

SOP: RR 403 Version No: 1 Effective Date: 01/01/07	CONTINUING REVIEW - ONGOING	Supersedes Document Dated: 11/05
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1. POLICY

No Investigator has a right to conduct research within this institution. Rather, it is a privilege granted by society as a whole and the Administrative and Medical Staff of Sparrow Health System in particular.

IRB approval may be withdrawn at any time if warranted by the conduct of the research. The regulations authorize IRB to establish procedures for the concurrent monitoring of research activities involving human subjects. Periodic review of research activities is necessary to determine whether approval should be continued or withdrawn. All research involving human subjects must be reviewed no less than once per year.

IRB approval for the conduct of a study may be withdrawn if the risks to the subjects are determined to be unreasonably high, for example, more than an expected number of adverse events, unexpected serious adverse events; or evidence that the Investigator is not conducting the investigation in compliance with IRB or Institutional guidelines. Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated. Continuing review includes, but may not be limited to the following activities:

- Site Visits and Third Party Verification
- Review of Serious and Unexpected Adverse Events
- Amendments
- Review of Significant New Findings
- Reports from Employees, Staff and Faculty
- Noncompliance

Specific Policies

1.1 Site Visits and Third Party Verification

The IRB has the authority to observe, or have a third party observe, the informed consent process of research it has approved, and to verify that the study is being conducted as required by the IRB and within the Institutional policies and procedures and site-specific procedures, as appropriate. IRB staff or members may perform site visits (Form RR 403-C) or use another party, either affiliated or not with the institution, to verify information in the study application, or in any interim or continuing review submissions.

The criteria for selecting Investigators to be visited may include but not limited to:

- Investigators who conduct studies that involve a potential high risk to subjects,
- Studies that involve vulnerable populations,
- Investigators who conduct studies that involve large numbers of subjects, and

- Investigators selected at the discretion of the IRB.

Other means of verification may include questionnaires sent to investigative staff to verify information submitted by the Investigator. Sponsors may be asked to submit copies of monitoring reports, or may be requested to complete a questionnaire regarding the protocol and/or the investigative site.

Investigators may be asked to submit copies of signed informed consent forms or other documents to ensure their compliance with IRB requirements. The IRB may conduct interviews with screened and/or enrolled subjects as deemed necessary.

1.2 Serious and/or Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

Subject safety is of the greatest importance for both the individual subject and the goals of the clinical study. The purpose of continuing review and monitoring of an on-going study is to ensure that the research remains justified and that the rights and welfare of the participants continue to be fully protected. Accordingly, if a local research subject sustains any unanticipated problem that causes risks or harm to the subject that is related, or possibly related, to the research intervention this encompasses a reportable event.

Definitions of Unanticipated Reportable Problem:

(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 (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involving in the research); and

(3) **Serious** 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; and may include, but not limited to:

- 1) results in death, or
- 2) is life-threatening, or
- 3) requires inpatient hospitalization or prolongation of existing hospitalization, or
- 4) results in persistent or significant disability or incapacity, or
- 5) results in a congenital anomaly or birth defect, or
- 6) causes cancer, or
- 7) is an overdose, or
- 8) is any medical event which requires treatment to prevent one of the medical outcomes listed above.

If the internal event is serious, related or possibly related, and unexpected, prompt reporting to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) and to the IRB is mandatory.

Definition of Reportable Adverse Event:

The term adverse event is not defined in the regulations, nor is there a widely accepted definition in the regulatory community. However, OHRP adopted a working definition in its January 15, 2007 Guidance, which states:

An **adverse event** is defined as:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

