DHR HEALTH INSTITUTE FOR RESEARCH & DEVELOPMENT
POLICY AND PROCEDURE

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
	PAGE: 1
DEPARTMENT: DHR Health Institute for Research & Development	OF: 9
	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21, 03/22

Purpose:
During the conduct of human subject research, unanticipated events may occur. These events must be reported to the IRB using the form provided to investigators on IRBNet.

Events involving risk to human subjects or others must be reported as "Unanticipated Problems Involving Risk to Human Subjects or Others". This category includes serious adverse events (medical occurrences) which meet the definition of an unanticipated problem involving risk to human subjects or others. This category can also include protocol deviations/non-compliance (which will now be referred to as "non-compliance") or other unanticipated problems that place subjects at risk of harm.

Non-compliance, which does NOT involve risk to human subjects or others may also need to be reported to the IRB. Incidents of non-compliance that adversely affect the rights and welfare of human subjects or significantly compromise the quality of the research data must be reported as "Non-Compliance". Incidents of non-compliance that do not meet this definition will not need to be reported to the IRB. However, logs can be maintained in the subject's research record or in a log maintained for the study and managed as part of the Data and Safety Monitoring Plan, as applicable. This documentation will be mandatory for research studies that are greater than minimal risk, meet the federal definition of a "clinical trial", and if required by the funding agency. It is strongly recommended that a log (or similar documentation) be kept for all other studies. This documentation should be made available upon request.

Applies To:
This policy applies to the following; staff and members of the IRB; potential research investigator; Physician staff employed by RMF and its affiliates; staff employed by DHR Health and its affiliates; faculty, fellows, residents, students of academic institutions with a current affiliation agreement with DHR Health Institute for Research & Development; staff and physicians of non-academic institutions with a current affiliation agreement with DHR Health Institute for Research & Development; Physicians with privileges to practice medicine in DHR Health, Physicians and staff employed by Starr County Memorial Hospital and its affiliates; faculty, fellows, residents, students of academic institutions with a current affiliation agreement with Starr County Memorial Hospital and its affiliates; staff and physicians of non-academic institutions with a current affiliation agreement with Starr County Memorial Hospital and its affiliates; Physicians with privileges to practice medicine in Starr County Memorial Hospital and its affiliates.

Management and Reporting of Unanticipated Problems Involving Risks to Human Subjects and Other Non-compliance
It is the policy of the DHR Health Institute for Research and Development Institutional Review Board to:

- Require the reporting of serious adverse events and unanticipated events which meet the definition of an "unanticipated problem involving risks to human subjects or others"
- Require reporting of non-compliance which:
    - significantly adversely effects the rights or welfare of participants or
    - significantly compromises the quality of the research data or
    - may represent serious and/or continuing non-compliance or is otherwise deemed reportable to the IRB

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
	PAGE: 2 OF: 9
DEPARTMENT: DHR Health Institute for Research & Development	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21, 03/22

- Review reports of non-compliance and determine which constitute serious or continuing non-compliance and/or an unanticipated problem involving risk to human subjects or others
- Fulfill reporting requirements to the appropriate entities (institutional officials, federal departments or agencies)

Definitions:

A. Adverse event: An unfavorable medical occurrence, which may include abnormal signs (for example, abnormal physical exam or laboratory finding), symptoms, or disease, temporally associated with, but not necessarily considered related to, the subject's participation in the research study. Not all adverse events meet IRB reporting guidelines.

B. Continuing non-compliance: Non-compliance that has been previously reported or a pattern of ongoing non-compliance that, in the judgment of the IRB, significantly adversely affects the rights and welfare of participants or significantly compromises the quality of the research data (i.e., negatively impacts the ability to draw conclusions from the study data).

C. External adverse event: An adverse event that occurs at a site external to the authority of the DHR Health Institute for Research and Development IRB and is reported to the investigator.

D. Internal adverse event: An adverse event that occurs at a site that falls directly under the authority of the DHR Health Institute for Research and Development IRB.

E. Non-compliance: Failure on the part of the investigator or any member of the study team to follow the terms of the IRB approved protocol or to abide by applicable laws or regulations, or DHR Health Institute for Research and Development IRB policies. This includes protocol deviations.

a) Incidents of non-compliance *on the part of research participants which do not involve risk* need not be reported to the IRB.

F. Possibly Related to the Research Intervention: In the opinion of the principal investigator, there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

G. Probably Related to the Research Intervention: In the opinion of the principal investigator, the incident, experience or outcome more likely than not was caused by the procedures involved in the research.

