Morehouse School of Medicine
Clinical Research Center

DATA AND SAFETY MONITORING PLAN (DSMP)

Part I. Purpose of DSMP – The purpose of this document is to provide the principal investigator (PI) and their staff the necessary background material on data and safety monitoring, and to give guidance on how to develop a data and safety monitoring plan (DSMP). Attached to this document is a template that can be used to create a DSMP for each clinical research proposal to be initiated or renewed by the Morehouse School of Medicines Clinical Research Advisory Committee (CRAC) and its Institutional Review Board (IRB). We hope this information is helpful to you for CRC projects as well as non-CRC clinical projects. Your feedback is greatly appreciated.

The National Institute of Health (NIH) / National Center for Research Resources (NCRR), and the Food and Drug Administration, the primary funding agencies for the Morehouse School of Medicines Clinical Research Center (CRC), requires that all CRC projects have a data and safety monitoring plan (DSMP). This directive is in keeping with recent recommendations from the NIH and the FDA.

(http://grants.nih.gov/grants/guide/notice-files/not98-084.html)
(http://www.fda.gov/cber/gdlns/clindatmon.htm)

These recommendations have evolved, in part, from a number of incidents in which the presence of greater ongoing oversight of clinical research might have reduced the risk to research volunteers. To assure participant safety and clinical research integrity, the process for routine data monitoring and safety review should be appropriate for the context of the studied disease, the level of risk to the patient, as well as the size and the complexity of the clinical study. Principal Investigators must submit a DSMP as part of the initial CRC research application packet. The DSMP is the responsibility of the Principal Investigator (PI) and is subject to review and approval by the CRC/ CRAC and the MSM/ IRB prior to any patient accrual. The SAC maintains a log of minutes related to the review of DSMPs, which may be requested or reviewed by the NCRR.

Part II. Principles and Definitions - ***Data and Safety Monitoring Plan (DSMP):*** Is a prospectively defined strategy to assess the assumptions made in the trial design while the study is in progress. A properly designed DSMP improves the scientific quality and yield from a clinical trial and the protection of human subjects. A prospective DSMP is required to assess the scientific progress of a trial without compromising the study's integrity. This requires appropriate blinding of interim reviews, if possible. The DSMP can be as simple as the investigator annually submitting his/her safety and

adverse event information to the IRB or as complex as having a Data and Safety Monitoring Committee/Board.

In the DSMP, the PI must provide a brief description of the study and outlines the framework for data and safety monitoring including the routine review and evaluation of enrollment data, outcomes, and adverse events (see also attached Template). The DSMP should describe who is responsible for monitoring, how adverse events (AEs) will be reported, and to whom (e.g. CRC, IRB, NIH, FDA etc.) and how often they will be reported.

Note*: Data and safety monitoring functions, including oversight of such activities, are distinct from the requirement for study review and approval by the Institutional Review Board. However, DSMPs and reports prepared as part of the DSMP will be forwarded to the IRB. In addition, all correspondence to and from the IRB regarding patient safety issues (i.e., SAEs, periodic reviews, etc.) should be forwarded to the CRCs RSA without delay.*

The role of the **Research Subject Advocate (RSA**) - is responsible for

- providing technical assistance to each investigator in preparing a DSMP and,
- assuring that the CRC approved plan is fully implemented.
- assuring that the research carried out at the CRC is in compliance with NIH and FDA, Good Clinical Practice (GCP), and local institutional (e.g., IRB and CRC) guidelines.
- provides oversight to assure that **serious adverse events** (SAEs) are reported in a timely fashion to the CRC, IRB and other relevant federal agencies.
- coordinating with the IRB and CRAC that the approved monitoring plan is fully implemented;
- ensuring that the protocol carried out at the CRC complies with the IRB and CRAC approved protocol, through random audits of the study population (completion of pertinent study documents [CRC protocol file, clinical records, clinical flow sheets, etc.]).

II. a. **Core Principles** - *Core Principles for conducting all clinical trials on the CRC must be aware of, and address, the following areas:*

1. All protocols involving human subjects must have a DSMP.
2. The creation and implementation of the DSMP is the responsibility of the PI.
3. The DSMP must be approved through a formal process Clinical Research Center Advisory (CRAC).

4. The individual plan must be appropriate to an individual study's objectives, design and risks. (e.g. The higher the risk of a trial or the lower the certainty with which risk can be defined, the more frequent and intensive the interim reviews).
5. Participant privacy and confidentiality must be maintained throughout the monitoring process, even if interim reviews are unblinded. (e.g**. HIPPA Guidelines** etc.)
6. The integrity of the DSM process must be maintained and potential conflict of interest avoided. This requires independent review, especially in high-risk situations.
7. Issues of unblinding during the review must be addressed. Monitoring must not compromise the scientific integrity of the study.
8. The DSMP has at least the following elements:
   a. Brief description of the study.
   b. Categorization of risk (e.g., minimal, moderate, or significant/high risk).
   c. Selection criteria for the monitors/reviewers; a listing of their names, qualifications, potential conflicts, and contact information.
   d. Designation of study contact person for communication with RSA/CRC.
   e. Type of data to be reviewed at each monitoring periodic review and the rationale for selecting the data. Some examples are:
      i. Number of subjects screened and enrolled
      ii. Number of dropouts
      iii. Efficacy parameters such as primary/secondary endpoints (if appropriate)
      iv. Categorization and classification of adverse events including number and severity (e.g., use the NCI CTC II scale [http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf]or the WHO scale [http://www.accessdata.fda.gov/scripts/cder/onctools/toxicity.cfm])
      v. All serious adverse events (SAEs) and deaths
      vi. Frequency of review and rationale for the recommended frequency
      vii. Interim analysis (blinded, unblinded)
   f. Preliminary criteria for decision making regarding continuation, modification or termination of the clinical study.
   g. Statement indicating key personnel has completed the required training in the protection of research subjects.

