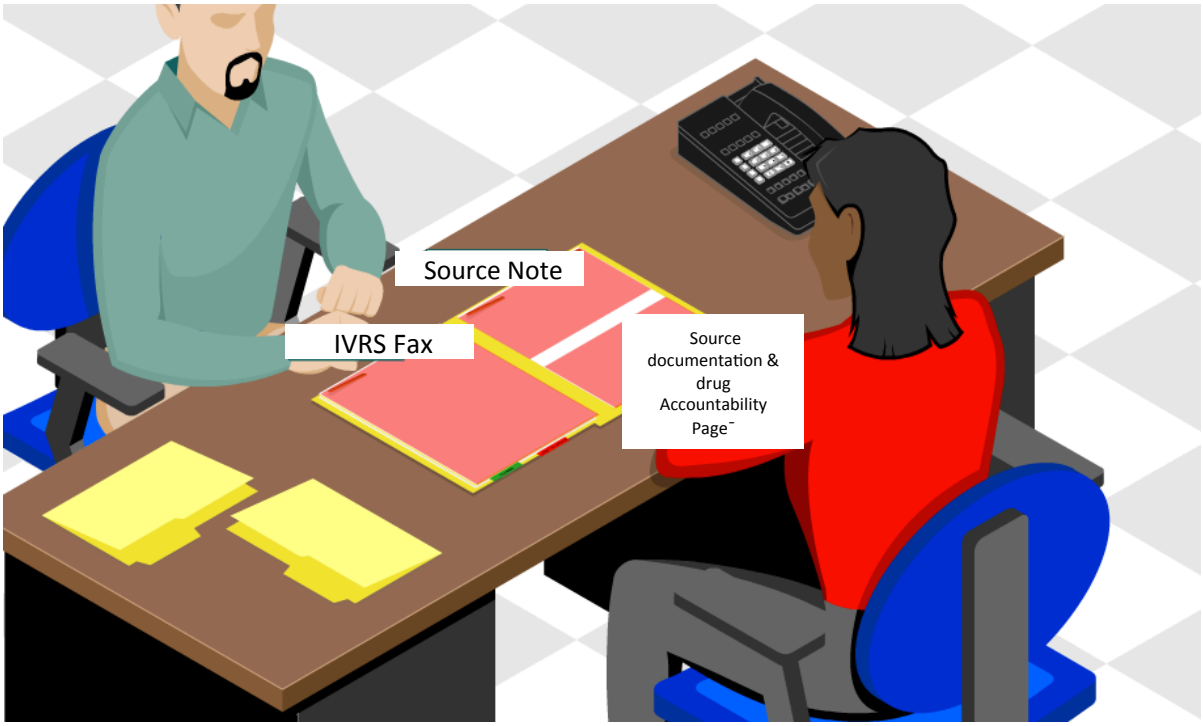
Investigational Product Documentation, Part 2:



Click on the Source Note on the desk.

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Investigational Product Documentation, Part 2:

QUESTION 8:

Does the source note adequately document that the study subject was provided with instructions for the correct use of the investigational product?

☑ Yes

☐ No

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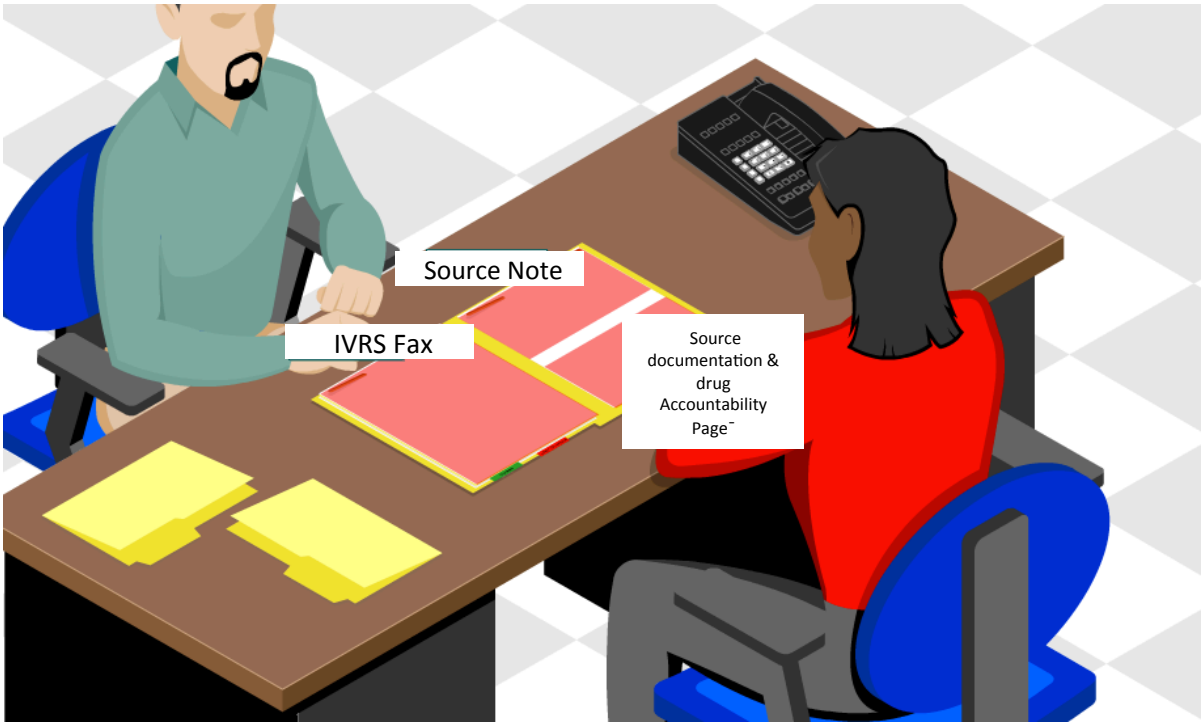
Investigational Product Documentation, Part 2:



Click on the Source documentation & drug Accountability page.

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Investigational Product Documentation, Part 2:

QUESTION 9:

Do these documents provide adequate documentation?

☐ Yes

☒ No

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Source Documentation & Data Capture:

As the Principal Investigator, you are responsible for ensuring that the data collected and entered onto the case report form or into the Electronic Data Capture system from your study site are authentic, accurate, complete, timely and legible.

- Authentic
- Accurate
- Complete
- Timely
- Legible
- Supported by source documentation

All data captured for the purpose of the study must be supported by source documentation in your site's records. A source document is defined as the first recording of an observation or result that is collected pertaining to the clinical trial.

The only exception where a supporting source document is not required is for data that is directly recorded by the subject into a remote data entry device such as an electronic diary.

Along with the subject source documentation, all study correspondence will need to be maintained. This includes correspondence from the sponsor, ethics committee and any other study information. Organizing and filing this information as it is received makes this task more manageable. At the end of the study, all of the study documents will need to be stored in a secure location until you are notified by the Merck that you may discard them.

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Data Correction:

For verification purposes it is critical to be able to determine who captured all data points for a study. Therefore, it is essential for the individuals capturing study data, sign and date ALL original source documents with either their full signature or initials.

Consistent with GCP, if it is necessary to correct or update data, the corrections must be made without compromising the original data entry. The original data in question must be crossed out with a single line and the correct information recorded on the document as appropriate. The correction must be signed and dated by the individual making the change. If a correction is not self-explanatory, a brief explanation should be included.

BP should be taken in the patients non-dominant arm.
Arm used for BP measurement? ☐ Right arm ☒ Left arm (Use same non-dominant arm from Visit 3)

Reading	Time (12 hr clock)	Systolic	Diastolic
1	07:30am	~~144~~ 142	86
2	07:31 am	146	84

Data Value(s) | Queries | Audit Trail | Comment

Day 1:VITAL SIGNS — Patient: ---/002100002

3. Blood Pressure (Systolic/Diastolic) — 120 / 80 mmHg

Server	Date	User	Value	Reason
ISERV404	13/Feb/2008 16:01:28 (GMT-05:00)	autoquery	Query 1: Closed	Close Auto Query
ISERV404	13/Feb/2008 16:01:28 (GMT-05:00)	CRC20	Data Entry: 120 / 80 mmHg	Transcription Error
ISERV404	13/Feb/2008 16:01:17 (GMT-05:00)	autoquery	Query 1: Opened	Systolic Blood Pressure is not within the expected range of 80 to 180 mmHg; please verify
ISERV404	13/Feb/2008 16:01:17 (GMT-05:00)	CRC20	Data Entry: 220 / 80 mmHg	Initial Entry

In the Electronic Data Capture environment an audit trail is automatically created for all changes made to the data. The system records who made the change, the date and time the change was made along with the reason for the change.

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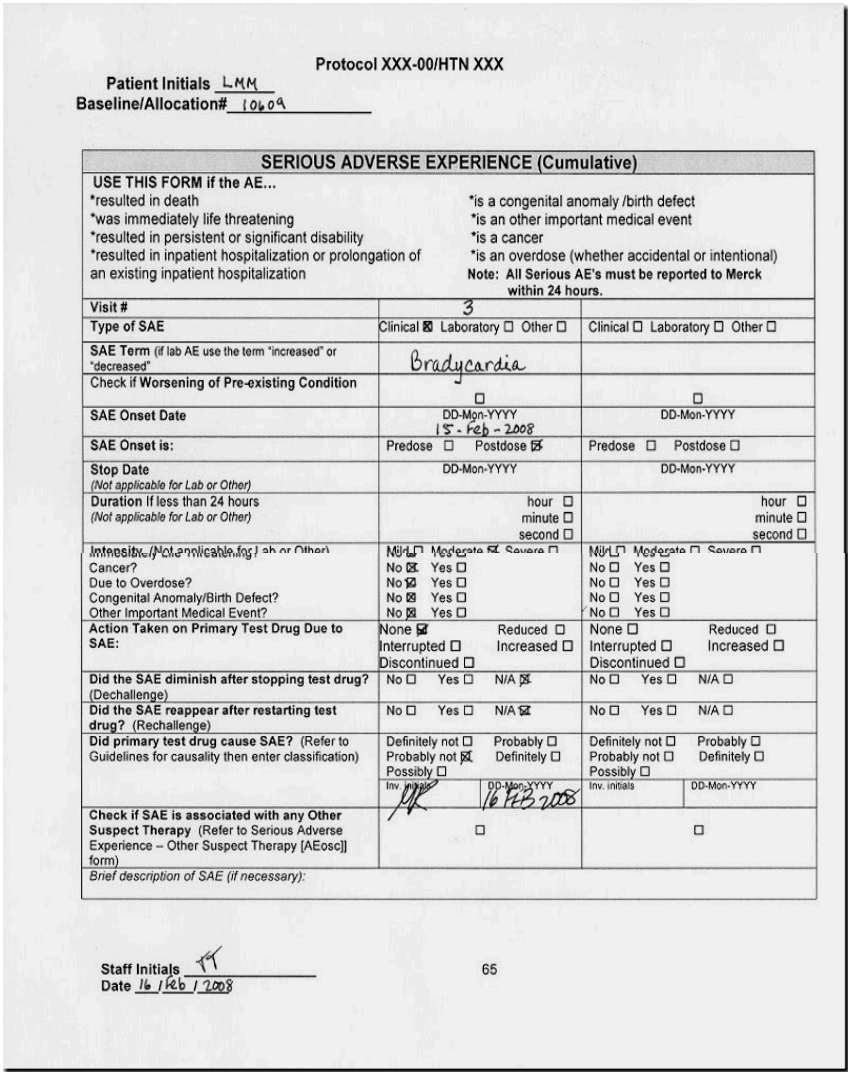
Serious Adverse Experience:

As mentioned at the beginning of this presentation, clinical trials must be conducted with the utmost regard for the safety and well being of the participants. Therefore any adverse experience that occurs to a study subject at your site that is considered to be "Serious" must be reported to Merck within 24 hours of learning of the event.