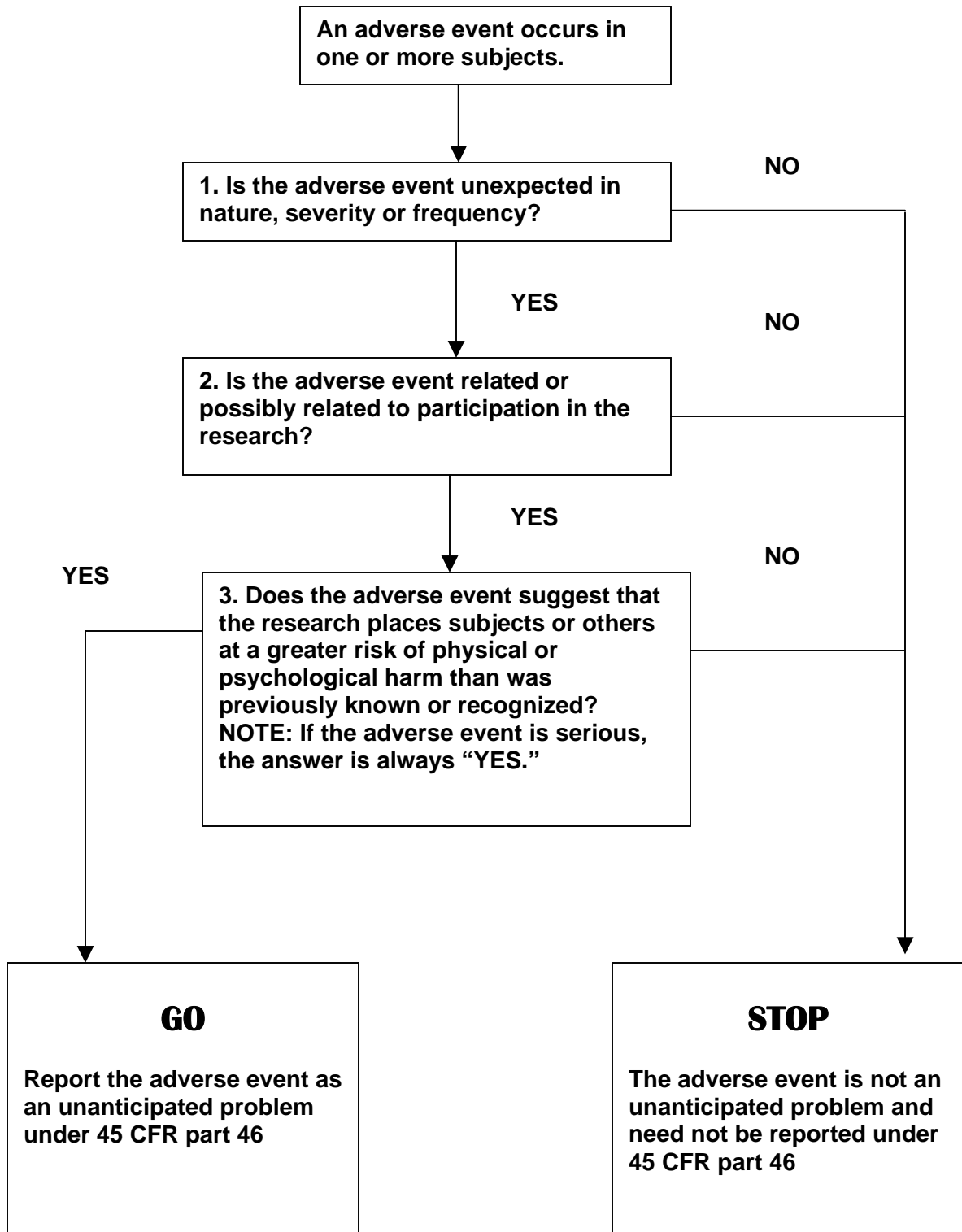
Adverse events encompass both physical and psychological harms. They occur most frequently in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of Multicenter clinical trials, adverse events can be characterized as either *internal adverse events* or *external adverse events*. From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

In the case of an *internal adverse event* at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of *external adverse events*, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

OHRP has provided the following algorithm for determining whether an adverse event is an unanticipated problem:

**Algorithm for Determining Whether an Adverse Event
is an Unanticipated Problem**



1.2.1. Internal Reportable Problem.

To determine if an adverse event is an unanticipated reportable problem, the investigator should answer the following questions:

- 1) Is the adverse event unexpected?
- 2) Is the adverse event related or possibly related to participation in the research?
- 3) Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and prompt reporting to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) and the IRB are mandatory. The investigator should also report events that in the judgment of the investigator alter or potentially alter the risk to participants in the study.