II. b Training – All research project personnel who work with study subjects and/or their samples or data must complete the NIH and MSM/ IRB required training in the protection of research participants. The NIH program, Human Participant Protections Education for Research Teams, is found at http://cme.nci.nih.gov. In addition, all research project personnel are expected to attend workshops and seminar series to be designed by the CRC RSA and Director staff.

Part III. DSMP Methods of Protocol Monitoring

Methods used to assess the scientific progress of a trial without compromising the study's must involve the utilization of any one of four standard models/ methods for conducting data and safety monitoring activities. Data reports and reporting formats may vary based on the appropriate method selected. These methods include the following:

Method **1**: **Principal Investigator** performs CRC DSM – appropriate for investigator-initiated Phase I and Phase II studies involving a single site and small numbers of study subjects and/or nonrandomized studies of ***minimal (low)risk.*** The PI will perform ongoing review, monitoring and analysis of individual and cumulative adverse events, and preparation of all summary reports.

Method **2**: **External / Independent Monitor** performs CRC DSM – a qualified health professional not involved with the study, and without any **conflict of interest** (e.g. financial, study-related, or interpersonal) performs the CRC DSM functions. This method is appropriate for use in investigator-initiated, single site studies of ***moderate or minimal (low) risk*****.** External / Independent Monitor will perform ongoing review, monitoring and analysis of individual and cumulative adverse events, and preparation of summary all reports. External / Independent Monitors will be those individuals who are:

2. i. Experts in the disciplines identified as key to interpretation of the research data and information (e.g. epidemiologist, clinicians, bio-statisticians, bio-ethicists, community representative etc.)

2. ii. Unassociated with the investigators or other entities with proprietary interest in the outcome of the trial

Method **3**: **Data and Safety Monitoring Committee (DSMC)** performs DSM– appropriate for investigator-initiated Phase I, Phase II and/or for Phase III studies involving single or multiple sites, randomized studies, blinded or vulnerable populations or for studies of ***moderate or greater than minimal risk*****.** The DSMC will perform ongoing review, monitoring and analysis of individual and cumulative adverse events and their severity, assess the progress of the study including the number of subjects enrolled and dropouts and, prepare summary reports. They will also determine likelihood of the study achieving the anticipated results.

Data and Safety Monitoring Committee Members: Individuals who are qualified to conduct the review and, when appropriate, independent of the investigator. Potential conflicts of interest must be avoided. The committee should have or will have a multidisciplinary membership that includes experts in the relevant clinical field or specialty, individuals with experience in the conduct of clinical trials, epidemiologists, and biostatisticians knowledgeable in study design and analysis.

> **Note:** Not all clinical research projects require a committee or board to monitor safety and data. In minimal (low) risk circumstances the PI alone or an individual independent of the PI can serve in this capacity. The size and composition of the monitor group will depend on the complexity and risk level of the research protocol.

DSMP Instruction /Guidelines and a DSMP Template are attached to assist in the development of your plan.

DATA AND SAFETY MONITORING PLAN

GUIDELINES AND INSTRUCTIONS

for
TEMPLATE COMPLETION

PART II. DSMP TEMPLATE INSTRUCTIONS

1. Brief Description of Study

Include a concise summary of the proposed research study (may use protocol abstract).

2. Training

All research project personnel who work with study subjects, subject data or subject research samples must complete the NIH training in the protection of human research participants. The course, Human Participant Protections Education for Research Teams, may be accessed at http://cme.nci.nih.gov. It incorporates interactive modules, case studies, and exercises. Additionally, all research personnel who work with study participants are required to completed the Collaborative

Please submit a copy of both the NIH and CITI completion certificates for every individual involved in your clinical study with the CRC application. The CRC application will not be considered complete until all certificates are received.

In addition, all Principal Investigator, sub-investigators and research staff are required to attend all workshops/seminars to be scheduled by the RSA and CRC Director.

3. Risk Categorization

Please use the appropriate risk profile outlined below to guide you in describing the risk categorization for your protocol.

Minimal Risk – There are certain categories of low/no risk human subjects' research which have been designated as exempt from human subjects review. An Application for Exemption from Human Subjects Review must be completed and submitted to the MSM /IRB. .

Research activities that present no more than minimal risk to human subjects, and involve only procedures listed in one or more of the following categories and, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 may involve minimal risk.

Note: For studies involving minimal risk, the investigator alone or individual not directly involved in the study may provide data and safety monitoring.

Moderate Risk – Low risk intervention in a population at risk for serious clinical events based on underlying disease; intervention of undefined risk or intervention with low frequency of serious adverse events. Low risk studies in vulnerable populations such as pregnant women, children or prisoners. Study may require the oversight of a DSMC/DSMB.