As a sponsor of a clinical trial, Merck has a regulatory obligation to review and report serious, unexpected, drug-related Adverse Experiences to Regulatory Authorities. Either the site or Merck will report the event to the ethics committee. As the investigator, it is your responsibility to know who is responsible for reporting the event to the ethics committee overseeing the trial.



Protocol XXX-00/HTN XXX

Patient Initials LMM
Baseline/Allocation# 1069

SERIOUS ADVERSE EXPERIENCE (Cumulative)

USE THIS FORM if the AE...
*resulted in death
*was immediately life threatening
*resulted in persistent or significant disability
*resulted in inpatient hospitalization or prolongation of an existing inpatient hospitalization
*is a congenital anomaly /birth defect
*is an other important medical event
*is a cancer
*is an overdose (whether accidental or intentional)
Note: All Serious AE's must be reported to Merck within 24 hours.

Visit #	3	
Type of SAE	Clinical ☒ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐
SAE Term (if lab AE use the term "increased" or "decreased"	Bradycardia	
Check if **Worsening of Pre-existing Condition**	☐	☐
SAE Onset Date	DD-Mon-YYYY 15-Feb-2008	DD-Mon-YYYY
SAE Onset is:	Predose ☐ Postdose ☒	Predose ☐ Postdose ☐
Stop Date *(Not applicable for Lab or Other)*	DD-Mon-YYYY	DD-Mon-YYYY
Duration If less than 24 hours *(Not applicable for Lab or Other)*	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐
Intensity (Not applicable for Lab or Other)	Mild ☐ Moderate ☒ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Immediately Life Threatening	No ☒ Yes ☐	No ☐ Yes ☐
Cancer?	No ☒ Yes ☐	No ☐ Yes ☐
Due to Overdose?	No ☒ Yes ☐	No ☐ Yes ☐
Congenital Anomaly/Birth Defect?	No ☒ Yes ☐	No ☐ Yes ☐
Other Important Medical Event?	No ☒ Yes ☐	No ☐ Yes ☐
Action Taken on Primary Test Drug Due to SAE:	None ☒ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐	None ☐ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐
Did the SAE diminish after stopping test drug? (Dechallenge)	No ☐ Yes ☐ N/A ☒	No ☐ Yes ☐ N/A ☐
Did the SAE reappear after restarting test drug? (Rechallenge)	No ☐ Yes ☐ N/A ☒	No ☐ Yes ☐ N/A ☐
Did primary test drug cause SAE? (Refer to Guidelines for causality then enter classification)	Definitely not ☐ Probably ☐ Probably not ☒ Definitely ☐ Possibly ☐ Inv. initials DD-Mon-YYYY 16 Feb 2008	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. initials DD-Mon-YYYY
Check if SAE is associated with any Other Suspect Therapy (Refer to Serious Adverse Experience – Other Suspect Therapy [AEosc]] form)	☐	☐
Brief description of SAE (if necessary):		

Staff Initials
Date 16 / Feb / 2008

65

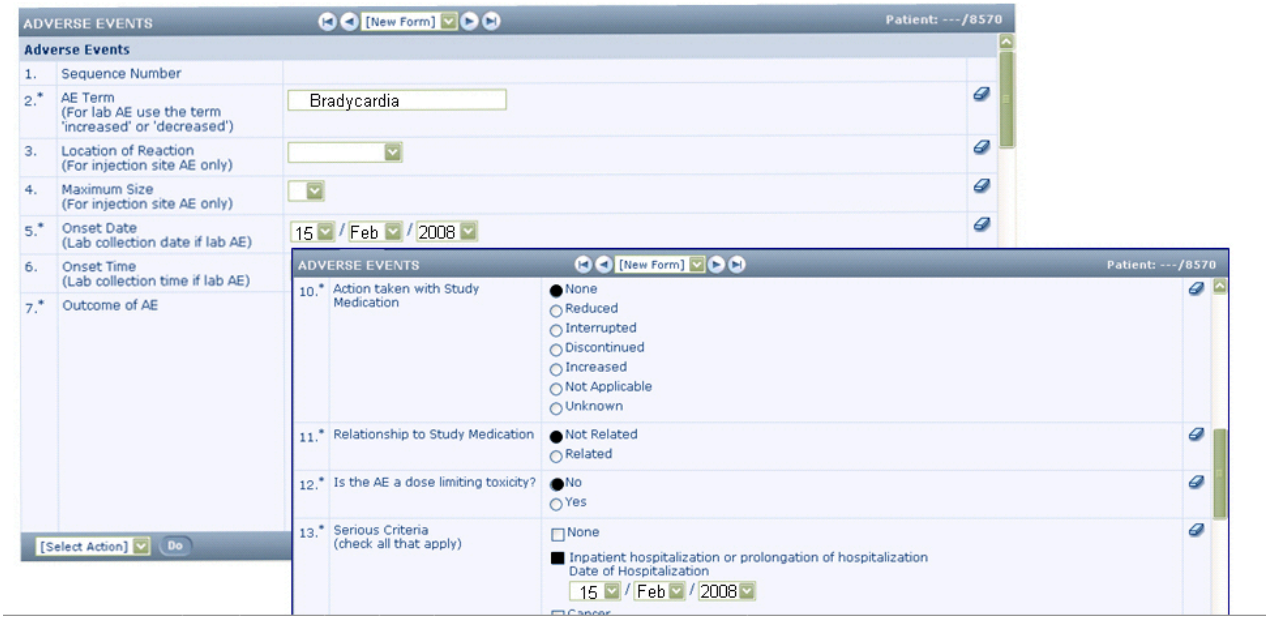
Good Clinical Practice Training

Serious Adverse Experience (Contd.):

In addition, adverse experience causality assessment is vital to both establish and monitor the safety profile of new and approved drugs and vaccines; therefore, it is essential that all aspects of adverse experiences be reviewed by a qualified physician, particularly the potential relationship of the investigational product to the adverse experience. This assessment should be documented by the reviewing physician's initials or signature together with the date this assessment was made.

In addition, it is Merck's expectation that all laboratory safety data be reviewed by a qualified physician for clinical significance and possible adverse experiences.

The data regarding the adverse event will need to be entered into the EDC system, or for a paper based study, entered onto the paper Case Report Form. The source document must support what is entered into the EDC system or onto the paper Case report form.



Good Clinical Practice Training

Serious Adverse Experience (Contd.):

In addition, adverse experience causality assessment is vital to both establish and monitor the safety profile of new and approved drugs and vaccines; therefore, it is essential that all aspects of adverse experiences be reviewed by a qualified physician, particularly the potential relationship of the investigational product to the adverse experience. This assessment should be documented by the reviewing physician's initials or signature together with the date this assessment was made.

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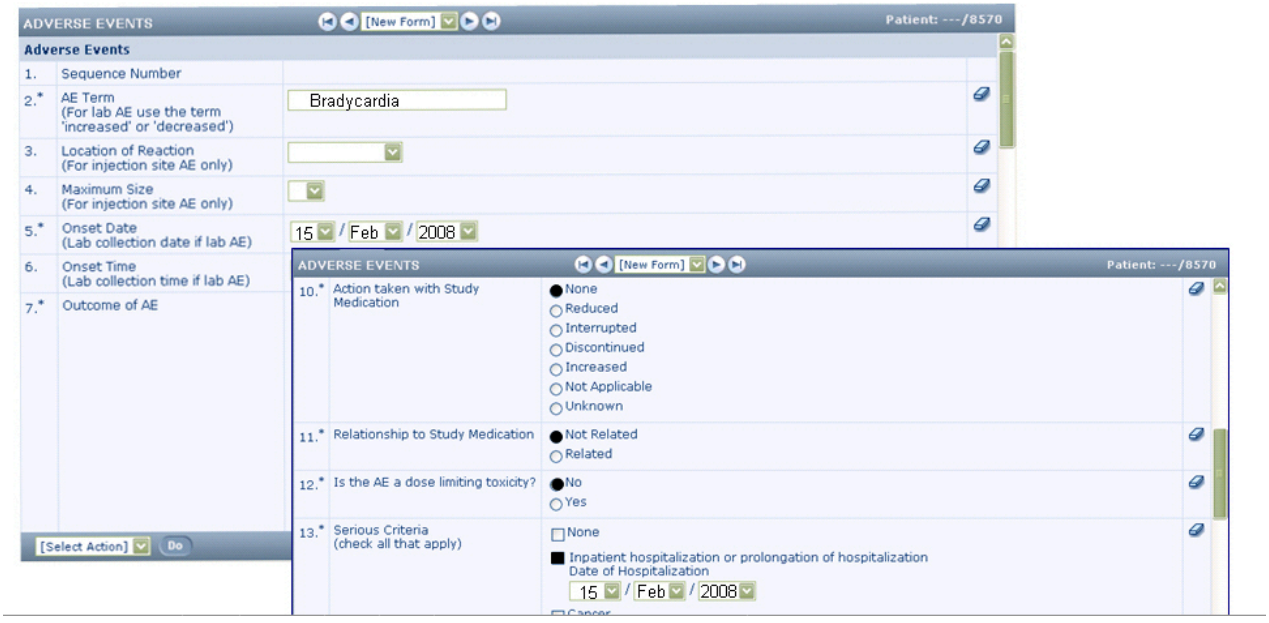

Good Clinical Practice Training

Medical Care Scenario Introduction:

In this last scenario, the study coordinator and sub investigator are seeing study patients. Pay attention to how they manage this busy day.

Good Clinical Practice Training

Medical Care Scenario Part 1:

Ms. Terrific, the study coordinator, is reviewing upcoming study visits in the appointment book for patients enrolled in a hypertension study being conducted at the office. Dr. Reg is the Principal Investigator and currently out of the office attending a 3-day conference. To date, the site has successfully enrolled 15 subjects into the 6-month hypertension study. Dr. Compliance is serving as one of the sub-investigators for this trial, and will see study subjects for their regular visits while Dr. Reg is away.

Ms. Terrific: Dr. Compliance is really busy today. She's seeing three Merck hypertension study subjects and trying to finish some other work before leaving on her two-week holiday. However, I think I can organize the visits so that everyone is seen quickly and all the protocol requirements are performed.

