

# The Carle Foundation

## IRB Policy 801

<b>Subject</b>	Unanticipated Problems and Other Events Requiring Prompt Reporting				
<b>Approval</b>	Dec 2006	<b>Review</b>	Jun 2009	<b>Revision</b>	Jun 2009
<b>Scope</b>	These policies and procedures apply to all clinical investigators, the Carle Foundation Institutional Review Board (IRB) and to all clinical research under the jurisdiction of the IRB.				
<b>Purpose</b>	To ensure the protection of the rights and welfare of individuals participating in research, and to describe procedures for ensuring compliance with required regulations				

### Statement of Policy

1. Investigators are required to report, (i) unanticipated problems involving risks to subjects and others, including certain adverse events, (ii) information involving noncompliance, and (iii) other information specified by applicable laws and by the IRB.
  - a. Specific Policy 1 of this Policy applies to non-exempt human subject research conducted or supported by HHS that is subject to HHS regulations (45 CFR 46). Based on policy and guidance provided by the HHS Office for Human Research Protection (OHRP), the Carle Foundation has set forth the requirements related to the review and reporting of unanticipated problems involving risks to subjects or others, as well as certain other events. It is the IRB's responsibility to ensure that risks to subjects are minimized and that risks to subjects or others are reasonable in relation to any anticipated benefits to subjects. [45 CFR 46.111(a)]. To ensure that the IRB meets its obligations, the investigator has responsibilities for reporting to the IRB. HHS guidance clarifies that only a subset of adverse events occurring in human subjects participating in research constitutes Unanticipated Problems that must be reported under 45 CFR 46. To determine if a problem, including an adverse event, is an Unanticipated Problem that must be reported to the IRB, the following hierarchical decision tree should be used: (1) Is the event unexpected? (2) If so, is it possibly related to participation in the research? (3) If so, does it suggest that the research places subjects or others at greater risk of harm than previously recognized? At this stage of the decision tree, the event would always be reported to the IRB.
  - b. In addition, it is the investigator's responsibility to determine if the clinical study is subject to regulation by the Food and Drug Administration (FDA). The obligations of the investigator are specific to FDA-regulated clinical studies [21 CFR 312, 21 CFR 812, 21 CFR 56, 21 CFR 50] and are not identical to the responsibilities of investigators who participate in non-exempt human subjects research conducted or supported by HHS (45 CFR 46). Required reporting under FDA regulations is addressed in Specific Policy 2. In studies regulated by the FDA, investigators have specific obligations to the IRB that include the reporting of all Unanticipated Problems involving risks to human subjects or others, including adverse events that constitute Unanticipated Problems. Investigators have additional reporting responsibilities to the IRB and the sponsor related to the protection of human subjects to ensure that the IRB and sponsor can comply with their obligations to FDA.

### Specific Policies

1. **Specific policies related to clinical studies subject to HHS policy that are not subject to FDA regulations.**
  - a. **Definitions**
    - **Unanticipated Problems Involving Risks to Subjects or Others (Unanticipated Problems):** Includes any incident, experience or outcome that meets **all** of the following criteria:
      - 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;
      - Related or possibly related to participation in the research (with *possibly related* meaning there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research); and
      - 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.
    - **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.
    - **Serious Adverse Event** – An adverse event that results in death, a life-threatening injury, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity/change in psychosocial status, a congenital anomaly or birth defect, or an outcome that jeopardizes the subject's health and may require a medical or surgical intervention to prevent one of these other outcomes.

## Specific Policies (cont.)

- **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.
- **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 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.
- **Internal** – Events occurring at sites where the Carle Foundation IRB has oversight responsibility for the research.
- **External** – Events occurring at sites in the clinical study where the Carle Foundation IRB has no oversight responsibilities.