Significant/High Risk – Interventions associated with risk of serious adverse events at high or uncertain frequency; studies in populations associated with very high risk of serious adverse clinical events based on underlying disease or in whom assessment of treatment-associated adverse events may be difficult. Study will require a DSMC/DSMB

4. Monitoring and Safety Review

Monitoring and safety review will continue throughout the progress of a study until all patients have completed their treatment and for an additional month after their last visit.

a. Who will monitor?

Data and Safety Monitoring may be accomplished by:

- *Principal Investigator* - may be appropriate for an investigator-initiated, single-site, non-randomized low risk study.
- *Independent Monitor* - may be appropriate for an investigator-initiated, single-site, randomized low or moderate risk study.
- *Data and Safety Monitoring Committee/Board* - may be appropriate for an investigator-initiated, single-site or multicenter randomized moderate risk or high-risk study.

Not all clinical research projects need a committee or board to monitor safety and data. Under some circumstances the PI alone or an individual independent of the PI can do this (see template instructions). The size of the committee and its composition are based on the complexity of the study and risk assessment.

b. What will be monitored?

a. Number of subjects screened and enrolled
b. Drop-outs
c. Primary and secondary efficacy parameters (if applicable).
d. Categorization and classification of AEs (may use http://www.accessdata.fda.gov/scripts/cder/onctools/toxicity.cfm]).

c. How frequently will data be monitored and reported?

All PIs are required to report on the study status on an annual basis. The annual report will be submitted to the CRC at the same time that IRB periodic review occurs. For low risk studies a copy of the IRB annual renewal report may suffice. For moderate or high-risk protocols a more frequent reporting schedule will be necessary as described in the DSMP.

For high risk studies data reports may include, but should not be limited to, review of interim data analysis, cumulative adverse event summary, recruitment and retention summaries, analysis of data quality, and for studies with an external DSMC/ DSMB, a summary report or minutes of DSMC/DSMB meeting.

Audits of research records may be performed, either on a random basis or as part of a planned audit, of moderate or high-risk protocols, by the RSA.

d. What are the plans for interim analysis? If none, please state.

e. For a study with an external sponsor (i.e., pharmaceutical company, NIH, foundation, etc.), please provide a summary of the DSMC/DSMB organization, responsibilities and operating procedures. Please include the following:
   1. Membership information including appropriate scientific and biostatistical expertise and conflict of interest disclosure for voting and non-voting members.
   2. Frequency and documentation of DSMC/DSMB periodic reviews, submittal of written summary or minutes to RSA and CRAC of the CRC.
   3. Plans for interim analyses to determine whether the trial should continue as originally designed.
   4. Mechanism for distributing the DSMC / DSMB periodic review to all participating investigators, IRBs and other agencies as required.

5. Plan for Adverse Event Reporting

The MSM/ IRB has developed a Template that must be used to report each on-site (MSM research site) Adverse Event (AE). The DSMP Template (see pages 15-24) below includes a copy of this Template along with instructions on how it is to be filled and returned to the IRB. Before completing this form, refer to the definitions and discussion found at the end *of the IRB AE Template*.

This reporting requirement applies to injury, harm, or any problem physical or otherwise, that may occur with any human research subject while enrolled in any research protocol under the control and direction of Morehouse School of Medicine.

Note: A copy of the current consent form should be attached to all Serious Adverse Event (SAE) Report Forms.

DATA SAFETY MONITORING PLAN

CRC # _____ IRB # _____

Protocol Title:

Adherence and Monitoring Statement: The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the Morehouse School of Medicine Institutional Review Board (IRB). An IRB-approved written informed consent will be obtained from each subject at entry into the study; elements of informed consent will include: (a) having the subject and/or parent/guardian/proxy review the study consent form; (b) having the investigator(s) or study staff meet with the subject and/or guardian/proxy to review the consent, confirm understanding, and answer any questions; and (c) once the investigator(s) or study staff are convinced that the protocol is understood and that there is agreement to participate, having the consent signed in the presence of a witness.

The Principal investigator (PI) will review all data collection forms at least annually for completeness and accuracy of the data as well as protocol compliance. The PI will review this protocol on a continuing basis for subject safety and include the results of the review in annual progress reports submitted to the IRB, and CRC Research Subjects Advocate (RSA) and the sponsoring institution. As with all MSM CRC protocols, AEs and SAEs will also be reviewed by the IRB, CRC Data and Safety Monitoring Committee and the CRC RSA as needed. The MSM/CRC DSMC will perform ongoing review, monitoring and analysis of individual and cumulative adverse events and their severity to assess the progress of the study, including the number of subjects enrolled and dropouts, and prepare summary reports.

Principal Investigator:	_____	Telephone:	_____
		Fax:	_____
		Pager:	_____
		E-mail	_____
Sub Investigator(s):	_____	Telephone:	_____
	_____	E-mail	_____
		Telephone:	_____
		E-mail	_____
Study Coordinator (s):	_____	Telephone:	_____
	_____	Fax:	_____
		E-mail	_____
Other Key Study Personnel:	_____		
	_____		
	_____		
	_____		

Primary Study Contact for CRC-RSA:	Winifred Smith, MPH	Telephone:	404-752-1140
		Fax:	404-752-1128
		Pager:	
		E-mail:	wsmith@msm.edu

1. **Brief Description of Study** - Protocol abstract or equivalent.