The investigator must submit an IRB Report of Unanticipated Internal Problem or Adverse Event (Form RR 403 -A) to the IRB within 48 hours, but no later than five (5) days, of the reportable event. The IRB will expect the investigator to also provide them with a determination of whether or not the investigator finds modifications to the informed consent form are necessary as a result of these adverse event reports.

The internal unanticipated problems and/or adverse event reports will be reviewed by the IRB Chairperson or designee. If the Chairperson determines that action may be needed to protect the safety of research subjects due to the nature or frequency of reported adverse events, he/she may take such action and/or the full IRB or designated subcommittee will review the adverse events and study in question to determine action, if any, by the IRB. The IRB, or designated subcommittee, will review summaries of all unanticipated problems and serious adverse events as soon as possible at a convened meeting.

Incidents of serious medication adverse events must be reported to the Sparrow Hospital Pharmacy and Therapeutic Committee as well as the IRB.

1.2.2. External Adverse Events (Multicenter clinical trials)

Reports of individual external (or events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial, or “non-local”) adverse events often lack sufficient information to allow investigators or IRBs engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or other at a greater risk of physical or psychological harm than was previously know or recognized.

Under current OHRP and FDA guidance, it is neither useful nor necessary for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all

institutions conducting the research. Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB per the federal regulations.

Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

To that end, the IRB will expect investigators to only submit, upon receipt, the DSMB/DMC or other study monitoring entity's report when a particular external adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem. Additionally, the IRB will expect sponsors to provide local investigators with periodic summary reports or aggregated adverse event information in place of individual safety reports to be submitted to the local IRB.

The DSMB/DMC or other monitoring entity reports submitted to the IRB by investigators should include:

- 1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem;
- 2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem; and
- 3) a recommendation for or against changes to the informed consent form.

When an investigator receives a report of an external adverse event, before submitting the report to the IRB, the investigator should review the report and assess whether it identifies the adverse event as being:

- 1) unexpected;
- 2) related or possibly related to participation in the research; and
- 3) serious or otherwise suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the DSMB/DMC or other monitoring entity report(s) as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems.

If an external adverse event(s) is not an unanticipated problem (as clearly defined above), the report(s) will no longer be reviewed by the IRB.

1.3 Other Unanticipated Problems

All unanticipated problems must be reported promptly to the IRB. An unanticipated problem is defined as any unforeseen event or events that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research. Examples of an unanticipated problem include, but are not limited to: difficulty recruiting subjects, higher than expected adverse

events (Policy RR 406), higher than expected subject drop out rate, higher than expected protocol deviation rate, loss of multiple staff members, injury to a staff member while conducting study-related procedures, or subject difficulty understanding the informed consent.

1.4 Amendments

Changes in approved research, during the period for which approval has already been given, may not be initiated without prior IRB review (full or expedited review, as appropriate) and approval, except where necessary to eliminate apparent immediate hazards to human subjects. Such amendments initiated for the alleviation of immediate hazards to human subjects must be reported as soon as possible to the IRB and submitted for the next convened IRB meeting.

Investigators are required to promptly inform the IRB of any suspension or change in the research environment or new information indicating greater risk to the human subjects than existed with the protocol was previously reviewed and approved.

Investigators or Sponsors must submit requests for changes to the IRB in writing (Form FO 301-C – Application for Revision and/or Amendment). Upon receipt of the protocol change, the Chairperson or IRB Administrator/IRB Coordinator, will determine if the revision meets the criteria for minimal risk. If the change represents more than a minimal risk to subjects, it must be reviewed and approved by the IRB. Minor changes, involving no more than minimal risk to the subject, will be reviewed by the expedited review procedure. (SOP RR 401-Expedited Review).

