

# The Carle Foundation Research Policy 108

<b>Subject</b>	Reporting Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others, and Noncompliance		
<b>Approval</b>	Feb 2011	<b>Review</b>	<b>Revision</b>
<b>Purpose</b>	To describe the requirements for reporting adverse events, unanticipated problems involving risks to subjects or others, and noncompliance to The Carle Foundation officials, IRB(s) of record, sponsor(s), and regulatory agencies when appropriate.		

## Statement of Policy

1. This policy applies to all non-exempt research performed at The Carle Foundation and to the Principal Investigator and other key research personnel.
2. The Principal Investigator is responsible for ensuring the proper reporting of safety issues, including adverse events, unanticipated problems involving risks to subjects or others or noncompliance issues that arise during the course of a research study. Proper reporting means in accordance with the requirements of The Carle Foundation, IRB of record, sponsor (funding agency), and the appropriate regulatory agencies.
3. The Institutional Official is responsible for ensuring prompt reporting to appropriate institutional officials, OHRP, FDA, if applicable, and any sponsoring federal department or agency head of events meeting the following criteria:
  - a. Any unanticipated problems related or possibly related to the research that places subjects or others at a greater risk of harm;
  - b. Any serious or continuing noncompliance with the regulations or requirements of the IRB; and
  - c. Any suspension or termination of IRB approval for research.
4. If the Principal Investigator is also the sponsor of a research study, there may be additional reporting requirements such as to the FDA.

## Definitions

**Adverse Event** – 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.

**Continuing Noncompliance** – A pattern of non-compliance that if allowed to continue is likely to increase risks to subjects, adversely affect the rights, welfare and safety of research subjects, or adversely affect the scientific integrity of the study. Examples of continuing non-compliance include: repeated instances of allowing a study to expire before it is re-approved; repeated failure to respond to The Carle Foundation's inquiries or requests for documentation; or repeated failure to respond to and resolve any study contingencies.

**Investigational Agent** – Drug or device that is part of the research protocol, which could include placebo.

**Key Research Personnel** – Investigators and other individuals who contribute to the scientific development or execution of a research study or research project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. These individuals participate in the conduct, reporting, supervision and management of human subjects' research.

**Noncompliance** – Failure to follow the regulations, institutional policies governing human subjects' research, or requirements or determinations of the IRB. This may pertain to the investigator, the research staff, The Carle Foundation officials, the IRB of record, and the IRB administrative staff.

**Principal Investigator** - The investigator/ researcher who is responsible for the conduct of a research study at an institutional site.

**Serious Adverse Event** – Any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred),
3. Results in inpatient hospitalization or prolongation of existing hospitalization,
4. Results in a persistent or significant disability/incapacity, or
5. Results in a congenital anomaly/birth defect.

Based upon appropriate medical judgment, a Serious Adverse Event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

Serious adverse event is interchangeable with serious adverse experiences.

## Definitions (cont.)

**Serious Noncompliance** – Non-compliance that creates an increase in risk to subjects, adversely affecting the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study. Willful violation of policies, state laws, and/or federal regulations may also constitute serious non-compliance.

**The Carle Foundation** – Includes all legal entities part of The Carle Foundation such as Carle Foundation Hospital, Carle Physician Group, Mills Breast Cancer Institute, and Carle Cancer Center.

**Unanticipated Problem** – Although federal regulations require prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others, the phrase is not defined in either HHS or FDA regulations. In January 2007, OHRP released new guidance to assist IRBs in fulfilling this requirement. According to the guidance document OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

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; **and**
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 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.

## Procedure

1. Reporting Requirements for Studies Utilizing Carle Institutional Review Board (IRB) for Study Oversight:
  - a. Refer to Carle *IRB Policy 801 Unanticipated Problems and Other Events Requiring Prompt Reporting* for reporting requirements.
  - b. Any reports sent to Carle IRB will also be routed to the institution's Human Protections Administrator for further evaluation and forwarded onto the Institutional Official when necessary for reporting.
2. Reporting Requirements for Studies Utilizing an External (non-Carle) IRB for Study Oversight:
  - a. The Principal Investigator must adhere to the policies for the external IRB having oversight of the research as well as this policy in reporting unanticipated problems to the Human Protections Administrator.
  - b. Identifying Reportable Events. In more than minimal risk studies, the Principal Investigator is expected to have a mechanism to identify and capture any adverse events.
  - c. Reporting to Human Protections Administrator.

If an **Unanticipated Problem occurs**, the Principal Investigator must report, in writing, this to the Human Protections Administrator within 10 working days of becoming aware of the event. This information about the incident can be submitted either using the form found in Attachment A or in a written format that provides the same information. Severe adverse events that are unexpected and possibly related to participation in the research should be reported with more urgency. In addition, the Principal Investigator needs to determine whether the IRB with oversight of the study and the study sponsor also needs to be contacted. **Reporting any unanticipated problems or unexpected adverse events to the Human Protections Administrator does not take the place of any reporting that is required by the IRB overseeing the conduct of the research.**

Principal investigators must also report each event of **serious or continuous noncompliance** relating to human subjects research within 10 working days using the form in Attachment A or in a written format that provides the same information.