Ms. Terrific (on phone): "Good morning Dr. Compliance, I just wanted to call and remind you that three study subjects enrolled in the Merck hypertension study will be coming in today for their regular study visit. I know how busy you are today, so I'll have everything organized for you to see the patients, perform the required procedures and review the individual subject's information.

Good Clinical Practice Training

Medical Care Scenario:

After taking the subject's vital signs, Ms. Terrific asks the subject about changes to his health or medications. She documents a new adverse experience that he reports to her. She is quite familiar with this subject and the study so while recording the new adverse experience she also assesses and documents whether or not the study drug may have caused the adverse event. As the sub-investigator performs the required physical exam, Ms. Terrific records the findings. Please click on the **Adverse Event source document** to view it. After you have finished viewing it, click on the **Lab Report**.

***Lab Report:** Lab results for the subject were drawn during an unscheduled visit late last week are on the chart and have not been reviewed by a physician. Ms. Terrific notes that the subject's fasting blood glucose was elevated. The subject is a diabetic and the results are fairly typical for this patient and in an effort to save time, Ms. Terrific notes that the lab values were not clinically significant and files the report in the subject's folder**.**

Good Clinical Practice Training

Medical Scenario:

Question 10:

Was the assessment of the patient's laboratory data handled appropriately?

☐ Yes

☑ No

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Medical Care Scenario Part 3:

This time, Ms. Terrific takes the subject's vital signs and asks the subject about changes to his health or medications. She records the new adverse experience the subject shared with her and also assesses and records causality of the adverse experience. As the sub- investigator performs the required physical examination, Ms. Terrific records her findings, but this time she does not initial the assessment of the adverse experience or the physical examination findings.

MS. Terrific also notes that the out-of-range lab values are not clinically significant, but does not initial her notation.

Please click on the **AE** and **Laboratory report source documents** for viewing.

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Medical Care Scenario Part 3:

When Dr. Compliance returns to the office two weeks later. She reviews the recorded Adverse Experience and Lab Reports. She also signs and dates the physical exam that was performed and initials and dates each AE and Lab Result to indicate her review and agreement with the documented causality.

Question 11:

Do you agree with Ms. Terrific and Dr. Compliance's approach?

☐ Yes I agree

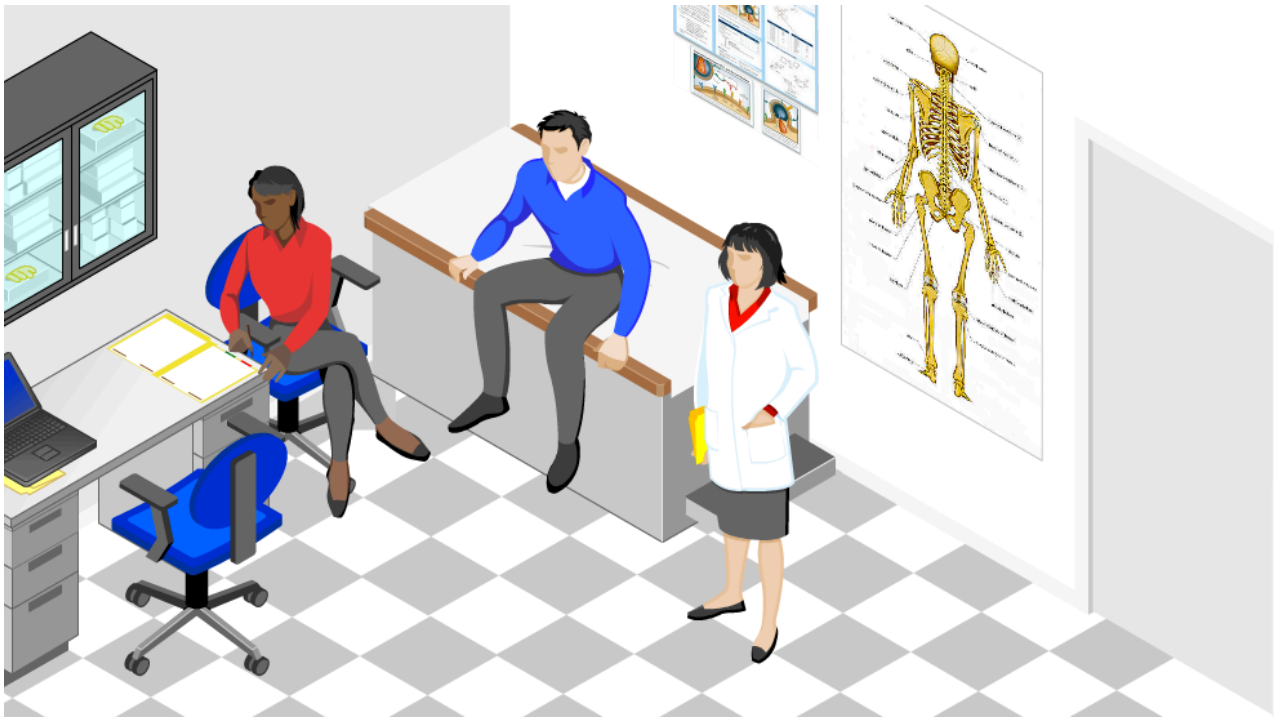
☑ No I do not agree

Good Clinical Practice Training

Examining Room Answer:

As Dr. Compliance finishes the physical exam, she reviews the Adverse Event and assesses and records the causality on the source document. As the exam is finished she initials and dates the source document to indicate her review. Ms. Terrific highlights the out-of-range lab value and provides the subject's previous lab reports for comparison. Dr. Compliance denotes clinically significant or not-clinically significant on all lab values that are outside of normal limits. If there were any labs noted as clinically significant, appropriate adverse events would be captured. Dr. Compliance would initial and date the reports after her review.

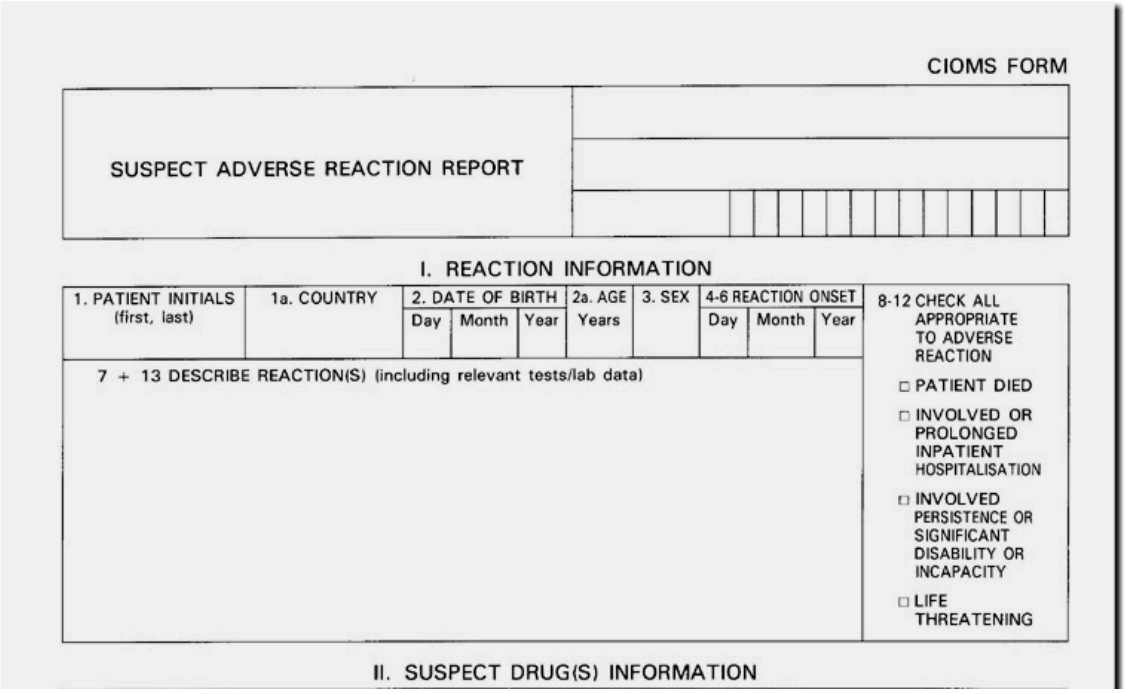
This practice most clearly demonstrates the direct involvement of the "qualified physician" and that an appropriate and timely medical review has occurred.



Good Clinical Practice Training

Safety Updates:

In compliance with Good Clinical Practices and Merck standards, you will be receiving a copy of a government report form for all serious, unexpected and drug or vaccine-related adverse experiences occurring with the investigational product that is being studied. An example of one type of form is shown here. You must review these reports and provide them to your ethics committee in a timely manner in order for them to evaluate the effect of the new safety information on the clinical trial.



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
										☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
										☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

Other Responsibilities:

In addition to the responsibilities just reviewed, it is also necessary that you, as the Principal Investigator, have detailed knowledge of the disease process under study, protocol and medication that is being investigated.

Furthermore, you must have qualified study staff and the necessary resources available to execute the trial as outlined in the protocol. This also includes sufficient time, appropriate storage facilities, as well as having a sufficient patient population that will allow you to meet the timeline requirements of the protocol.

- Detailed knowledge of the disease, protocol and medication
- Qualified study staff/adequate facilities
- Potential for recruiting the required number of subjects within the agreed period
- Accept monitoring and audit/inspections
  - Provide access to source documentation

Good Clinical Practices mandate that sponsors conduct routine monitoring of all investigative sites. This is done by a Merck Clinical Research Associate. The purpose of monitoring is to verify that the rights of subjects are protected, and reported trial data are accurate, complete and verifiable from source documents. The CRA will also verify that the conduct of the trial is in compliance with the approved protocol and amendments, regulatory requirements and Good Clinical Practice.

Your site may also be chosen for a routine Merck audit. Site audits are performed by representatives of Merck's Worldwide Clinical Quality Assurance Resources department or WCQAR. WCQAR is an independent department within Merck and is not linked to any specific study protocol or clinical team. We are very committed to working with you to ensure that you understand your obligations and responsibilities under GCPs.

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Other Responsibilities:

You must also be aware that your clinical trial site may be inspected by a regulatory authority. Inspections can occur during an ongoing trial, or after completion of the trial. Ethics Committees may also inspect your clinical trial site to ensure that studies are conducted in compliance with the protocol and GCPs.

Click HERE View Tips: Preparing for an Audit document

If you receive notification of a regulatory authority or Ethics Committee inspection, please notify your Merck CRA as soon as possible. Your CRA will provide guidance regarding Merck's expectations of your communication prior to, during, and after the inspection. We will also provide you with a contact name and number that you may utilize during the inspection as needed. Attached to this learning module is a document entitled 'Tips: Preparing for an Audit' that you may find beneficial to review. If you are notified that your study site will be inspected, this document will be provided to assist you with preparing for the inspection process.