2. **Training** – All research project personnel previously listed above who work with study subjects, subject data or subject research samples must complete the NIH training in the protection of human research participants. Please attach a copy of the certificate if not already on file at the GCRC.

☐ NIH training module completed.
☐ MSM/IRB Training Course taken.

3. **Risk Categorization** – Please choose the appropriate level of risk associated with this study and use the space provided to justify the risk level associated with this study.

Minimal Risk

☐ Study is eligible for exemption from IRB review (see also Template Completion Instructions)
☐ Study is eligible for expedited IRB review (see also Template Completion Instructions)
☐ Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.
☐ Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- ☐ from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week;
- ☐ from other adults and children[1], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn

1 Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

☐ Prospective collection of biological specimens for research purposes by noninvasive means.

☐ Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

☐ Other: Please describe:

Moderate Risk

☐ Low risk intervention in a population at risk for serious clinical events based on underlying disease. (see also Template Completion Instructions)

☐ Intervention of undefined risk or intervention with low frequency of serious adverse events.

☐ Low risk studies in vulnerable populations such as pregnant women, children or prisoners. Study may require the oversight of a DSMC/DSMB.

☐ Other: Please describe:

High Risk /Significant Risk

☐ Interventions associated with risk of serious adverse events at high or uncertain frequency (see also Template Completion Instructions)

☐ Studies in populations associated with very high risk of serious adverse clinical events based on underlying disease or in whom assessment of treatment-associated adverse events may be difficult. Study will require a DSMC/DSMB

☐ Other: Please describe:

4. **Monitoring and Safety Review**

a. Who will monitor? (Identify the monitor (s)/reviewer (s), committee members, qualifications, potential conflicts of interest and contact information).

Primary Study Monitor _____ Telephone: _____
_____ Fax: _____
Pager: _____
Email: _____

Qualifications?

Conflicts of interest? ☐ No, If ☐ Yes, please describe.

A Data and Safety Monitoring Committee (DSMC) will perform DSM as appropriate for the _____ study. DSMC will perform ongoing review, monitoring and analysis of individual and cumulative adverse events and their severity to assess the progress of the study including the number of subjects enrolled and dropouts and, prepare summary reports. They will also determine likelihood of the study achieving the anticipated results.

The MSM CRC Data and Safety Monitoring Committee Membership is composed of a multidisciplinary team of health professionals who are qualified to conduct frequent monitoring and ongoing safety review of MSM/IRB approved protocols. These committee members are experts in relevant clinical fields or specialties, are experienced in the conduct of clinical trials, are not currently involved with CRC studies and are without any conflict of interest financially, study-related, or interpersonally.

Current CRC DSMC Members:

- **William Cleveland**, **MD**, President, Southwest Atlanta Nephrology & Clinical Associate Professor, Medicine, Chair
- **Maurice Williams, MD**, University of Texas, Assistant Professor, Internal Medicine, Division of Oncology/Hematology, Co-Chair
- **Loretta Patrick, RN, JD**, Executive Director, Medical Network for Education & Research
- **Verna Welch, PhD, MPH**, Biostastician, Associate Professor, Morehouse School of Medicine
- **Dale Mack, BS**, Director, Radiation Safety, Morehouse School of Medicine
- **Suzanne Alexander**, Research & Development Administrator, Office of Sponsored Research Administration, Morehouse School of Medicine

Ex-officio Members:

- **Winifred Smith, MPH,** Research Subject Advocate
- **Patricia Jackson, RN**, Clinical Trials Manager, Clinical Research Center
- **Tomekia Ndubisi, BA**, Regulatory Research Assistant, Clinical Research Center

A written report by the DSMC is to be made upon completion of each meeting. This report is to contain findings/ minutes of the review and recommendations from the Committee. Recommendations include corrective actions required for major and minor concerns/deviations noted and the possible need for follow-up reviews. The RSA is to forward report results of DSMC reviews directly to the Investigator, the CRC CAC, and the IRB with recommendations for further action as necessary. DSMC reports prepared as part of the DSMP are to be forwarded to the IRB. In addition, all correspondence to and from the IRB regarding patient safety issues (i.e., SAEs, periodic reviews, etc.) should be forwarded to the CRC RSA without

delay.

b. What will be monitored? (Please describe all that apply)

- Number of subjects screened and enrolled.
- Dropouts.
- Primary and secondary efficacy endpoints
- Adverse Events (serious and non-serious) using an accepted scale.

c. How frequently will data be monitored and reported?

☐ Every 12 months (coincides with IRB periodic review)
☐ Every 6 months
☐ Every 3 months
☐ Other: Please describe:

d. What are the plans for interim analysis?
☐ None
☐ Other: Please describe:

e. Does the sponsor have a DSMC/DSMB in place or planned for this trial? ☐ Yes ☐ No
(If yes, please submit a copy of its charter including a description of the planned meeting frequency and how information will be distributed to investigators.)

5. **Plan for Adverse Event (AE) Reporting**

Describe, briefly, in this section the plan for reporting non-serious anticipated and unanticipated adverse events as well as serious adverse events to the IRB, CRC, funding and regulatory agencies and any other appropriate body. Below is the Template from the MSM/IRB to be used in reporting all AEs. **(Please also contact the MSM/IRB Office for additional clarification on AE reporting)**

The plan for reporting all adverse events, expected and unexpected, will be recorded and reported using the official approved Morehouse School of Medicine/Institutional Review Boards mandated format.