H. Serious Adverse Event or Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious non-compliance: Non-compliance that, in the judgment of the IRB, significantly adversely affects the rights or welfare of participants, or significantly compromises the quality of the research data. Examples of non-compliance that are considered to meet the definition of serious non-compliance include, but are not limited to:

a) performing non-exempt human subject research without obtaining prospective IRB approval
b) implementing substantial modifications to a research study without obtaining prospective IRB approval
c) failing to systematically obtain research subjects' informed consent as required by the IRB approved protocol
d) failing to comply with federal regulations governing human subject protections

I. Unanticipated: Unforeseeable at the time of its occurrence.

J. Unanticipated Problem Involving Risks to Human Subjects or Others: Any accident, experience, or outcome that meets all of the following criteria:
a) Unexpected in terms of nature, severity, or frequency;
b) Related, or possibly related, to a subject's participation in the research;
c) Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

K. Unanticipated Adverse Device Effect: Any serious adverse effect on health, safety or any life-threatening problem or death cause by, or associated with, a device, if that effect, or problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Reporting Responsibilities of the Investigator:

General Reporting requirements for unanticipated Adverse Events

Outlined below are the requirements for reporting to the IRB. Note that investigators may have additional reporting obligations as specified by the study sponsor or oversight agency. Investigators who serve as sponsor-investigators of an IND or IDE also have additional reporting obligations to the FDA. Sponsor-investigators must also maintain a log of adverse events. Maintenance of an adverse event log is a best practice for all clinical investigators.

Unless subject to different IRB reporting requirements by a federal agency, investigators must report to the IRB:

1. Internal Adverse Events that are (i) Unexpected, (ii) Related or Possibly Related to the Research Intervention, and (iii) serious or otherwise suggests that the research places the subject or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.
2. External Adverse Events that are (i) Unexpected; (ii) Related to the Research Intervention and (iii) Serious or otherwise suggests that the research places subjects or others at greater risk than was previously recognized.

General IRB Reporting timelines for adverse events

Adverse Events that meet the IRB's reporting requirements must be reported to the IRB office as follows:

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
	PAGE: 4
DEPARTMENT: DHR Health Institute for Research & Development	OF: 9
	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21, 03/22

Internal Adverse Events

- Internal Adverse Events which are unexpected, fatal or life-threatening, and related or possibly Related to the Research Intervention must be reported to the IRB within 24 hours of learning of the event. (Note: It is recognized that the information available during this 24-hour period may not be sufficient to permit accurate completion of the required adverse event reporting forms. However, the IRB should, at a minimum, be notified of the fatal or life-threatening internal adverse event during this time frame, with subsequent follow-up submission of a more detailed written report.)
- All other internal Adverse Events will be reported to the IRB within 10 working days of the investigator learning of the event.

External Adverse Events

- External Adverse Events which are Unexpected, Serious AND suggest that the research places subjects or others at greater risk than was previously recognized and Related to the Research Intervention will be reported to the IRB within 30 working days of their receipt by the DHR Health Institute for Research and Development investigator. (Note: Only sponsor-generated safety reports that meet the Adverse Event reporting of the IRB should be submitted to the IRB.)
- Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted to a monitoring entity for review and analysis.
- The report of the adverse event to the DHR Health Institute for Research and Development IRB should include confirmation as to whether the external site reported the event to their IRB and to a monitoring entity.
- The external adverse event reported to the IRB will be placed on a Committee agenda for review as determined by the IRB Chair.
- The IRB may act with regard to the local study in response to the external adverse event (e.g., suspend the local study enrollment, but will not report the event to a federal agency or sponsor, unless required by the local action).

General Reporting Requirements for Unanticipated Problems Involving Risk to Subjects or Others and Non-compliance

1. Unanticipated problems which meet the following definition of "any accident, experience or outcome" that meets all three of the following criteria must be reported:
   - unexpected in terms of nature, severity, or frequency;
   - related, or possibly related, to a subject's participation in 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;

   Examples of types of unanticipated problems that must be reported to the IRB include:
   - any accidental or intentional deviation from the IRB-approved protocol that involves risks (e.g., missed safety labs, incorrect dosing or labeling);

- any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a given research subject;
- any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected increase in the risk to benefit ratio of the research;
- any complaint of a subject that indicates an unanticipated risk or which cannot be resolved by the research staff;
- any other untoward event that affects the welfare or the privacy, confidentiality or other rights of research subjects or members of their family (e.g. lost or stolen research data);
- any other untoward event that presents a risk to investigators and research staff involved in the conduct of the research.