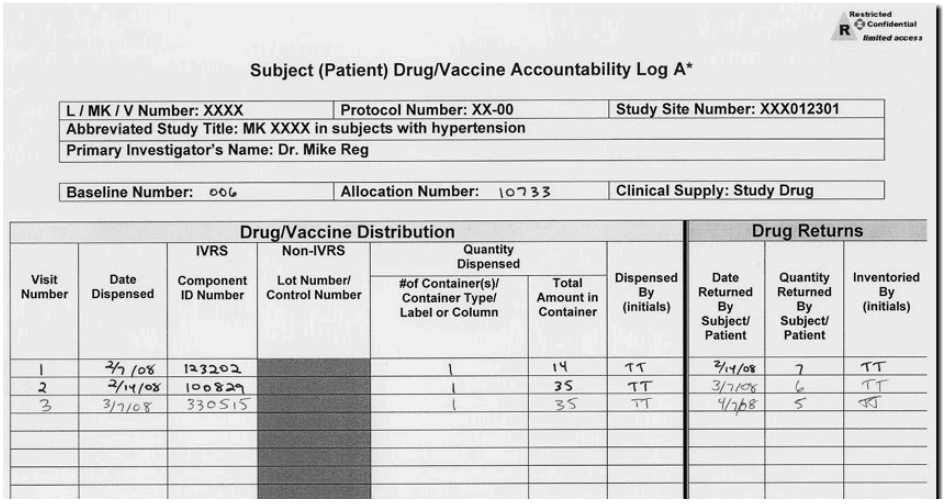
All monitoring, auditing and inspection activities may involve the review of individual subject data, and regulatory documents, including correspondence with the Ethics Committee and Merck's study team. By organizing and maintaining your study documents throughout the course of the study, you will be better prepared for such inspections.

Good Clinical Practice Training

Study Close Out:

Once you have reached the end of the clinical trial, that is, all study subjects from your site have completed their last study visit and all data have been recorded, there are a few more items that will require your attention.

First, final investigational supplies accountability for each subject must take place before being returned to Merck. This means that all drug accountability forms need to be finalized for each study subject, including screen failures.



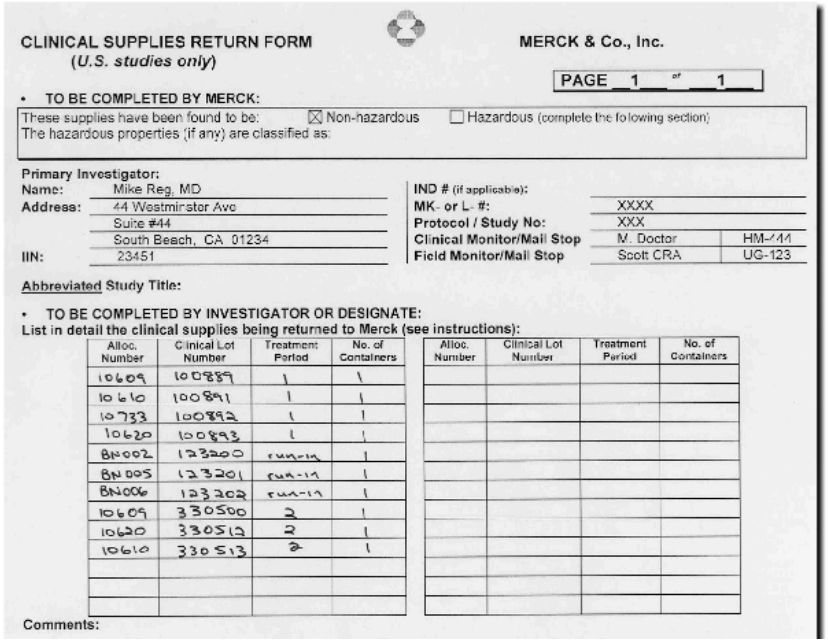
Restricted Confidential *limited access*

Subject (Patient) Drug/Vaccine Accountability Log A*

L / MK / V Number: XXXX	Protocol Number: XX-00	Study Site Number: XXX012301
Abbreviated Study Title: MK XXXX in subjects with hypertension		
Primary Investigator's Name: Dr. Mike Reg		

Baseline Number: 006	Allocation Number: 10733	Clinical Supply: Study Drug

Drug/Vaccine Distribution							Drug Returns		
Visit Number	Date Dispensed	IVRS Component ID Number	Non-IVRS Lot Number/ Control Number	Quantity Dispensed: #of Container(s)/ Container Type/ Label or Column	Quantity Dispensed: Total Amount in Container	Dispensed By (initials)	Date Returned By Subject/ Patient	Quantity Returned By Subject/ Patient	Inventoried By (initials)
1	2/7/08	123202		1	14	TT	2/14/08	7	TT
2	2/14/08	100829		1	35	TT	3/7/08	6	TT
3	3/7/08	330515		1	35	TT	4/7/08	5	TT



CLINICAL SUPPLIES RETURN FORM
(U.S. studies only)

MERCK & Co., Inc.

PAGE 1 of 1

- **TO BE COMPLETED BY MERCK:**

These supplies have been found to be: ☒ Non-hazardous ☐ Hazardous (complete the following section)
The hazardous properties (if any) are classified as:

Primary Investigator:
Name: Mike Reg, MD
Address: 44 Westminster Ave
Suite #44
South Beach, CA 01234
IIN: 23451

IND # (if applicable):
MK- or L- #: XXXX
Protocol / Study No: XXX
Clinical Monitor/Mail Stop M. Doctor HM-111
Field Monitor/Mail Stop Scott CRA UG-123

Abbreviated Study Title:

- **TO BE COMPLETED BY INVESTIGATOR OR DESIGNATE:**

List in detail the clinical supplies being returned to Merck (see instructions):

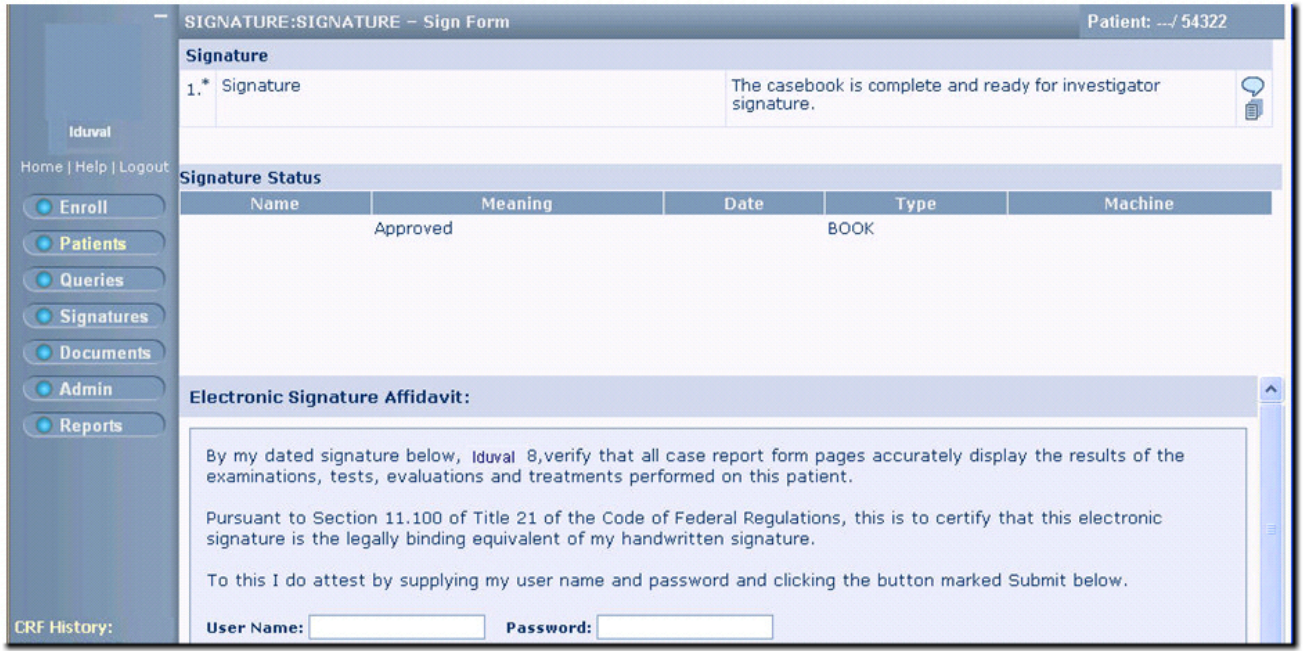
Alloc. Number	Clinical Lot Number	Treatment Period	No. of Containers	Alloc. Number	Clinical Lot Number	Treatment Period	No. of Containers
10609	100889	1	1				
10610	100891	1	1				
10733	100892	1	1				
10620	100893	1	1				
BN002	123200	run-in	1				
BN005	123201	run-in	1				
BN006	123202	run-in	1				
10609	330500	2	1				
10620	330513	2	1				
10610	330513	2	1				

Comments:

Good Clinical Practice Training

Study Close Out (Contd.):

Second, as the Principal Investigator you will need to log onto the EDC system when the data is frozen, and review, and electronically sign off on the e-CRFs for all the study subjects at your site.



Study Close Out (Contd.):

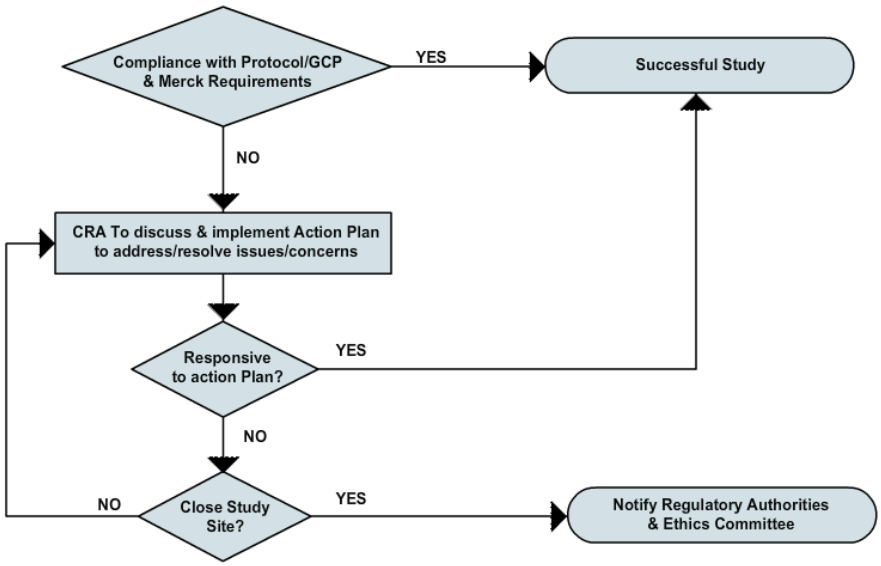
Third, you must establish a process to properly retain and archive all essential trial documents until notification to discard them is provided by Merck. Final communication with Merck is essential to ensure all necessary progress reports and final trial summary reports have been sent to the relevant Ethics Committee.