All adverse events (AEs) in the _____ study will be graded as to their attribution (unrelated to protocol, or possibly, probably, or definitely related to protocol). Any AE that is reported to either the PI or their designated research associates by a study subject or by medical staff caring for the subject and which meets the criteria will be documented as such. This study will be entered into the Morehouse School of Medicine CRC computerized database system to permit tracking of adverse events. This system will then be used by all investigators to report "expected" AEs (predefined AEs which will be monitored over the course of the trial – see below), "observed" AEs (AEs which occur but which may or may not have been anticipated), and all serious adverse events (SAEs, see below); this system will be used in this trial. Serious adverse events are predefined as: any experience that suggests a significant hazard, such as events which: a) are fatal, b) are life threatening, c) result in permanent disability, d) require inpatient hospitalization, or e) involve cancer, a congenital anomaly, or drug overdose.

Any AEs will be reported to the Morehouse School of Medicine IRB, CRC Research Subject Advocate (RSA), within 7 days of the event and any SAEs will be reported to the RSA and the MSM IRB within 24-48 hours of the event. The standard Morehouse School of Medicine IRB reporting guidelines for AE and SAE reporting will also be followed. The investigators and staff will enter all AEs into the CRC RSA database, and evaluate the SAEs, in close coordination with the CRC DSM Committee and the Morehouse School of Medicine IRB. The IRB annual report from the P.I. will also be transmitted to the RSA and stored both in the RSA database and as a hard copy file. The P.I. will also personally discuss the study and any observed AEs or SAEs on a regular basis with the RSA (at least once a year and more often as indicated).

6. Confidentiality

All information and materials for the _____ study will be obtained for research purposes only and the data will be kept in strict confidence in accordance with HIPAA Privacy *45 CFR 164.501, 164.508, 164.512(i) and 45 CFR 164.514(e), 164.528, 164.532*. Further, this confidentiality will be assured by the use of subject codes rather than personal identifiers. The study database will be secured, and information will only be entered using subject identifier codes rather than personal identifiers. Electronic communication will involve only coded, unidentifiable information. CRC adverse event tracking will utilize password-protected access, and all adverse event reports and annual summaries will not include subject-identifiable material. The above detailed data and safety plans should assure data accuracy and protocol human safety compliance for this CRC based study. These include computerized database management, and both CRC RSA and IRB oversight and communication. This plan, together with proposed monitoring by the RSA and the IRB, should be sufficient in addition to a CRC DSM Committee.

In addition, guidelines issued by the **Office for Protection from Research Risks (OPRR)** ***Issues to Consider in the Research Use of Stored Data or Tissues*** will be followed under this study.

_____	_____	_____
(Principal Investigator)	Signature	Date

ON-SITE UNANTICIPATED PROBLEM/ADVERSE EVENT REPORT FORM
Morehouse School of Medicine
Institutional Review Board

INSTRUCTIONS

This form must be used to report **on-site (MSM research site)** **research-related** adverse events and unanticipated problems involving risks to subjects or others. Attach supporting documentation, if applicable. Please type or print in black ink. **This reporting requirement applies to any injury, harm, or problem, physical or otherwise, under conditions defined below, that happened to any human research subject (or other person(s) involved or connected to the research) while enrolled in any research protocol under the control and direction of Morehouse School of Medicine. This reporting requirement applies as well to harm of any nature giving rise to any unanticipated problems (including adverse events) involving risks to human subjects or others as a result of the conduct of any human subjects research study under the direction and control of Morehouse School of Medicine. Nothing in the reporting requirement represented by this policy is meant to alter investigator or institutional responsibility for reporting adverse events/ adverse effects as may otherwise be required by the FDA, DHHS or sponsors.**

In order to meet the definition of REPORTABLE "unanticipated problems (including adverse events)," ***all*** of the following criteria must be met:

(1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

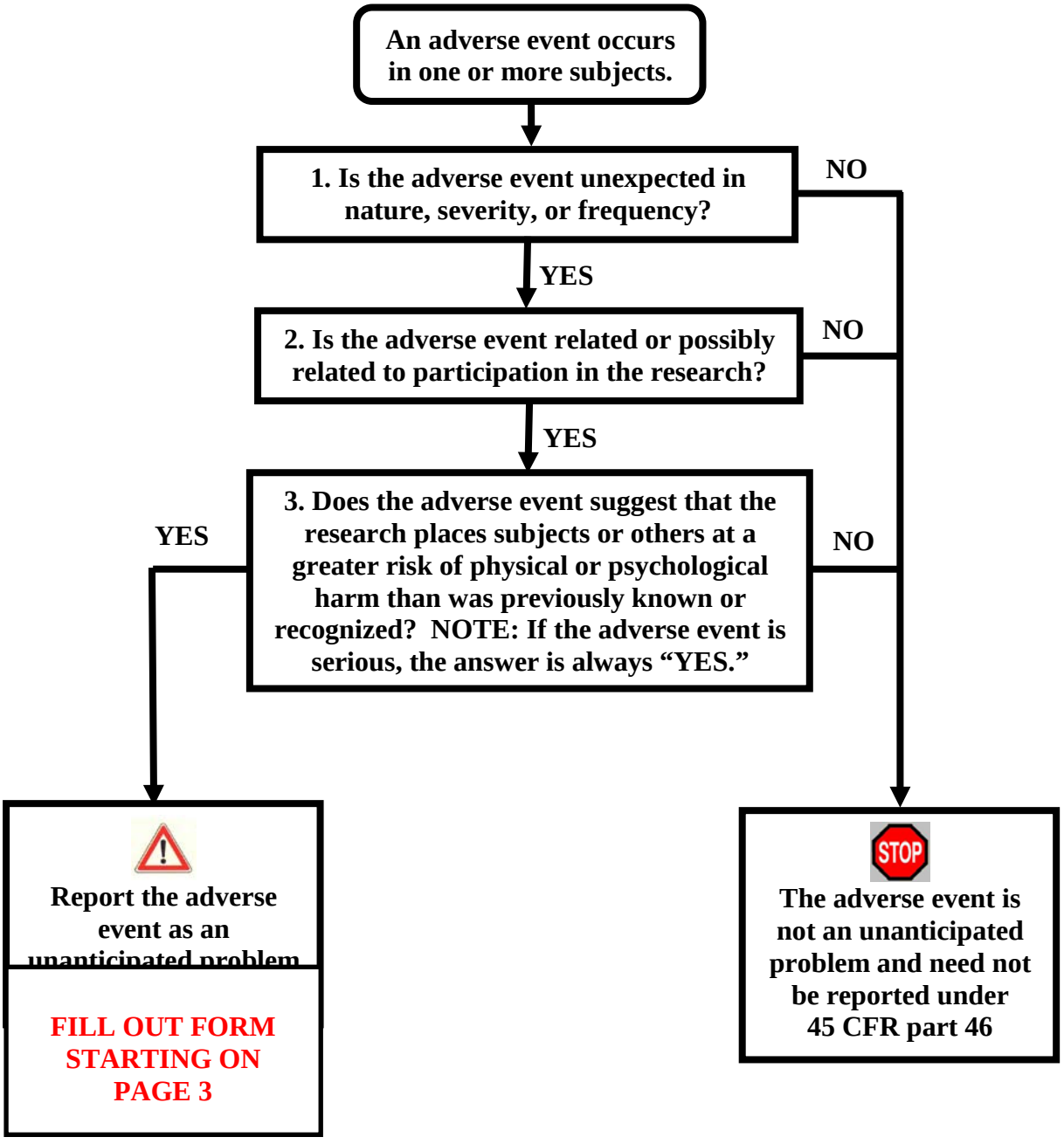
(2) related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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

Unanticipated problems (including adverse events) need not be reported unless all of the criteria above are met.
Please note that unanticipated problems/adverse events may involve a breach in confidentiality as well as emotional or physical harm.

Refer to the decision-making algorithm on the following page.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



Title of Protocol:

Protocol ID Number(s):

Sponsor(s):

***Principal Investigator**:* ***Phone**:*

Research Coordinator: **Phone**:

This unanticipated problem/adverse event involved:
[ ] A research subject [ ] Other person

<u>Describe the adverse event or unanticipated problem</u> and all measures taken to address, correct or otherwise minimize harm to the research subject. Do not use abbreviations without first spelling out the term. <u>The information may be typed below or attached.</u>

Date adverse event/unanticipated problem occurred:

Location at which event occurred:

***This adverse event/unanticipated problem first came to the attention of:**
on (date)*:

This report is: [ ] Initial* [ ] Follow-up

*NOTE: An initial adverse event/unanticipated problem report is due no later than 10 calendar days following discovery of the event/problem; EXCEPT, in the case of the death of a subject, the IRB must receive notification within 48 hours of the time the subject's death becomes known to the investigator.

Outcome/Intervention:

Did the unanticipated problem/adverse event require medical or surgical intervention to prevent (check all that apply):

[ ] death
[ ] a life-threatening experience
[ ] persistent or significant disability
[ ] inpatient hospitalization
[ ] prolongation of existing hospitalization
[ ] incapacity
[ ] a congenital anomaly/birth defect
[ ] emotional/psychological distress
[ ] other (specify, such as physical injury, etc.)

Describe the intervention, if any, administered to the subject or other person(s):

Did the unanticipated problem/adverse event involve any of the following claimed or real aspects (check all that apply): The event placed the subject or other person(s)at risk of

[ ] criminal liability
[ ] civil liability
[ ] damage to financial standing
[ ] damage to employability
[ ] damage to reputation

This unanticipated problem/adverse event likely occurred as the result of:
[ ] Deviation from the protocol [ ] Inadvertent error (e.g., drug administration error) [ ] Improper enrollment [ ] Subject noncompliance [ ] Inadvertent release or disclosure of confidential information [ ] Other (describe):

List below all persons involved in the investigation of this adverse event:

In the judgment of the principal investigator:

1. **The severity of the incident would best be classified as:**
   [ ] Mild [ ] Moderate [ ] Moderately severe [ ] Severe

Mild:	An unanticipated problem/adverse event that does not significantly influence the performance (ability to conduct daily activities), health status, or other personal quality of the subject or is not otherwise uncomfortable to the subject. Generally, the event does not require intervention or alteration or cessation of the subject's participation in the study.
Moderate:	An unanticipated problem/adverse event that noticeably and negatively impacts upon the subject's performance, health status, or other personal quality or otherwise causes the subject to experience bothersome discomfort. Intervention may be required to address the adverse event. The subject should be evaluated for continued participation in the study, especially so if the event is not anticipated to subside.
Moderately Severe:	An unanticipated problem/adverse event that significantly influences the subject's performance, health status, or other personal quality and causes discomfort requiring intervention to ablate. The investigator should make an informed judgment as to whether the subject should continue to participate in the study.
Severe:	An unanticipated problem/adverse event that results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or any event in the opinion of the investigator that may jeopardize the subject or may require intervention to prevent an outcome or treat an injury as listed above under

"Outcome/Intervention." A serious adverse event may also include one in which the subject requires counseling or psychological intervention for corrective action.