2. Incidents of non-compliance, which meet the following must be reported:
    - Failure on the part of the investigator or any member of the study team to follow the terms of an DHR Health Institute for Research and Development IRB approved protocol or to abide by applicable laws or regulations, or DHR Health Institute for Research and Development IRB policies that:
        - adversely affect that rights and welfare of human subjects, or
        - significantly compromises the quality of the research data. Incidents of non-compliance on the part of research participants which do not involve risk need not be reported to the IRB (i.e., failure to turn in medication diary).

    Examples of non-compliance that must be reported to the IRB include (but are not limited to):
    - Performing non-exempt human subject research without obtaining prospective DHR Health Institute for Research and Development IRB approval;
    - Implementing protocol modifications without obtaining prospective IRB approval;
    - Initiating research activities prior to obtaining consent
    - Altering from the informed consent process as described in the IRB approved protocol
    - Having research activities performed by individuals who are not sufficiently trained or credentialed to perform the task.
    - Obtaining consent using an outdated consent form, when the new consent form contained new information that may have caused the subject to change their mind about participating;
    - Conducting research during a lapse in IRB approval;
    - Not adhering to inclusion/exclusion criteria;
    - Enrolling more subjects than were approved in the protocol of a greater than minimal risk study;
    - Performing research at an unapproved site:
    - Failure on the part of IRB staff involved in research review or oversight to abide by applicable laws or regulations, or DHR Health Institute for Research and Development IRB policies.
3. Incidents of non-compliance which are not required to be submitted to the IRB:
    Incidents of non-compliance which do not meet criteria for reporting should be logged in real time and should be available upon request. An example of a non-compliance log is available on the Office of Human Research Protection Program website. The IRB expects that the investigator and study team

will regularly monitor the log.

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
	PAGE: 6 OF: 9
DEPARTMENT: DHR Health Institute for Research & Development	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21 ,03/22

Non-Compliance Log requirements are mandatory for:

- Greater than minimal risk studies
- Studies that meet the federal definition of a "clinical trial"
- Studies for which reporting is required by the funding agency

Non-Compliance logs are not required to be submitted at annual review but must be available upon request. Failure to maintain a log as required may be determined by the IRB to represent serious or continuing noncompliance.

Non-Compliance Logs are recommended but non-mandatory for all other studies.
Examples of non-compliance that are not reportable but should be documented in a log:

- Obtaining consent using an outdated consent form when there were no substantive differences between the consent form that was used and the consent form that should have been used (i.e., dates in the footer)
- Protocol deviations that do NOT adversely affect the rights and welfare of human subjects or significantly compromise the quality of the research data

- Subject non-compliance that doesn't involve risk or alter the data
- Performing non-safety related research procedures outside the protocol specified window, i.e., involuntarily administering a questionnaire outside of the protocol specified window.

General Reporting Timelines for Unanticipated Problems Involving Risk to Human Subjects or Others and Non-Compliance:

Investigators are to submit all Unanticipated Problems Involving Risks to Human Subjects or Others that are Possibly or Definitely Related to the research and incidents of reportable Non-compliance within 10 working days of the investigator becoming aware of the reportable event/reportable new information.

Responsibilities of the IRB:

Internal and External Adverse Events

Internal Adverse Events (IAE) and External Adverse Events (EAE) reported to the DHR Health Institute for Research and Development IRB are received and processed promptly.

Adverse events that meet the DHR Health Institute for Research and Development IRB's definition of an "unanticipated problem involving risk to human subjects or others" may be brought to the attention of the IRB Chair or, in his/her absence, the Co-Chair. In processing adverse events that appear to meet the IRB's definition of an unanticipated problem involving risks to human subjects or others, the Human Research Protection Program Administrator will:

- Place the events on the agenda for review at the next convened IRB meeting. If there are potential risks to subjects which require action prior to a convened meeting, an emergency meeting may be convened (with the members attending either in person or via teleconference) or in exceptional safety circumstances, the Chair has the authority to suspend some or all of the

research activities. When this authority is exercised by the Chair, it will be reported at the next

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
DEPARTMENT: DHR Health Institute for Research & Development	PAGE: 7 OF: 9
	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21 ,03/22

convened IRB meeting.

- Perform a retrospective review of adverse events reported for the research protocol. If the adverse event was reported by the investigator as being related to a research intervention, then an assessment of the adverse events across other research protocols involving the same experimental intervention will be performed.
- Make an initial determination as to whether protocol and/or consent form modifications are required to address the reported adverse event. In making this determination, the Human Research Protection Program Administrator will take into consideration the severity of the event, the number of reports describing the same or similar event, and the current consent form and research protocol risk statements.