Now that we have reviewed the necessary steps in conducting a clinical trial, we would like to focus on Merck's continued commitment to quality and compliance.

Good Clinical Practice Training

Good Clinical Practice Compliance

Merck takes Good Clinical Practice obligations very seriously. Merck's expectation is that our clinical investigators do so as well.



If we identify or are made aware of areas of GCP deficiency or non-compliance at your site, we will take immediate action to correct the situation by working with you to outline an action plan and review the necessary steps to bring your site back into compliance. If corrective action is not taken, and the decision is made to discontinue the study at your site, Merck as the study sponsor, is obligated by regulation to notify the Regulatory Authorities and the Ethics Committee that the study has been discontinued and/or data from your study site will not be included in the analysis due to questionable data integrity or significant GCP deficiencies.

Within the pharmaceutical industry, there has been a heightened awareness of the potential fabrication of study results. Merck does not tolerate falsification of study records and as such, we have a policy and procedure in place for reporting and evaluating concerns pertaining to potential fraud and misconduct in clinical trials.

Good Clinical Practice Training

Summary

This concludes our presentation on Good Clinical Practices in the conduct of a clinical trial. We have reviewed your responsibilities as they relate to the medical care of trial subjects, the types of communications you will have with Ethics Committees, and discussed the importance of compliance with the protocol. We introduced you to the informed consent process, discussed your responsibilities with regard to handling investigational product, data collection, reporting and storage of study documents. We also touched on adverse experience assessment & reporting which is also reviewed in more detail in another module.

We hope you have a clear understanding of your responsibilities as a Principal Investigator and will contact your local CRA if you have any questions or concerns. Please complete the test following this page to receive credit for viewing this training module.

Thank you for your attention. We look forward to conducting a successful clinical trial at your study site!

Good Clinical Practice Training

Interactive Quiz

Question 1:

Which of the following healthcare professionals can assess casualty of an adverse event?

- ☐ A) The individual to whom the subject first described the adverse event
- ☑ B) An investigator who is a medically qualified physician?
- ☐ C) A Pharm. D who is the principal investigator for the study
- ☐ D) The clinical monitor for the study

Good Clinical Practice Training

Interactive Quiz

Question 2:

The investigator is responsible for investigational product(s) accountability at the trial site(s). This responsibility includes:

- ☐ A) Storage of the investigational product(s) as specified by the Sponsor
- ☐ B) Providing documentation of the receipt of the investigational product(s) from the Sponsor
- ☐ C) Documenting the distribution to and return of investigational product(s) from the study subject
- ☐ D) Documenting the return or disposition of unused investigational product
- ☐ E) Ensuring that the investigational product(s) are used in accordance with the approved protocol
- ☐ F) Providing study subjects with instructions on the correct use of the investigational product(s)
- ☐ G) A, B, C D
- ☑ H) A, B, C, D, E, F

Good Clinical Practice Training

Interactive Quiz

Question 3:

Data reported on the Case Report Form (CRF) or entered into the electronic CRF (eDC) must have what characteristics?

☒ A) Be consistent with the source documents and if there is a discrepancy, the discrepancy should be explained

☐ B) Be legible

☐ C) Changes or corrections should be dated, initialed and explained (if necessary)

☐ D) Retained for at least 15 years after the last approval of a marketing application in an ICH region

☑ E) A, B, C

☐ F) A, B, C, D

Good Clinical Practice Training

Interactive Quiz

Question 4:

Per the ICH GCP Guideline the investigator may deviate from the protocol without agreement by the Sponsor or prior approval/favorable opinion of the IRB/IEC if:

- ☐ A) The deviation is necessary to eliminate an immediate hazard(s) to study subjects
- ☐ B) The deviation only impacts one study subject
- ☐ C) The deviation involves only logisitical or administrative aspects of the trial (e.g. change of telephone number)
- ☐ D) The deviation is minor (e.g.ei
- ☑ E) A & C
- ☐ F) A, B, C

Good Clinical Practice Training

Interactive Quiz

Question 5:

Informed consent is a process which includes the open exchange of clinical trial related information with the potential study subject(s). Which of the following are NOT TRUE:

☐ A) Adequate time should be allotted to ensure that all information in the consent form is clearly and completely presented to the subject and that all questions are sufficiently

☐ B) The potential study subjects must be informed of the nature of the trial, trial-related obligations, and the risks and benefits to participating

☑ C) Wash out or tapering of medication to ensure study timelines are met should be completed prior to obtaining informed consent

☐ D) For Merck sponsored clinical trials both Merck and an Independent Ethics

☐ E) B & C

Good Clinical Practice Training

Interactive Quiz

Question 6:

It is Merck's expectation based of GCP standards that all trial-related medical decisions are made by a qualified physician. Trial-related medical decisions include all EXCEPT:

- ☐ A) Review and interpretation of ECGs and all laboratory results
- ☐ B) Casualty assessment of adverse experience
- ☑ C) Completion of all source documents
- ☐ D) Adjustment or discontinuation of study medication or concomitant medication
- ☐ E) Any decisions that impacts the medical management of the subject in the trial

Good Clinical Practice Training

Interactive Quiz

Question 7:

The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties

☑ A) True

☐ B) False

Good Clinical Practice Training

Interactive Quiz

Question 8:

The Investigator is responsible for investigational product(s) accountability at the trial site(s). This responsibility INCLUDES:

- ☐ A) Storage of the investigational prodcut(s) as a specified by the Sponsor
- ☐ B) Providing documentation of the receipt of the investigational product(s) from the study subject
- ☐ C) Documenting the distribution to and return of investigational product(s) from the study subject
- ☐ D) Documenting the return or disposition of unused investigational product
- ☐ E) Ensuring that the investigational product(s) are used in accordance with the approved protocol
- ☐ F) Providing study subjects with instructions on the correct use of investigational product(s)
- ☐ G) A, B, C, D
- ☑ H) A, B, C, D, E, F

Good Clinical Practice Training

Interactive Quiz

Question 9:

The international Conference of Harmonisation Guideline for Good Clinical Practice was developed to do the following EXCEPT:

- ☐ A) Protect the rights of the subjects
- ☐ B) Protect the safety of the subjects
- ☐ C) Protect the welfare of the subjects
- ☐ D) Protect the confidentiality of the subjects
- ☑ E) Protect the rights of the principal investigator and sponsor
- ☐ F) Ensure the quality and integrity of the data collected

Good Clinical Practice Training

Appendix

Quiz Answers

Question 1 – B

Question 2 – H

Question 3 – E

Question 4 – E

Question 5 – C

Question 6 – C

Question 7 – A

Question 8 – H

Questions 9 - E

Appendix

Answers

Question 1 – No

Explanation: Dr. Compliance's suggestion to use a food other than applesauce would be a deviation from the protocol that would require both sponsor and IRB/IEC approval

Question 2 – Yes

Explanation: In accordance with ICH/GCP, the investigator should not implement any deviation from the protocol without agreement by the sponsor and prior review and documented approval from the IRB/IEC. An exception to this is where the deviation is necessary to eliminate an immediate hazard to the trial subject, or when the change involves only logistical or administrative changes to the trial., such as a change in telephone number. As there is no immediate hazard to the trial subject, the sponsor should be contacted to see if similar inquiries have been made from other sites and if there is a formal protocol amendment that would allow for alternative food, temperature variants and or optional dosing times

Good Clinical Practice Training

Appendix

Answers

Investigational Product Storage Scenario Clipboard Answers

Locked Door - Compliant
Merck Drug Kits – Compliant
Temperature Log – Non-Compliant

Question 3
Investigational Product Handling Question – **NOT in Compliance**

Explanation: Study Supplies should be kept in a secured location as outlined in Merck Protocols. ICH-GCP guideline 4.6.4 states that investigational product should be stored as specified by sponsor

Appendix

Answers

Question 4
Investigational Product Documentation, Part 1

Shipping Invoices Question– **Not Compliant**

Explanation: Study Supplies should be kept in a secured location as outlined in Merck Protocols. ICH-GCP guideline 4.6.4 states that investigational product should be stored as specified by sponsor

Question 5
Drug Accountability Invoices – **Not Compliant**

Explanation: The dispensing sections of the Drug Accountability form are complete and have the required information. Even though the return of study product box has been initialed, the date the study product was returned by the subject as well as the quantity returned by the subject is not captured on the form. This information is necessary to provide accurate drug accountability. 4.6.3.

Appendix

Answers

Question 6
Site Signature & Responsibility – **Yes**

Explanation: The delegation of handling study drug is appropriately documented per guideline 4.6.2 & 4.1.5. Investigational Product Documentation, Part 2

Question 7
IVRS Fax – **Inventory at the site and Unique code number of investigation product assigned to trial subject**

Question 8
Source Note– **Yes**

Explanation: The note states that the subject was instructed to take one tablet in the morning before breakfast. Because the subject was a screen failure, documentation to verify proper adherence to the correct use of the investigational product is not necessary.

Appendix

Answers

Question 9
Source documentation and Drug Accountability page – **No**

Explanation: The source note does provide documentation to demonstrate due diligence on the site's part to have study drug returned. However, the drug accountability form does not reflect that the study drug is permanently missing which would need to be captured per ICH Guideline 4.6.3 in order to reconcile the investigational product.

Appendix

Answers

Question 10
Assessment of patient's laboratory data – **No**

You're right, as outlined in ICH-GCP 4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub - investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Part of this responsibility involves the timely and thorough review of (1) all laboratory safety data for adverse events and clinically significant trends and changes and (2) all adverse experiences for the assessment of causality and the medical management of the patient. While it is entirely appropriate for the study coordinator to ask the subject about any changes to medication or any new health-related issues which may be potential adverse experiences and document them in the chart, the primary investigator or sub-investigator who is a medically-qualified physician, is responsible for a thorough review of this information and for evaluating any and all parameters that require medical input, including, but not limited to drug relationship or causality

Even though the abnormal fasting blood glucose was fairly typical for this subject, the sub-investigator (who is a medically-qualified physician) needed to review the lab values to assess if the out of range value was significant from either a laboratory or clinical perspective. If she considered it was significant, it would be necessary to document a new adverse experience.

