

## Research Policy IRB801

<b>Subject</b>	Unanticipated Problems and Other Events Requiring Prompt Reporting
<b>Department / Location</b>	Research / Carle Institutional Review Board (IRB)
<b>Owner</b>	Manager of Human Subject Protection
<b>Stakeholder/ Reviewer(s)</b>	
<b>Approver(s)</b>	Manager of Human Subject Protection; Executive Director of the Research Institute; VP of Research and Chief Academic Officer
<b>Review Frequency</b>	Yearly
<b>Effective Date</b>	12/06
<b>Review Date</b>	04/11; 08/29/11
<b>Revision Date</b>	04/11; 08/29/11

### Purpose

- A. To clarify the requirements for reporting unanticipated problems, protocol changes made to research without IRB approval to eliminate apparent immediate harm to subjects, protocol violations, noncompliance, and other reportable events to Carle IRB in order to protect the rights and welfare of individuals participating in research.

### Definitions

- A. **Approved Terminology – AD100A (future link)** is a glossary of common terms that can be used in P & P's without defining them in the document.
- B. **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.
- C. **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.
- D. **External Event**– Events occurring at sites in the clinical study where the Carle IRB has no oversight responsibilities.
- E. **Human Subjects Protection Office (HSP)** – Human Subjects Protection office at Carle, which supports the Carle IRB administratively.
- F. **Internal Event**– Events occurring at sites where the Carle IRB has oversight responsibility for the research.
- G. **Minor Protocol Violation** – Any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB of record and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.
- H. **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.
- I. **Principal Investigator** – The investigator/ researcher who is responsible for the conduct of a research study at an institutional site.
- J. **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.
- K. **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.
- L. **Protocol Violation** – Any accidental, unintentional or intentional deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data.

**M. 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;
5. Results in a congenital anomaly/birth defect; or
6. Based upon appropriate medical judgment, 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 severe adverse experiences.

**N. Unanticipated Adverse Device Effect** – Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**O. 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.

**Statement of Policy**

- A. Principal Investigators are required to promptly report to Carle IRB any unanticipated problems involving risks to subjects or others, including any adverse events or situations of noncompliance. The timeline for reporting to the Carle IRB is specified in the following procedures for prompt reporting.
- B. The Principal Investigator is responsible for ensuring that all reporting obligations required by the protocol and the sponsor of the research are satisfied.
- C. Carle IRB must ensure that risks to subjects and others are minimized. Carle IRB must also ensure that certain incidents are promptly reported to Office for Human Research Protections (OHRP), including (a) any unanticipated problems involving risks to subjects or others, (b) any serious or continuing noncompliance with Department of Health and Human Services (HHS) policy or the requirements or determinations of the IRB; and (c) any suspension or termination of Carle IRB approval.

**Procedure**

**A. Prompt Reporting of Events to the Carle IRB**

1. **The Principal Investigator must report to the Carle IRB within five (5) working days** of becoming aware of the following events:
  - a. Any serious adverse event (defined above) determined by the Principal Investigator to constitute an Unanticipated Problem (defined above).
  - b. Changes to the protocol and conduct of the research made without IRB approval to eliminate apparent immediate harm to subjects.
  - c. Any departure from the protocol (violation or deviation) that causes harm to subjects or others, places them at increased risk of harm, impacts the scientific integrity, and/or has the potential to recur or represent possible serious or continuing noncompliance with the applicable federal regulations, guidance or IRB policies.
2. **The Principal Investigator must report to the Carle IRB within ten (10) working days** of becoming aware of the following events:
  - a. Any event determined by the Principal Investigator to constitute an Unanticipated Problem but **do not** meet the definition of a "serious adverse event."
  - b. Breach of confidentiality.

- c. Incarceration of a subject in a protocol not approved to enroll prisoners.
- d. Information indicating an unexpected change to the risks or potential benefits of the research such as a publication, interim analysis, safety monitoring report, or updated investigator's brochure.
- e. Reports from a clinical study monitoring body [such as a sponsor, coordinating center, or Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)] of external adverse events that the monitoring body or investigator have determined to constitute Unanticipated Problems.
- f. Changes in FDA labeling or withdrawal from marketing of a drug, biologic, or device used in the research.
- g. Subject complaints that indicate that the complaint could constitute an Unanticipated Problem, or an event which cannot be resolved by research staff.
- h. Administrative hold by an investigator or sponsor (sponsor-imposed suspension) due to risk.
- i. Observed or apparent serious or continuing noncompliance with protocol requirements or IRB policies.
- j. Any additional reporting requirements specified by the IRB as a condition of approval.

### 3. Reporting and Submission Process

- a. Any reports to the Carle IRB for events listed above should be reported using the Carle IRB *Prompt Reporting Form* and submitted to the IRB via IRBNet within the required timeframe.
- b. Supporting documentation may be submitted along with the *Prompt Reporting Form*. Examples of this documentation may include: case report forms, DSMB/DMC reports, updated investigator brochures, amendment applications with revised protocol or consent form, and/or sponsor communications.

## B. Review of Reportable Events by the Carle IRB

### 1. Initial Review by the Carle HSP Office

- a. The HSP staff reviews the reports for completeness. If necessary, the HSP staff may contact the Principal Investigator for further explanation for incomplete reports or those requiring modification or additional information.
- b. The HSP staff shares all Prompt Reporting Form submissions to the Carle IRB chair or designee and all other IRB members via IRBNet, the electronic submission system used by the Carle IRB. The Chair (or designee) is provided with Carle IRB *Prompt Reporting Form*, any supporting documents and the protocol file, which includes the currently approved protocol, consent form, investigational brochure and previous reports of Unanticipated Problems in the clinical study.