Unanticipated Problems Involving Risk to Subjects or Others

- Unanticipated problems received or identified by the Office of Human Research Protection Program are brought to the attention of the IRB Chair, or in his absence, the Co-Chair.
- The IRB Chair (or Co-Chair) will determine if the report of an unanticipated problem contains complete information that will allow an adequate review for human subject protections. If, in the opinion of IRB Chair (or Co-Chair), the information is incomplete, s/he may request appropriate additional information from the individual submitting the report.
- The IRB Chair (or Co-Chair) will review the corrective action plan provided by the investigator and will determine if the plan is appropriate. If the corrective action plan is found to be inadequate in the opinion of the IRB Chair (or Co-Chair), s/he may request changes to the corrective action plan.
- The IRB Chair (or Co-Chair), will determine if the reported unanticipated problem may involve a risk to human subjects or others or non-compliance with the federal regulations or the requirements or determinations of the IRB.
- Unanticipated problems that may represent an “unanticipated problem involving risks to human subjects or others,” “serious non-compliance” or “continuing non-compliance” as defined above, will be referred to a convened IRB meeting.
- For those reports that clearly do not represent either i) an unanticipated problem involving risks to human subjects or others, ii) serious non-compliance, or iii) continuing non-compliance, the IRB Chair or designee will determine if any additional actions are warranted and, if applicable, will communicate that in writing to the individual who initiated the report.
- The unanticipated problem report, the determination of the IRB Chair (or Co-Chair), and a record of the requested actions, if applicable, will be documented in the IRB file.
- Failure to comply with actions requested by the IRB Chair (or Co-Chair), in the absence of a suitable justification, constitutes an unanticipated problem of non-compliance and will be brought to the attention of the convened IRB committee.

SUBJECT: Serious Adverse Events, Unanticipated Problems and Non-Compliance	Policy #: CRP-1028
	PAGE: 8 OF: 9
DEPARTMENT: DHR Health Institute for Research & Development	EFFECTIVE: 02/19
APPROVED BY: Sohail Rao, MD, D.PHIL, President & Chief Executive Officer (Institutional Official, OHRP, DHHS)	REVIEWED/REVISED: 02/19, 02/20, 11/20, 01/21, 04/21, 05/21, 03/22

Management of Research Participant Complaints

It is the policy of the DHR Health Institute for Research and Development IRB to investigate all complaints or concerns reported by study participants to the IRB.

All consent documents must include telephone numbers for the principal investigator so that participants can call if they have questions, concerns or complaints.

The IRB will investigate all participant complaints received and will complete the Documentation of Patient/Subject Complaint Form. Actions taken to resolve complaints might include referring the complaint to:

- the Human Research Protection Program Administrator;
- the Principle Investigator;
- the IRB via the electronic submission process.

The Office of Human Research Protection Program maintains files of research subject complaints as well as the actions taken by the IRB Office staff, IRB committee, or investigators to resolve such complaints. Such files are maintained until 3 years following termination of IRB approval of the research study.

Distribution of Information, Review Assignment and Presentation to a Convened IRB Committee:

A. Adverse Events that are Unanticipated Problems

All members of the convened committee will have access to the following:

- the adverse event report;
- the IRB-approved research protocol and consent documents;

Each adverse event will be assigned to two primary reviewers with relevant scientific expertise.

The primary reviewers will summarize the adverse event and their decision or, in the event of disagreement, propose alternate actions. After the presentation from the primary reviewers, all members of the convened committee will be given the opportunity to comment on the recommendations.

B. Unanticipated Problems and Non-compliance

All members of the convened Committee will have access to the following:

- all available documentation regarding the reported unanticipated problem
- the IRB-approved research protocol and consent documents, if necessary;

No primary reviewer system will be utilized for reviewing unanticipated problems involving risk to human subjects or others (that are not adverse events) or Non-compliance.

All cases of non-compliance will be summarized by the IRB Chair or Co-Chair. All members of the convened committee will be given the opportunity to comment on the recommendations.

C. IRB Vote and Documentation in the Meeting Minutes

The IRB will determine the recommended actions, call for a vote and document the outcome in the Committee minutes. The IRB votes as to whether the event represents an unanticipated problem

involving risks to human subjects or others, serious non-compliance and/or continuing non-compliance. This vote will be recorded in the meeting minutes. If the IRB votes to suspend or terminate the research study, the reasons for the suspension or termination will be documented.