Appendix

Answers

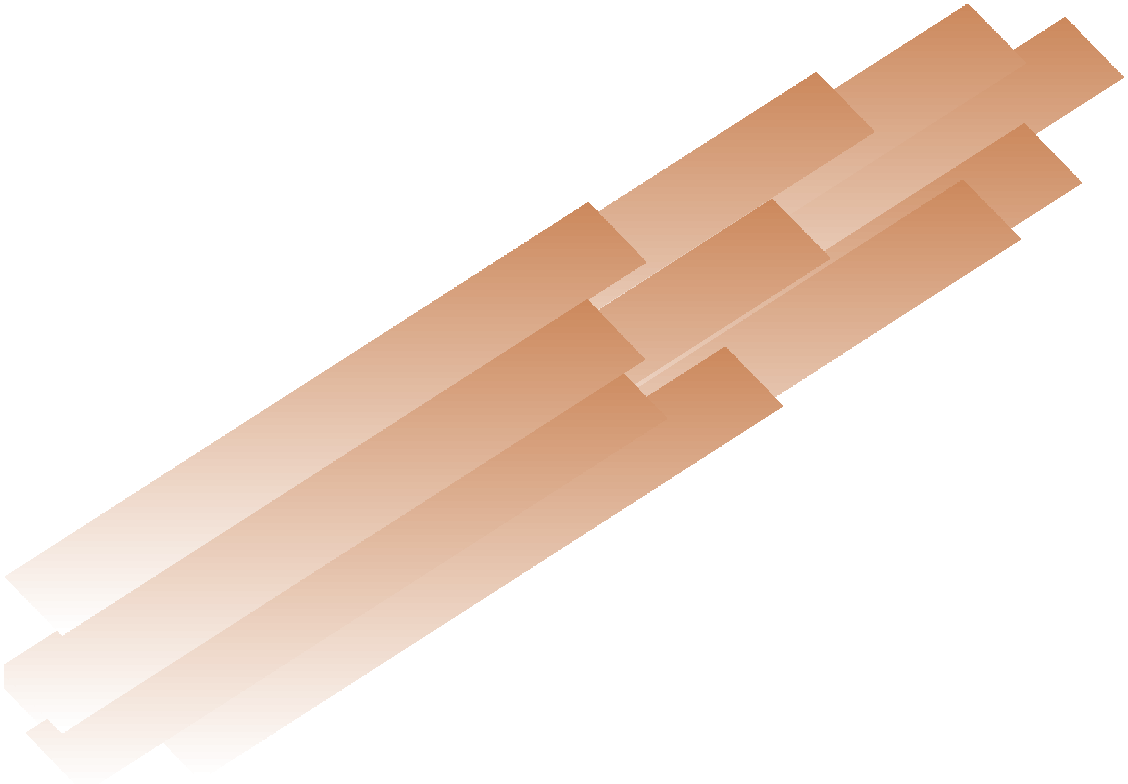
Question 11
Is Ms. Terrific's assessment correct? – **No I do not agree**

While it is acceptable for the study coordinator to ask the subject about any changes to medication or new health-related occurrences which may be potential adverse experiences and document them, the investigator is responsible for assessing causality. This practice does not demonstrate the direct involvement of the "qualified physician" or that an appropriate and timely medical review has occurred. Dr. Compliance's assessment would be more meaningful at the time of the examination.

Alternatively, when Dr. Reg returned to the office after his conference he could review and assess the study data which would be more timely than waiting for Dr. Compliance's return.

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance

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Table of Contents

GUIDANCE FOR INDUSTRY[1]

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INTRODUCTION

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guidance may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse drug reaction (ADR): In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal

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[1] This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, April 1996. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the United States. This guidance was published in the *Federal Register* on May 9, 1997 (62 FR 25692), and is applicable to drug and biological products. This guidance represents the Agency's current thinking on good clinical practices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse event (AE): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol): See Protocol Amendment.

1.4 Applicable regulatory requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where trial is conducted.

1.5 Approval (in relation to institutional review boards (IRBs)): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

1.6 Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit certificate: A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit report: A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit trail: Documentation that allows reconstruction of the course of events.

1.10 Blinding/masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s)

being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case report form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

1.12 Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

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

1.16 Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

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

1.20 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.

1.21 Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see section 8. "Essential Documents for the Conduct of a Clinical Trial").

1.24 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.

1.25 Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance.

1.28 Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

1.29 Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB): An independent body constituted of medical, scientific, and nonscientific 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 trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product: 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.

1.34 Investigator: 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. See also Subinvestigator.

1.35 Investigator/Institution: An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."

1.36 Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects (see section 7. "Investigator's Brochure").

1.37 Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

1.39 Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

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

1.41 Nonclinical Study: Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee): The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record: See Source Documents.

1.44 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. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA): 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 GCP and the applicable regulatory requirement(s).

1.47 Quality Control (QC): 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.

1.48 Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guidance, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see section 1.29). These bodies are sometimes referred to as competent authorities.

1.50 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.

(See the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.51 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

1.53 Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 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. The term does not include any person other than an individual (e.g., 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.

1.55 Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator: Any individual 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). See also Investigator.

1.57 Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

1.59 Trial Site: The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.61 Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- Approval/favorable opinion;
- Modifications required prior to its approval/favorable opinion;
- Disapproval/negative opinion; and
- Termination/suspension of any prior approval/favorable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

3.1.6 When a nontherapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see sections 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s)

adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see section 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions, and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.
(b) At least one member whose primary area of interest is in a nonscientific area.
(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see sections 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see section 1.21) to all trial- related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see section 6.), the ICH Guidance for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct.

5.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

(b) Maintain SOPs for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see sections 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see section 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed (see section 4.9.5).

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see sections 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;

(b) To comply with procedures for data recording/reporting: and

(c) To permit monitoring, auditing, and inspection (see section 4.1.4).

(d) To retain the essential documents that should be in the investigator/institution files (see section 8.) until the sponsor informs the investigator/institution these documents are no longer needed (see sections 4.9.4, 4.9.5, and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Duties and Functions

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available. (See section 7. "Investigator's Brochure.")

5.13 Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 **Purpose** The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

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

5.18.2 **Selection and Qualifications of Monitors**

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 **Extent and Nature of Monitoring**

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 **Monitor's Responsibilities**

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see sections 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorized procedures.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

> (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.
>
> (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
>
> (iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
>
> (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
>
> (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents. (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 **Monitoring Procedures**

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 **Monitoring Report**

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 **Purpose**

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 **Selection and Qualification of Auditors**

(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 **Auditing Procedures**

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.

(e) Where required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guidance for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicenter Trials

For multicenter trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial 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 include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including (for example):

(a) Randomization.
(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for

subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Recordkeeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with

the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guidance delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator- sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guidance.

7.2 General Considerations

The IB should include:

7.2.1 **Title Page** This should provide the sponsor's name, the identity of each

investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 **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.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 **Table of Contents** An example of the Table of Contents is given in Appendix 2.

7.3.2 **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.

7.3.3 **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.

7.3.4 **Physical, Chemical, and Pharmaceutical Properties and Formulation**

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.

7.3.5 **Nonclinical Studies**

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 unfavorable 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.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product 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)).

(b) 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.

(c) 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 sensitization);
Reproductive toxicity;
Genotoxicity (mutagenicity).

7.3.6 **Effects in Humans**

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 from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) 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)).

(b) 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).

(c) 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 summarized (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.

7.3.7 **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.

7.4 Appendix 1

TITLE PAGE OF INVESTIGATOR'S BROCHURE (Example)

Sponsor's Name:

Product:

Research Number:

Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 Appendix 2

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

- Confidentiality Statement (optional)

- Signature Page (optional)

1. Table of Contents

2. Summary

3. Introduction

4. Physical, Chemical, and Pharmaceutical Properties and Formulation

5. Nonclinical Studies
    - 5.1 Nonclinical Pharmacology
    - 5.2 Pharmacokinetics and Product Metabolism in Animals
    - 5.3 Toxicology

6. Effects in Humans
    - 6.1 Pharmacokinetics and Product Metabolism in Humans
    - 6.2 Safety and Efficacy
    - 6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter.

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	Information given to trial subject - Informed consent form (Including all applicable translations)	To document the informed consent	X	X
	- Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.6	Signed agreement between involved parties, e.g.: - Investigator/institution and sponsor - Investigator/institution and CRO - Sponsor and CRO - Investigator/institution and authority(ies) (Where required)	To document agreements	 X X X	 X X (where required) X X
8.2.7	Dated, documented approval/favorable opinion of IRB/IEC of the following: - Protocol and any amendments - CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) - Subject compensation (if any) - Any other documents given approval/favorable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
8.2.8	Institutional review board/independent ethics committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	Regulatory authority(ies) authorization/approval/ notification of protocol (where required)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
8.2.12	Medical/laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
8.2.15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
8.2.16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial.		X
8.2.17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applic-able)
8.2.18	Master randomization list	To document method for randomization of trial population		X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.19	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	Any revisions to: - Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to subjects - Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial	X	X

8.3.3	Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following:
	
	- Protocol amendment(s)
	- Revision(s) of:
	  - Informed consent form
	  - Any other written information to be provided to the subject
	  - Advertisement for subject recruitment (if used)
	-Any other documents given approval/favorable opinion
	- Continuing review of trial (see section 3.1.4)
		To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X

8.3.4	Regulatory authority(ies) authorizations/ approvals/notifications where required for: - Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum vitae for new investigator(s) and/or subinvestigators	(See section 8.2.10)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see section 8.2.11)	X	X
8.3.7	Updates of medical/ laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period (see section 8.2.12)	X (where required)	X
8.3.8	Documentation of investigational product(s) and trial-related materials shipment	(See section 8.2.15)	X	X
8.3.9	Certificate(s) of analysis for new batches of investigational products	(See section 8.2.16)		X
8.3.10	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
8.3.11	Relevant communications other than site visits - Letters - Meeting notes - Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see section 8.2.3)	X	
8.3.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	Documentation of CRF corrections	To document all changes/ additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 4.11.2 and 5.16.2	X (where required)	X
8.3.18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
8.3.21	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
8.3.22	Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
8.3.23	Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol	X	X
8.3.24	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
8.3.25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	Audit certificate (if required)	To document that audit was performed (if required) (see section 5.19.3(e))		X
8.4.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	Final report by investigator/institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies) (see section 4.13)	To document completion of the trial	X	
8.4.8	Clinical study report (see section 5.22)	To document results and interpretation of trial	X (if applicable)	X

Merck & Co., Inc
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck & Co., Inc. ("Merck") conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be consistent with standards established by the Declaration of Helsinki and in compliance with all local and/or national regulations and directives.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Study Conduct

1. Study Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design and conduct of a study (i.e., patient population, duration, statistical power) must be adequate to address the specific purpose of the study. Research subjects must meet protocol entry criteria to be enrolled in the study, unless specifically exempted by the Merck study monitor.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to study initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency: data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud and/or misconduct are suspected, the issue is investigated: when necessary, the clinical site will be closed and, if appropriate, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. Patient Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or local medical director (non-U.S. studies) will approve the patient informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care. Patients are never denied access to appropriate medical care based on participation in a Merck clinical study.

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll patients in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the study. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g. to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S, those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

Shipment ID #	511635

Merck & Co., Inc. MK-XXXX-XXX

Investigator Name:	Mike Reg, M.D.
Site Number:	XXX012301
Date Requested:	01/Feb/2008
Special Instructions:	NONE

Shipping Address

Site Name: Research Center
Address 1: 44 Westminster Ave
Address 2: Suite 44
Address 3:
Address 4:
City: South Beach State/Region: CA Zip: 01234
Country: United States
Site Drug Contact: Teri Terrific Drug Contact Phone: XXX-XXX-XXXX

For receiving site/pharmacy use only

ATTENTION!!