2. **Should the consent form be revised?**
   [ ] Yes [ ] No [ ] Uncertain at this time
   (If "yes," suggest revision to be approved by the IRB.)

3. **Should the protocol be revised?**
   [ ] Yes [ ] No [ ] Uncertain at this time
   (If "yes," suggest revision to be approved by the IRB as well as the sponsor.)

4. **Should currently enrolled subjects be notified of this event in light of the consent form stating that subjects will be notified of any new information that may have a bearing on their decision to continue to participate in the study?**
   [ ] Yes [ ] No (If "no," provide justification for not informing subjects.)

5. **In light of this event, further enrollment in the study should be**
   [ ] continued
   [ ] discontinued pending resolution or further clarification of safety issues (State issues to be clarified.)

6. **In light of this event, the study should be**
   [ ] continued without further change
   [ ] continued only with suggested changes (Attach suggestions.)
   [ ] discontinued

The current status of this unanticipated problem/adverse event is:

[ ] Resolved [ ] Unresolved (A follow-up report will be submitted within 30 days of the date of this report.)

Current status of the subject:

[ ] has already completed the study
[ ] remains on the study
[ ] temporarily removed form the study*
[ ] permanently removed from the study*
[ ] elected to voluntarily discontinue the study*

***Describe the process of removal/discontinuation in light of what was considered best for the subject under the circumstances and any alternatives or advice presented to the subject.**

This unanticipated problem/adverse event was brought to the attention of the(check all that apply):

[ ] Sponsor [ ] Dean [ ] Department Chair [ ] Agency (specify):
(Provide written documentation of any notification(s) identified above.)

Acknowledgement of Principal Investigator: ***I have personally reviewed this report and agree with the above assessment. I shall promptly notify the IRB of anything that comes to my attention that would confirm or change the contents of this report.***

_____
Printed Name of PI

_____ **_____**
Signature of PI **Date**

ON-SITE UNANTICIPATED PROBLEM/ADVERSE EVENT REPORT FORM
Morehouse School of Medicine
Institutional Review Board

IRB Office Use Only

Date Received: _____ Date Reviewed: _____

Reviewed By: _____
Signature of Reviewer

Recommendation(s) made:
[ ] No changes [ ] Change consent [ ] Change protocol [ ] Suspend approval
[ ] Withdraw approval (Justify recommendation on separate page.)
[ ] Bring to the attention of convened IRB: Date:_____
[ ] Reported to Sponsored Research Administration: Date: _____ (Attach correspondence)
[ ] Other:

Action(s) taken on recommendation:

Notification of action(s) taken sent to PI on: _____

End of Report

Unanticipated Problem/Adverse Even Information

Do not submit this section with the report.

The unanticipated problem/adverse event reporting procedure closely follows federal regulations governing the conduct of research on human subjects as well as policy guidance and directives published and distributed by federal agencies (e.g., agencies under DHHS). For example, on June 5, 2000, NIH released a notice guidance – "FURTHER GUIDANCE ON A DTATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS" – the text of which may be retrieved at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html . The following information, "Adverse Events" Lexicon, was derived from research on current federal regulations:

"Adverse Events" Lexicon – Terminology and Context of Adverse Event Reporting

Of note: The terms "adverse events" or "serious adverse events" do not appear in 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, or 45 CFR 46 – the major regulations governing the conduct and reporting requirements of human subjects research. The Investigational New Drug Application regulation, 21 CFR 312, does not state limits of time reporting while 21 CFR 812 (Investigational Device Exemptions) expresses specific timing of reporting.

Researching key words related to the topic of **"adverse events"** in the regulations cited above resulted in the following findings:

21 CFR 56.113 uses the phrase ***"[u]nexpected serious harm to subjects…."*** in the context of suspension or termination of IRB approval of research. The same expression is used in 45 CFR 46.113.

21 CFR 56.108(b)(1) uses the phrase ***"Any unanticipated problems involving risks to human subjects or others[;]…"*** in the context of IRB functions and operations relating to the requirement for the IRB to follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and the Food and Dug Administration. 45 CFR 46.103(b)(5) essentially mirrors this requirement and expression, replacing "Department or Agency head" for "FDA." For example, this type of harm or injury may include the risk of disclosure of information outside of the context of research that could reveal sensitive information involving family members or persons associated with the subject. Physical harm to others may involve injuries related to radiation exposure.

21 CFR 312.64(b)[Safety Reports]: "Investigator shall promptly report to the sponsor any "***adverse effect***" ….. reasonably caused by, or probably caused by the drug. If the "***adverse effect***" is "***alarming,***" the investigator shall report the effect immediately." [Note: no time limit of reporting is specified, except "promptly" and "immediately."]