### 2. IRB Chair Review

- a. The Carle IRB Chair (or designee) considers whether the event meets the criteria for an Unanticipated Problem and addresses any concerns raised by IRB members. After reviewing the materials, the Chair (or designee) documents the results of the review and all determinations. This is added to the protocol file, communicated to the investigator and the Human Protections Administrator in writing, and reported to Carle IRB and via the agenda for convened IRB review at the next meeting.
- b. Preliminary assessments by the Chair (or designee) prior to referral to and review by the convened IRB may include:
  - Additional information and/or supporting documents are needed in order to adequately review the event;
  - The event likely does **not** meet the criteria of an Unanticipated Problem;
  - The event likely represents an Unanticipated Problem **and** the event does **not** modify the prior determination by Carle IRB that risks to subjects are minimized and that risks to subjects (or others) are reasonable in relation to anticipated benefits, if any, to subjects. (45 CFR 46.111(a));
  - The event likely represents an Unanticipated Problem **and** the event **does** have the potential to modify the prior determination by Carle IRB that risks to subjects are minimized and that risks to subjects (or others) are reasonable in relation to anticipated benefits, if any, to subjects.
  - Referral to the convened IRB is required; or
  - No further action is required.
- c. The IRB Chair must also refer the following reports to the convened IRB:
  - Subject complaints, including those that constitute Unanticipated Problems;
  - Protocol violations that harmed subjects or others;
  - Changes to a protocol made without Carle IRB approval to eliminate apparent immediate harm to subjects.
- d. For events that are referred to the Carle IRB, the Chair (or designee) may also determine if **emergency action is needed** to protect the rights and welfare of human subjects prior to the scheduled meeting of the convened IRB. Actions may include, but are not limited to:
  - Suspension of part (e.g. new subject recruitment) or all of the research (45 CFR 46.113);

- Emergency convening of the Carle IRB.

### 3. Convened IRB Review

- For any event referred to the convened IRB, the Chair (or designee) may assign one or more primary reviewer(s) to conduct a thorough review of the information and present the report to the convened IRB.
- Carle IRB members will receive and review, at a minimum:
  - *Prompt Reporting Form*;
  - Any supplemental or follow-up information provided about the event;
  - Protocol summary (with all members provided access to the complete protocol file);
  - Other documents as requested, such as the currently approved consent document, previous reports of Unanticipated Problems in the approved research study, or a complete protocol.
- Determinations by the convened IRB may include:
  - Additional information or modifications are needed before making a final decision;
  - The event does not meet the criteria for an Unanticipated Problem. Agreement with the Chair (or designee)'s preliminary recommendation that the event represents an Unanticipated Problem **and** does **not** modify the prior determination by Carle IRB that risks to subjects are minimized and that risks to subjects (and others) are reasonable in relation to any anticipated benefits to subjects. (45 CFR 46.111 (a)). Actions accompanying this final determination by the convened IRB will include documentation in the minutes and follow-up report with the investigator, and any other actions deemed appropriate by Carle IRB. Reporting by Carle IRB to the Institutional Official, Human Protections Administrator, VP of Research and Chief Academic Officer and by the Institutional Official to HHS/OHRP is required.
  - Corrective actions are warranted in order to protect the safety, welfare, or rights of research subjects or others. These corrective actions may include, but are not limited to:
    - Termination of the research;
    - Suspension of the research;
    - Modification of the information disclosed during the consent process;
    - Notification of current subjects when such information may related to the subject's willingness to continue participation;
    - Providing additional information to past subjects;
    - Requiring current subjects to re-consent using an approved modified consent form to continue to participate;
    - Alteration of the frequency of continuing review;
    - Monitoring of the research or the consent process;
    - Modification of protocol and research activities, including the monitoring process to ensure patient safety.
- For reports involving changes to the protocol made without Carle IRB approval to eliminate apparent immediate harm to subjects, the Carle IRB will review the event to determine (a) whether the change was necessary to eliminate apparent immediate hazards to the subject, and (b) whether there was insufficient time for Carle IRB review. If both of these conditions are not met, the incident also represents a protocol violation.
- The determinations and any Carle IRB stipulated actions are noted in the protocol file, meeting minutes, and are communicated to the investigator in written form.

### 4. Facilitated Review

- For studies reviewed and approved by the National Cancer Institute's Central IRB (NCI CIRB), the Carle IRB performs a facilitated review of local context information in accordance with Carle IRB Policy 414—Facilitated Review. The Carle IRB will review serious adverse events, unanticipated problems, and reports of serious or continuing noncompliance described in that policy in manner described in Sections B1-3 of this policy.
- The list of reportable events for studies undergoing facilitated review is located in Carle IRB Policy 414—Facilitated Review.

### C. Reporting to the Institutional Official, Human Protections Administrator, Regulatory Agencies, and Sponsors

- Any event determined to constitute (a) Unanticipated Problems, (b) suspension or termination of approval, or (c) serious or continuing noncompliance are reported to the Carle Institutional Official, Human Protections Administrator, Vice President of Research and Chief Academic Officer, as well as appropriate regulatory agencies (OHRP, FDA, etc.)
- Carle IRB will carry out all required reporting of events and IRB determinations to the Institutional Official, Human Protections Administrator, and Vice President of Research and Chief Academic Officer.

3. The Institutional Official (or designee) will carry out all required reporting to appropriate regulatory agencies and sponsors of the research.

**Attachments** N/A

**Other Related Links** N/A

**References**

- Carle IRB Policy 414—Facilitated Review
- OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (01/15/07)
- 45 CFR 46.103(b)(5);45 CFR 46.113
- FDA Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs - Improving Human Subject Protection. Final. (01/2009)
- 21 CFR 56.108(b); 21 CFR 56.113
- 21 CFR 312.66
- 21 CFR 812.150(a)(1)

**Electronic Approval on File**

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