THIS MEDICATION WILL NOT BE ACTIVATED FOR DISPENSING UNTIL THIS SHIPMENT IS CONFIRMED VIA THE IVRS

Directions for confirming and activating drug in the IVRPhone:

1. Call IVRPhone (800-xxx-xxxx)
2. Enter you assigned user ID and PIN
3. Choose the confirm shipment menu option from the Main Menu
4. Enter Shipment ID at the top right hand corner of this page
5. Follow the directions in the system to activate the shipment
6. **If you have missing or damaged supplies please call the IVRPhone Help Desk at 888-xxx-xxxx.**

Signature:_____ Date: _____

Please file this document in the Investigator Regulatory Binder.

Subject (Patient) Drug/Vaccine Accountability Log A*

L / MK / V Number: XXXX	Protocol Number: XX-00	Study Site Number: XXX012301
Abbreviated Study Title: MK XXXX in subjects with hypertension		
Primary Investigator's Name: Dr. Mike Reg		

Baseline Number: 001	Allocation Number:	Clinical Supply: Study Drug

Drug/Vaccine Distribution							Drug Returns		
Visit Number	Date Dispensed	IVRS Component ID Number	Non-IVRS Lot Number/ Control Number	Quantity Dispensed: #of Container(s)/ Container Type/ Label or Column	Quantity Dispensed: Total Amount in Container	Dispensed By (initials)	Date Returned By Subject/ Patient	Quantity Returned By Subject/ Patient	Inventoried By (initials)
1	2/5/08	123199		1	14	TT			

*Utilize the Subject (Patient) Drug/Vaccine Accountability Log A Instructions when completing this form.

Distribution: Original - investigator site
Copy - sponsor

Restricted Confidential
limited access

Subject (Patient) Drug/Vaccine Accountability Log A*

L / MK / V Number: XXXX	Protocol Number: XX-00	Study Site Number: XXX012301
Abbreviated Study Title: MK XXXX in subjects with hypertension		
Primary Investigator's Name: Dr. Mike Reg		

Baseline Number: 003	Allocation Number: 9001	Clinical Supply: Study Drug

Drug/Vaccine Distribution							Drug Returns		
Visit Number	Date Dispensed	IVRS Component ID Number	Non-IVRS Lot Number/ Control Number	Quantity Dispensed: #of Container(s)/ Container Type/ Label or Column	Quantity Dispensed: Total Amount in Container	Dispensed By (initials)	Date Returned By Subject/ Patient	Quantity Returned By Subject/ Patient	Inventoried By (initials)
2	3/1/08	100895		1	35	TT			TT

*Utilize the Subject (Patient) Drug/Vaccine Accountability Log A Instructions when completing this form.

Distribution: Original - investigator site
Copy - sponsor

Merck & Co., Inc.
MK-XXXX-XXX
Screening Confirmation

Site Information

Caller Name:	Teri Terrific
Investigator Name:	Mike Reg, M.D.
Site Number:	XXX012301
Date/Time of Call:	05/FEB/2008 07:02 a.m. EST

Subject Information

Visit Number:	Screening – Placebo Run-In
Visit Date:	05/FEB/2008
Baseline Number:	0123001
Date of Birth:	01/Jun/1940
Component ID#	123199

This visit registration was successful

2/26/08	T T	Subject called @ home, has not returned study drug. Subject said she thought she would be able to bring in last week, but will try to bring by later today.
2/28/08	T T	Phoned Subject again @ home. Subject reports that she can not locate the study drug bottle and believes her husband threw it out. Subject said if she located it she would still bring in but she really believes it is gone.

Subject (Patient) Drug/Vaccine Accountability Log A*

L / MK / V Number: XXXX	Protocol Number: XX-00	Study Site Number: XXX012301
Abbreviated Study Title: MK XXXX in subjects with hypertension		
Primary Investigator's Name: Dr. Mike Reg		

Baseline Number: 001	Allocation Number:	Clinical Supply: Study Drug

Drug/Vaccine Distribution							Drug Returns		
Visit Number	Date Dispensed	IVRS Component ID Number	Non-IVRS Lot Number/ Control Number	Quantity Dispensed: #of Container(s)/ Container Type/ Label or Column	Quantity Dispensed: Total Amount in Container	Dispensed By (initials)	Date Returned By Subject/ Patient	Quantity Returned By Subject/ Patient	Inventoried By (initials)
1	2/5/08	123199		1	14	TT			

*Utilize the Subject (Patient) Drug/Vaccine Accountability Log A Instructions when completing this form.

Distribution: Original - investigator site
Copy - sponsor

FINAL REPORT

Report Generated: 20-Mar-2008
Sponsor: Sponsor 2
Protocol Number: XXX

Accession Number: A30001802
Visit: Unscheduled

Investigator Site ID: 123
Principal Investigator Mike Reg
Site Coordinator: Terri Terrific

Initials: AAA
DOB: 20-Sep-1974
Gender: Male

Drawdate: 18-Mar-2008
Screen ID: 0003
Randomization ID: 9001

CHEMISTRY

TEST		RESULT	UNITS	REF RANGE	CS*	COMMENTS
Fasting Plasma Glucose	HC	128	mg/dL	70-100	Y (N)	
ALT		24	U/L	5 - 25		
Alkaline Phosphatase		70	U/L	32 - 72		
AST		21	U/L	8 - 22		
Bilirubin, Total		0.4	mg/dL	0.1 – 1.1		
Creatine Phosphokinase		47	U/L	2 - 120		
Albumin	H	3.8	g/dL	0.00 – 2.00	Y (N)	
Protein		6.9	g/dL	6.0 – 8.5		
Urea Nitrogen, Blood Urea Nitrogen		19	mg/dL	5 – 20		
Sodium		137	mEq/L	135 - 146		
Potassium	H	5.1	mEq/L	3.5 – 5.0	Y (N)	
Chloride		105	mEq/L	95 - 110		
Calcium		9.5	mg/dL	8.5 – 10.3		
Phosphorous		4.2	mg/dL	2.5 – 4.5		
Cholesterol	H	202	mg/dL	125 – 200	Y (N)	

HEMATOLOGY

TEST	RESULT	UNITS	REF RANGE	CS*	COMMENTS
RBC	4.34	X10^6/cu mm			
Hemoglobin	16.2	g/dL	14.0 – 18.0		
Hematocrit	48.0	%	40.0 – 54.0		
WBC	6.0	K/cu mm	3.7 – 11.0		
Neutrophils, Total	6.5	%	1.7 – 7.9		
Lymphocytes	35	%	12 – 46		
Monocytes	4	%	0 – 11		
Eosinophils	.6	%	0.0 – 0.8		
Basophils	0	%	0.0 – 0.3		
Platelet	223	K/cu mm	12 – 375		

END OF REPORT

Investigator Signature TT Date: 3/25/08

H = High L = Low HC = High Critical LC = Low Critical AB = Abnormal

* Clinically Significant: please circle Y (yes) or N (no)
Protocol Specific Reference Ranges used if applicable (see manual for standard lab ranges)

Patient Initials AAA
Baseline/Allocation# 9001

NONSERIOUS ADVERSE EXPERIENCES (Cumulative) – NSAEc

This page is to be reviewed at each visit.

If the AE...

*resulted in death
*was immediately life threatening
*resulted in persistent or significant disability
*resulted in inpatient hospitalization or prolongation of an existing inpatient hospitalization
*is a congenital anomaly /birth defect
*is an other important medical event
*is a cancer
*is an overdose (whether accidental or intentional)

STOP – Do NOT use THIS form, USE the SAE form

Visit #	3		
Type of NSAE	Clinical ☒ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐
NSAE Term *(if lab AE use the term "increased" or "decreased")*	Headache		
Check if **Worsening of Pre-existing Condition**	☐	☐	☐
Onset Date *(Lab date if Lab NSAE)*	DD-Mon-YYYY 23-Mar 2008	DD-Mon-YYYY	DD-Mon-YYYY
AE Onset is:	Predose ☐ Postdose ☒	Predose ☐ Postdose ☐	Predose ☐ Postdose ☐
Stop Date *(Not applicable for Lab or Other)*	DD-Mon-YYYY 24-Mar 2008	DD-Mon-YYYY	DD-Mon-YYYY
Duration If less than 24 hours *(Not applicable for Lab or Other)*	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐
Intensity *(Not applicable for Lab or Other)*	Mild ☒ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Action Taken on Primary Test Drug Due to NSAE:	None ☒ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐
Did primary test drug cause NSAE? *(Refer to Guidelines for causality then enter classification)*	Definitely not ☐ Probably not ☒ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: TT DD-Mon-YYYY: 3/25/08 (25 Mar)	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: DD-Mon-YYYY:	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: DD-Mon-YYYY:
Comments:			

Staff Initials TT
Date 3/25/08

FINAL REPORT

Report Generated: 20-Mar-2008
Sponsor: Sponsor 2
Protocol Number: XXX

Accession Number: A30001802
Visit: Unscheduled

Investigator Site ID: 123
Principal Investigator Mike Reg
Site Coordinator: Terri Terrific

Initials: AAA
DOB: 20-Sep-1974
Gender: Male

Drawdate: 18-Mar-2008
Screen ID: 0003
Randomization ID: 9001

CHEMISTRY

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Bilirubin, Total		0.4	mg/dL	0.1 – 1.1		
Creatine Phosphokinase		47	U/L	2 - 120		
Albumin	H	3.8	g/dL	0.00 – 2.00	Y (N)	
Protein		6.9	g/dL	6.0 – 8.5		
Urea Nitrogen, Blood Urea Nitrogen		19	mg/dL	5 – 20		
Sodium		137	mEq/L	135 - 146		
Potassium	H	5.1	mEq/L	3.5 – 5.0	Y (N)	
Chloride		105	mEq/L	95 - 110		
Calcium		9.5	mg/dL	8.5 – 10.3		
Phosphorous		4.2	mg/dL	2.5 – 4.5		
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HEMATOLOGY

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Neutrophils, Total	6.5	%	1.7 – 7.9		
Lymphocytes	35	%	12 – 46		
Monocytes	4	%	0 – 11		
Eosinophils	.6	%	0.0 – 0.8		
Basophils	0	%	0.0 – 0.3		
Platelet	223	K/cu mm	12 – 375		

END OF REPORT

Investigator Signature_____ Date:_____

H = High L = Low HC = High Critical LC = Low Critical AB = Abnormal

* Clinically Significant: please circle Y (yes) or N (no)
Protocol Specific Reference Ranges used if applicable (see manual for standard lab ranges)

Patient Initials AAA
Baseline/Allocation# 9001

NONSERIOUS ADVERSE EXPERIENCES (Cumulative) – NSAEc

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If the AE...