21 CFR 812.50(a)[Investigator reports](1)["***Unanticipated adverse device effect***]– An investigator shall submit to the sponsor and the reviewing IRB a report …. No later than 10 working days after the investigator learns of the effect."

21 CFR 812.3(s) "….. ***unanticipated serious problem*** associated with a device that relates to the rights, safety of welfare of subjects."

21 CFR 312.32 – IND Safety Reports – "***Serious adverse drug experience***" includes:

1. death
2. life-threatening
3. hospitalization or prolongation of hospitalization
4. persistent or significant disability/incapacity or congenital anomaly/birth defect
5. unexpected adverse drug experience (one that has not been previously observed)

Adverse events may be found also in the context of 45 CFR 46.101(b)(2)(ii) [general reference to survey, interview…] whereby disclosure of information outside the research could ***reasonably place the subjects at risk*** of criminal or civil liability or be damaging to the subjects financial standing, employability or reputation. Some believe this is especially applicable in the era of genetic research.

Definitions of terms in the context of conducting human subjects research:

Adverse:	Unfavorable, harmful.
Adverse Event:	An unfavorable or harmful occurrence, whether unexpected or not, resulting from procedures, treatment or intervention associated with the conduct of the research study.
Serious Adverse Event:	An adverse event that results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or any event in the opinion of the investigator that may jeopardize the subject or may require intervention to prevent an outcome listed above. A serious adverse event may also include one in which the subject requires counseling or psychological intervention for corrective action.
Unexpected:	Unanticipated, unforeseen
Unexpected Adverse Event:	Any adverse event of which the nature, severity or specificity could not have been reasonably determined or anticipated in advance of conducting the study or which is not otherwise consistent with experience, protocol or

	literature, or other guidelines associated with conducting the study. For purposes of research policy at Morehouse School of Medicine, the death of a research subject is never an expected adverse event, regardless of any predisposition or condition of the subject.
Problem:	Any event associated with the conduct of the research study that results in harm or injury (including: physical, social, legal, economic or psychological) or creates the potential for resulting in harm of injury to research subjects or others. Problems may fall under the category of "serious" (see serious adverse event, above) and may be "unexpected" as described above.
Unanticipated Problem Involving Risks to Subjects or Others:	An unexpected problem that reveals a significant increase in the study's risk/benefit relationship previously reviewed and approved by the IRB.
Harm:	Injury, hurt, loss, impairment
Injury:	A wrong or damage done to another either as to person, rights, reputation or property. In a legal context, employment and insurability would be considered to be property rights. An injury to a person that results in incarceration would be considered an infraction of a personal right (freedom).
Mild:	An adverse event that does not significantly influence the performance (ability to conduct daily activities), health status, or other personal quality of the subject or is not otherwise uncomfortable to the subject. Generally, the event does not require intervention or alteration or cessation of the subject's participation in the study.
Moderate:	An adverse event that noticeably and negatively impacts upon the subject's performance, health status, or other personal quality or otherwise causes the subject to experience bothersome discomfort. Intervention may be required to address the adverse event. The subject should be evaluated for continued participation in the study, especially so if the event is not anticipated to subside.
Moderately Severe:	An adverse event that significantly influences the subject's performance, health status, or other personal quality and causes discomfort requiring intervention to ablate. The investigator should make an informed judgment as to whether the subject should continue to participate in the study.
Severe:	An adverse event qualified under the definition of "Serious Adverse Event" above.

Not Related:	An adverse event that cannot be associated with having occurred within the context of study participation either as to the nature, severity or temporal relationship considering the subjects general state and condition.
Unlikely Related:	An adverse event that cannot be determined to result from the subject's participation as to the nature, severity or temporal relationship but that may be attributed to other factors such as the subject's general state or condition.
Possibly Related:	An adverse event that is considered to be within the possibility of the subject's participation considering the nature, severity or temporal relationship but although it cannot be excluded from causality does not fit a pattern of probability within a determination of more likely than not.
Probably Related:	An adverse event that is reasonably certain to be associated with the subject's participation and falls within the nature, severity and temporal relationship supporting the probability of more likely than not or giving rise to clear and convincing evidence of causality.
Definitely Related:	An adverse event that is associated with the subject's participation as to the nature, severity and temporal relationship of the adverse event being undeniably connected as to causality considering all factors involved in the protocol. No reasonable judgment would refute the relationship between participation and causality of the adverse event.

For completeness of the terms and definitions relative to the context of human subjects research, Title 21, Volume 5, Code of Federal Regulations Title 21 – Food and Drugs, Chapter I – Food and Drug Administration, Department of health and Human Services, Part 312 – Investigational New Drug Application, Subpart B – Investigational New Drug Application (IND), Sec. 312.32 IND safety reports (a) is reproduced below.

[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[CITE: 21CFR312.32]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--Continued

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION--Table of Contents

Subpart B--Investigational New Drug Application (IND)

Sec. 312.32 IND safety reports.

(a) Definitions. The following definitions of terms apply to this section:-

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. ``Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of safety information. The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(c) IND safety reports.

(1) Written reports—

(i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., ``IND Safety Report.'' Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previouos, similar reports.

(2) Telephone and facsimile transmission safety reports. The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

(3) Reporting format or frequency. FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and Research or the director of the products review division in the Center for Biologics Evaluation and Research which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d) Followup.

(1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

(4) Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

(e) Disclaimer. A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014) [52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 62 FR 52250, Oct. 7, 1997])