1.5 Significant New Findings

During the course of a study, the IRB may review reports generated from a Data and Safety Monitoring Board (DSMB), adverse event reports, current literature, and other sources to ascertain the status of the study and assess whether or not the risk/benefit balance is still acceptable. IRB will determine whether or not new information needs to be conveyed to subjects, or if a segment of the population may be bearing an undue burden of research risk or being denied access to promising therapy.

1.6 Reports From Employees, Staff and Faculty

It is the responsibility of the IRB staff and members to act on information or reports received from any source that indicate a study being conducted at any facility under the jurisdiction of the IRB could adversely affect the rights and welfare of research subjects.

1.7 Ensuring Prompt Reporting of Any Serious or Continuing Noncompliance with Applicable Regulations or the Requirements or Determinations of the IRB

All credible reports of inappropriate involvement of human subjects in research must be investigated by the OROC and referred to the IRB. The results of the investigation will be reported to the appropriate institutional official(s). Regulatory authorities or Sponsors may also be notified. Such reports of noncompliance may come from any source including IRB members, Investigators, subjects, institutional personnel, the media, anonymous sources or the public.

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB policies, is not in compliance with

federal regulations, or has been associated with unexpected serious harm to subjects. All such suspension and or terminations will be reported to the OHRP and FDA as appropriate. Minor infractions such as missing re-approval date for continuing review is not usually reported to other agencies. However, the study will be suspended during the time of non-approval.

2. SCOPE

These policies and procedures apply to all research submitted to the IRB.

3. RESPONSIBILITY

IRB Administrator is responsible for establishing the processes for conducting ongoing reviews of research.

IRB Chairperson (or designee) is responsible for preliminary assessments of adverse events, significant new findings and the need for third party verification.

4. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 812.64

21 CFR 56.108, 56.109, 56.113

45 CFR 46.103, 46.109, 46.115

FDA Information Sheets, 1998

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007

5. REFERENCES TO OTHER APPLICABLE SOPs

This SOP affects all other SOPs.

6. ATTACHMENTS

RR 403-A	IRB Reporting of Unexpected Internal Adverse Events
FO 301-C	Application for Revision and/or Amendment
RR 403-C	Site Visit Confirmation
RR 403-D	Site Visit Worksheet
RR 403-E	Site Visit Report

7. PROCESS OVERVIEW

All approved projects (expedited or full board) are required to submit a progress report at the time assigned within the approval letter received by the principal investigator for the project. These projects will be reviewed annually or more frequently as determined by the IRB. Appropriate action will occur upon receipt of the progress report even if approval has already expired. [During the expired period, the project may not enroll subjects and no activity may occur except for the health and safety of currently enrolled participants.] These actions may be continuing approval, approval upon recommended changes, suspension for cause, or termination for cause.

At times determined by the OROC, study sites may be reviewed by means of a site visit. Such site visits may result in review of documentation and/or review of informed consent process.

In the event of a Serious and/or Unexpected Adverse Event, the investigator is required to report the Adverse Event to the IRB as soon as possible, but no later than five (5) working days after the event.

8. PROCEDURES EMPLOYED TO IMPLEMENT THIS POLICY

A. Site Visits and Third Party Verification

Who	Task	Tool
<i>IRB Administrator or IRB Coordinator</i>	Call Investigator or contact key site personnel to set up a day and time to conduct a site visit. Three days prior to the site visit, confirm the date and time.	Site Visit Confirmation Letter
<i>IRB Administrator and/or Site Visitor, if indicated</i>	Bring a complete copy of the site's most recently approved protocol along with any current revisions and/or amendments, informed consent document, and any adverse event reports submitted. Confirm that the study is being conducted in compliance with the information provided on these documents by observation if possible, especially: the method of subject recruitment, and in particular, that there are safeguards in place for the recruitment of subjects vulnerable to coercion or undue influence, the process of obtaining informed consent, the consent form being used, the facilities available in an emergency. If appropriate, obtain information about any adverse events that may have been reported. If appropriate, obtain information about any adverse events that may not have been reported. If project is inactive, suspended, or terminated, obtain information regarding this status. Complete the Site Visit Report and submit it to the IRB Administrator if visit conducted by site visitor other than the IRB Administrator.	Site Visit Worksheet Site Visit Report
<i>IRB Administrator</i>	Provide Site Visit Report to the IRB Chairperson for review. Include discussion of site visit in agenda for next IRB meeting.	
<i>IRB Chairperson</i>	Review Report and determine any necessary follow-up action.	
<i>IRB Administrator</i>	Provide the Institutional Official with a summary report of the findings.	