*resulted in death
*was immediately life threatening
*resulted in persistent or significant disability
*resulted in inpatient hospitalization or prolongation of an existing inpatient hospitalization
*is a congenital anomaly /birth defect
*is an other important medical event
*is a cancer
*is an overdose (whether accidental or intentional)

STOP – Do NOT use THIS form, USE the SAE form

Visit #	3		
Type of NSAE	Clinical ☒ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐
NSAE Term *(if lab AE use the term "increased" or "decreased")*	Headache		
Check if **Worsening of Pre-existing Condition**	☐	☐	☐
Onset Date *(Lab date if Lab NSAE)*	DD-Mon-YYYY 23-Mar-2008	DD-Mon-YYYY	DD-Mon-YYYY
AE Onset is:	Predose ☐ Postdose ☐	Predose ☐ Postdose ☐	Predose ☐ Postdose ☐
Stop Date *(Not applicable for Lab or Other)*	DD-Mon-YYYY 24-Mar-2008	DD-Mon-YYYY	DD-Mon-YYYY
Duration If less than 24 hours *(Not applicable for Lab or Other)*	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐
Intensity *(Not applicable for Lab or Other)*	Mild ☒ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Action Taken on Primary Test Drug Due to NSAE:	None ☒ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐
Did primary test drug cause NSAE? *(Refer to Guidelines for causality then enter classification)*	Definitely not ☐ Probably not ☒ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's DD-Mon-YYYY
Comments:			

Staff Initials TT
Date 3/25/08

General Inspection Guidance for the Investigator

This information is offered to assist the investigator and site staff in preparing for a regulatory agency inspection. This document may be given to the investigator with instructions that this document need **not** be filed in the study administrative binder.

General Preparation

- Whenever possible, the Primary Investigator should be available for the duration of the inspection. Designate any/all other study staff members who will assist in facilitating the agency inspection (i.e., sub-investigator, study coordinator). This person should be familiar with the protocol. If the PI is not available for the duration of the inspection, it is advisable they be personally available or accessible via beeper/phone call for questions during the inspection. At a minimum, the PI should be available during the opening and closing meetings.
- Ensure adequate facilities (i.e., quiet work space work) for regulatory agency inspectors with access to telephone, fax, photocopy machine.
- Ensure that training records and curriculum vitae for site personnel involved in the conduct of the study are up-to-date and available upon request.
- Notify the Ethics Review Board, local hospital research administration, and other collaborating departments e.g. laboratory, ophthalmology, radiology of the dates of the inspection and the possibility that they may be visited and/or questioned during the inspection.

Document Preparation

- Ensure that all study-related documents (administrative binder, subject/patient charts, case report forms, source documentation) are available for review. Recommend that the site organize their study-related documents for ease of review by the inspector. Any restrictions to subject/patient charts/electronic databases should be identified and accessibility addressed prior to the inspector's arrival.
- Ensure ongoing drug/vaccine supplies reconciliation is up-to-date; ensure accurate and complete records of accountability.
- Ensure financial information is available upon request.

When the inspector arrives:

- Record the inspector's name. The inspector should present identification which verifies his/her name, title, credentials, and affiliation with the regulatory agency (badge/business card). If identification is not volunteered by the inspector, the PI or site personnel should request it. In the U.S., a Notice of Inspection (FDA 482) should be presented.

- Designated site personnel should provide an orientation to the protocol, the organization of the study-related documents, and an overview of how study activities were conducted and overseen at the site.
- Provide succinct, pertinent responses to the inspector's questions. Answer only questions asked. Do not volunteer additional, unsolicited information. If a question posed by the inspector is unclear, then additional clarification and/or additional information may be requested.
- If photocopies of study-related documents are requested, it is recommended that the site make two copies, one for the inspector and one reference copy for the site's files. While not part of the official study files, the copies may be helpful if further communication is necessary with the agency. When making photocopies, any personal subject/patient identifiers should be masked to ensure confidentiality.
- Request that the inspector review all observations prior to the conclusion of the inspection for the opportunity to clarify or provide an adequate explanation to the inspector's observation(s).
- Provide a response to any observations according to agency requirements. If an observation is sponsor-related, please consult with the Merck representative for guidance in providing a response to the agency.

Role and Expectations of Worldwide Clinical Quality Assurance:

- In collaboration with the Inspection Support Team (IST) assist the site with guidance in addressing GCP questions posed by the inspector, throughout the inspection (as needed). If questions posed by the inspector are directly related to the sponsor, Merck & Co., Inc. will provide an answer to the site to relay to the inspector.
- Provide study-related documentation (missing or clarifying documentation) to site personnel, as needed, along with the IST, as appropriate.
- Obtain ongoing (i.e., daily if possible) feedback from the site on the progress of the inspector's activities; e.g., participants, documents requested and reviewed, facilities toured, issues identified , general tone of the inspection and anticipated direction of inspection activities.
- Obtain a copy of inspection reports issued by the agency.
- Obtain a copy of the investigator's responses to the inspection report.
- Coordinate the preparation of responses to sponsor-related issues noted in the inspection report.

Site Signature & Responsibilities Form

Investigational drug/vaccine: MK XXXX Protocol number: XXX-00

Protocol title: MK XXXX in subjects with hypertension

Site number: XXX012301 Primary Investigator: Mike Reg M.D.

Name: Teri Terrific, RN From Date: 9/28/07 Through Date:

☐ Primary Investigator ☐ Sub-Investigator ☒ Other : Study Coordinator

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- ☐ Ensures each staff member is qualified by education, training & experience to perform assigned trial related tasks (investigator only)
- ☐ Responsible for medical management of subjects during the trial and for all trial related medical (or dental) decisions (investigator and sub-investigator only)
- ☐ Responsible for conduct of the trial and managing the study team (investigator and sub-investigator only)
- ☒ Responsible for organizing the logistical aspects among the investigator, the subject, the IRB/IEC, and the sponsor or CRO
- ☒ Compliance with protocol, Good Clinical Practice and applicable regulations
- ☒ Ensure the accuracy, completeness, legibility, timeliness of data reporting on case report form which are derived from source documents
- ☒ Ensure the accuracy, maintenance, and retention of required reports provided to the sponsor, IRB/IEC, regulatory agencies, and institutions which affect the conduct of the trial and/or increasing the risk to subjects.
- ☒ Authorized to make data entries and/or corrections on case report forms
- ☒ Recruit subjects
- ☒ Informed Consent Process: check all that apply
  - ☒ Conduct the informed consent discussions
  - ☒ Obtain informed consent
  - ☒ Sign informed consent form
  - ☒ Update subject with new safety information on test product
- ☒ Witness for obtaining study-related genetic specimens
- ☒ Responsible for adverse event reporting
- ☐ Responsible for evaluating causality of adverse event(s) in relationship to the test product(s)
- ☒ Clinical Supplies Storage/Storage Samples/Temperature Monitoring
- ☒ Receive study drugs from sponsor/pharmacy
- ☒ Dispense study drug to subjects
- ☒ Return study drug to sponsor/pharmacy
- ☒ Responsible for calibration/maintenance of critical equipment
- ☒ Maintain accurate records of the test product(s)
- ☐ Responsible for premature unblinding of test product(s) (investigator only)
- ☒ Measure vital signs
- ☐ Perform physical examinations
- ☒ Perform ECG tracing
- ☐ Perform blood drawing
- ☒ Prepares shipment of biological specimens (IATA certification as needed per regulations)
- ☒ Perform lab tests (e.g. dipstick, occult blood, urine pregnancy testing)
- ☐
- ☐

Mike Reg, MD 9/28/07

Primary Investigator (Signature*/Date)

MR

Primary Investigator's Initials/Short Signature
(for Primary Investigator's version of the form only)

Teri Terrific RN 9/28/07

Site Personnel (Signature*/Date)

TT

Site Personnel's Initials/Short Signature

*By signing this document, you recognize that certain personal identifying information (e.g., name, hospital or clinic address, curriculum vitae) may be made part of a regulatory submission and may be transmitted (either in hard copy or electronically) to all Merck & Co., Inc. subsidiaries/agents worldwide for internal study management purposes or as required by individual regulatory agencies. Additionally, your name, hospital/clinic address/phone number may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. Upon request, Merck will provide you with reasonable access to personal information about you, and you may request correction of any errors that you find. This form should include the primary and sub-investigator(s), and study team members who routinely perform significant trial related duties. This form should also include any contracted specialists performing protocol specific examinations. For US IND studies, all individuals listed on the FDA 1572 should be included. New or replacement staff should be added as appropriate throughout the trial.

PLEASE MAINTAIN THIS FORM WITH INVESTIGATOR TRIAL FILE

Study Progress Note
Study: MK-XXXX

Subject: LMM
Baseline: 001
Allocation: _____

Date	Initials	
2/5/08	T T	Reviewed with subject that study medication
		is to be taken in the morning before breakfast.
		Subject voiced understanding that she will take
		1 tablet every morning after taking her B/P
		& prior to eating her breakfast.
		1 kit containing 14 tablets provided to subject.
2/13/08	T T	Lab results back, subject does not meet criteria
		to continue in study. Discussed with Dr. Compliance.
		Subject to resume their Hyzaar.
		Subject called on phone, informed her that she
		did not meet criteria for study and she should
		stop taking study medication and restart on
		her Hyzaar. Subject voiced understanding and
		will come to office mext week to return
		study medication. Instructed to schedule
		a visit with her PCP to follow up her B/p care.

Patient Initials AAA
Baseline/Allocation# 9001

NONSERIOUS ADVERSE EXPERIENCES (Cumulative) – NSAEc

This page is to be reviewed at each visit.

If the AE...

*resulted in death
*was immediately life threatening
*resulted in persistent or significant disability
*resulted in inpatient hospitalization or prolongation of an existing inpatient hospitalization
*is a congenital anomaly /birth defect
*is an other important medical event
*is a cancer
*is an overdose (whether accidental or intentional)

STOP – Do NOT use THIS form, USE the SAE form

Visit #	3		
Type of NSAE	Clinical ☒ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐	Clinical ☐ Laboratory ☐ Other ☐
NSAE Term *(if lab AE use the term "increased" or "decreased")*	Headache		
Check if **Worsening of Pre-existing Condition**	☐	☐	☐
Onset Date *(Lab date if Lab NSAE)*	DD-Mon-YYYY 23-Mar 2008	DD-Mon-YYYY	DD-Mon-YYYY
AE Onset is:	Predose ☐ Postdose ☒	Predose ☐ Postdose ☐	Predose ☐ Postdose ☐
Stop Date *(Not applicable for Lab or Other)*	DD-Mon-YYYY 24-Mar 2008	DD-Mon-YYYY	DD-Mon-YYYY
Duration If less than 24 hours *(Not applicable for Lab or Other)*	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐	hour ☐ minute ☐ second ☐
Intensity *(Not applicable for Lab or Other)*	Mild ☒ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Action Taken on Primary Test Drug Due to NSAE:	None ☒ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐	None ☐ Interrupted ☐ Discontinued ☐ Reduced ☐ Increased ☐
Did primary test drug cause NSAE? *(Refer to Guidelines for causality then enter classification)*	Definitely not ☐ Probably not ☒ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: TT DD-Mon-YYYY: 3/25/08 (25 Mar)	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: DD-Mon-YYYY:	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ Inv. Initial's: DD-Mon-YYYY:
Comments:			

Staff Initials TT
Date 3/25/08