Even if the event is not thought to be reportable by the IRB, the Human Protections Administrator may determine the event is reportable from an institutional perspective.

- d. The Principal Investigator or designee shall maintain documentation of all safety reports and responses.
- e. In situations where individuals are concerned that appropriate reporting has not occurred, the Human Protections Administrator can be notified directly or anonymously through the Carle Ethics and Compliance Alertline at (888) 309-1566 or via email through the C-Web The Human Protections Administrator, in consultation with the Institutional Official, the VP of Research and Chief Academic Officer, and other experts as necessary, will determine if further investigation and/or corrective action are required. The Human Protections Administrator will ensure that any required investigation is timely and properly conducted and that any corrective action plan is developed and implemented.
- f. If any event is determined to fall within the prompt reporting guidelines for either OHRP or FDA, the Institutional Official will report to the appropriate agency within a month of receiving the report. The sponsor and IRB with oversight will be copied on the report.

**Procedure (cont.)**

- g. If at any time the Institutional Official determines that research subjects are being placed at additional risk, the Institutional Official must take action such as request extra safeguards, suspend, or terminate the research.

**Attachment(s):**

Attachment A: Reportable Events Evaluation Form to Human Protections Administrator

**References**

21 CFR 56, 312, 812

45 CFR 46.103

International Conference on Harmonization: Good Clinical Practice Consolidated Guideline, 62 Fed. Reg. 25692 (May 9, 1997)

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007 ([www.hhs.gov/ohrp/policy/AdvEvtGuid.htm](http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm))

FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs-Improving Human Subject protection, January 2009

Carle IRB Policy 801 Unanticipated Problems and Other Events Requiring Prompt Reporting

OHRP Compliance Oversight Activities: Significant Findings and Concerns of Noncompliance (October 12, 2005)

OHRP's Compliance Oversight Procedures for Evaluating Institutions (October 14, 2009)

**Electronic Approval on File**

Supersedes CCA Policies 5308 and 5309. No similar policy in effect for CFH.

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**Reportable Events Evaluation Form**

Date of Event: \_\_\_\_\_  
Subject Initials: \_\_\_\_\_  
Subject Clinic #: \_\_\_\_\_  
Subject Protocol ID: \_\_\_\_\_

Date of Notification: \_\_\_\_\_  
Protocol: \_\_\_\_\_  
IRB Protocol #: \_\_\_\_\_  
Subject Status: \_\_\_\_\_

**CRA Section:**

1. Describe the event/problem.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

2. Is the study federally funded?

Yes                      No

3. Is this study FDA regulated?

Yes                      No

4. Is there documentation regarding an IND or IDE decision by the FDA?

Yes                      No  
IND or IDE # \_\_\_\_\_

5. Does a Carle Investigator hold the IND or IDE?

Yes                      No

Comments:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Reporting CRA / Study Coordinator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Investigator Section:**

6. Is the event 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, or the Investigator Brochure; and (b) the characteristics of the subject population being studied?

Yes                      No

7. Is there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices, activities or procedures involved in the research?

Yes                      No

8. Does the event suggest 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?

Yes                      No

If **No**, please explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

9. Would you suggest a change to the consent or protocol because of this event/problem?

Yes                      No

If **Yes**, describe change: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

10. According to OHRP guidelines, is this event an unanticipated problem?

*(In order to circle yes here then questions 6, 7 and 8 above must be answered yes)*

Yes                      No

11. Does the event constitute serious non-compliance with a regulation, the protocol, or any direction or instruction of the supervising IRB? **(Note: Dosing errors, enrollment of an ineligible subject and failure to obtain informed consent unless waived by the supervising IRB are always considered "serious non-compliance." Also, an event need not pose risk to the subject or others to be considered "serious.")**

Yes                      No

12. Does the event constitute continuing non-compliance with a regulation, the protocol, or any direction or instruction of the supervising IRB? **(Note: The event or series of events need not pose risk to the subject or others, nor need it be serious non-compliance to constitute "continuing non-compliance." For example, performing a lab test a day or two out of range may not pose risk to the subject, and doing so probably would not be considered "serious non-compliance." But, repeatedly performing the lab test a day or two late would be considered "continuing non-compliance.")**

Yes                      No

Corrective Action/Additional Comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Treating Investigator Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**Study Principal Investigator Section**

I have reviewed this information and am aware of this event.

Comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Study PI Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**Research Internal Use Only**

Reported to HPA	Yes	or	No	Date: _____
Reported to OHRP	Yes	or	No	Date: _____
Reported to FDA	Yes	or	No	Date: _____
Reported to Sponsor	Yes	or	No	Date: _____
Reported to IRB	Yes	or	No	Date: _____

IRB of Record: \_\_\_\_\_

Discussed with appropriate department coordinators and staff members: \_\_\_\_\_

Staff Education Sheet Required/Completed: \_\_\_\_\_

Corrective Action on file in Research Office: \_\_\_\_\_