B. Serious and/or Unanticipated Adverse Events

Who	Task	Tool
<i>IRB Coordinator</i>	<p>A report of an internal Serious Adverse Event should be submitted electronically to the IRB.</p> <p>For internal Serious Adverse Event Reports, a copy of the report is immediately faxed to the IRB Chairperson.</p> <p>For external Serious Adverse Event Reports - The IRB will no longer accept individual external serious adverse event reports. The investigator is to promptly submit to the IRB only the summary analysis reports (or aggregated adverse event information) from the sponsor's DSMB/DMC or other monitoring entity.</p> <p>Attach all information related to the adverse event to the report and give to the IRB Administrator for review.</p>	Serious Adverse Event Report(s) – Internal or External
<i>IRB Administrator</i>	Review all serious or unexpected adverse event reports received. Triage, if necessary and give to the IRB chairperson for review.	
<i>IRB Chairperson or designee</i>	Review AE reports. If the reviewer determines that action may be needed to protect the safety of research subjects due to the nature or frequency of reported adverse events, he/she may take such action and/or the full IRB or designated subcommittee will review the adverse events and study in question to determine action, if any, by IRB.	Adverse Event Report
<i>IRB Coordinator</i>	Report all safety reports and serious adverse events on the agenda for the next convened meeting.	

C. Unanticipated Problems

Who	Task	Tool
<i>IRB Coordinator</i>	<p>A report of an unanticipated problem should be submitted to the IRB electronically.</p> <p>Upon receipt, date-stamp the current date on the upper right corner of the report.</p> <p>Attach all information related to the unanticipated problem and give to the IRB Administrator for review.</p>	
<i>IRB Administrator</i>	Review all unanticipated problem reports received. Triage, if necessary and give to the IRB chairperson for review.	

<i>IRB Coordinator</i>	Produce summaries of all unanticipated problems and place on the agenda for the next convened meeting.	
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D. Amendments

Who	Task	Tool
<i>IRB Coordinator</i>	<p>The OROC may be informed of an amendment or change in the research via fax, mail/delivery, or internet. Regardless of the method of initial reporting, the investigator is required to submit a signed original Application for Revision and/or Amendment Form.</p> <p>Upon receipt, date-stamp the current date on the upper right corner of the report.</p> <p>Attach all information related to the amendment to the study file and give to the IRB Administrator for initial review.</p>	Application for Revision and/or Amendment Form
<i>IRB Administrator</i>	Review all amendments received. Triage to determine which can be reviewed via expedited review, which must be reviewed by the IRB Chairperson (or designee) immediately, and which are to be placed on the agenda for the next meeting.	
<i>IRB Coordinator</i>	Complete processing as instructed by the Administrator. Add all amendments to the agenda for the next convened meeting.	

E. Reports of Noncompliance

Who	Task	Tool
<i>IRB Administrator or IRB Coordinator</i>	<p>A report of non-compliance may be received via fax, mail/delivery, phone, internet, or noted during a site visit.</p> <p>Upon receipt or written report, date-stamp the current date on the upper right corner of the report.</p> <p>If notified by phone, record the information conveyed (including contact information and date).</p> <p>Attach all information to the appropriate study file and give to the IRB Administrator for review.</p>	
<i>IRB Administrator</i>	Review all reports received, obtain additional information if needed or available. Notify the IRB Chairperson and/or the Institutional Official, and the appropriate regulatory agencies/sponsor if serious or unusual.	