### b. **Investigators must promptly report to the IRB any of the following:**

- Internal adverse events determined by the investigator to constitute Unanticipated Problems, such that the following three conditions are met: (a) the event is unexpected, (b) is related or possibly related to participation in the research and (c) places the subjects (or others) at a greater risk of harm than was previously known or recognized. Serious Adverse Events, as defined above, would meet the third condition relating to increased risk of harm.”
- External adverse events in a clinical study determined, by the investigator or the monitoring body, (sponsor, coordinating center or DSMB/DMC) to be an Unanticipated Problem (i.e. unexpected, related to participation in the research, and associated with a greater risk of harm than previously known or recognized).
- Unanticipated Problems that are **not adverse events** but that may involve risks to **research subjects or others**. Investigators must report an event that was not an adverse event but was (a) unexpected, (b) related or possibly related to participation in the research, and (c) placed the subject (or another party) at greater risk of physical harm than was previously known or recognized (As example, this includes risk of medical injury even if it did not actually occur, such as HIV exposure); or (d) placed the subject (or another party) at risk of nonphysical harm even if it didn't actually occur (as example, this includes identity theft, economic harm).
- Publication, interim analysis, safety monitoring report or updated investigator's brochure that indicates an unexpected change to the risks or benefits of the research;
- Change in FDA labeling or withdrawal from marketing of a drug, biologic or device used in the research;
- Subject complaints that indicate that the complaint could constitute an Unanticipated Problem, or an event which cannot be resolved by the research staff;
- Any change to the protocol and conduct of the research made without IRB approval that was done to eliminate **apparent immediate harm** to subjects;
- Protocol Violations that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity, have the potential to recur or represent possible serious or continuing noncompliance with the applicable federal regulations, guidance or IRB policies;
- Breach of confidentiality;
- Incarceration of a subject in a protocol not approved to enroll prisoners;
- Administrative hold by investigator or sponsor (sponsor imposed suspension);
- Observed or apparent noncompliance.

### c. **Expedited Reporting Timelines to the IRB**

- Reporting is required by the investigator within five (5) working days of becoming aware of the event for:
  - An internal serious adverse event, as defined above, regardless of whether it is an Unanticipated Problem, or was anticipated.
  - Changes to the protocol and conduct of the research made without IRB approval to eliminate apparent immediate harm to subjects.
  - Any Protocol Violation 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.
- Reporting is required by the investigator within ten (10) working days of discovering or being notified of the event for any other incidents listed in Section 1b.

### d. **Reporting to the IRB at Continuing Review**

- The investigator must ensure that adverse events and other problems involving risks to research participants that are known to the investigator, which do not require expedited reporting under C above (e.g., Minor

## Specific Policies (cont.)

Protocol Violations), are reported to the IRB at the time of continuing review of the study. This requirement includes adverse events that are anticipated or that constitute Unanticipated Problems.

### e. Protocol Reporting Requirements

- The investigator is responsible for ensuring that all reporting obligations required by the protocol and the sponsor of the research are satisfied.

### f. Reporting and Submission Processes

- The investigator should inform the IRB of a potential Unanticipated Problem, including those adverse events that constitute unanticipated problems, by submitting the **Carle Foundation IRB Prompt Reporting to the IRB form** to the Human Subject Protection (HSP) within five (5) working days of becoming aware of an occurrence listed in 1c, or within ten (10) working days for other incidents requiring prompt reporting.
- Examples of materials that should be submitted with the prompt reporting form include, when available, case report forms, DSMB/DMC reports, updated investigator brochures, amendment applications with revised protocol or consent form, or sponsor communications.
- Prior to processing the submission, the HSP staff ensures that (a) the report form is completed correctly, (b) reports of external adverse events include documentation indicating the event meets the criteria of an unanticipated problem, and (c) documentation (such as materials listed in 1f) are submitted.

### g. Initial Review by HSP

- The Human Subject Protection (HSP) staff reviews the reports for completeness and evaluates whether they meet the criteria for a reportable Unanticipated Problem, including those Unanticipated Problems that (a) are an adverse event that is also an Unanticipated Problem and (b) those that are **not adverse events** but that may involve risks to **human subjects** or **others**.
  - Incomplete reports or those requiring modification or additional information are returned to investigators with an explanation for revision.
  - The HSP screens the report to identify whether the event is (a) unexpected, (b) related or possibly related to participation in the research, and (c) suggests that the event caused harm or places the subjects or others at greater risk of harm or discomfort than was previously known or recognized.
- If the event is determined by the HSP **not** to meet the above 3 criteria, a letter is sent to the investigator with notice that the problem does not meet criteria for prompt reporting and whether other reporting requirements exist (i.e. continuing review). The IRB is notified of the HSP's action at the next scheduled meeting via the agenda.
- If the event is determined to potentially meet the criteria for an Unanticipated Problem, the HSP refers the submission to the IRB chair or designee.

### h. IRB Actions regarding Reporting and Review of Unanticipated Problems, including those which are Adverse Events

- The IRB must ensure that risks to subjects and others are minimized. The IRB must also ensure that certain incidents are promptly reported to HHS/Office of Human Research Protection, including (a) any unanticipated problems involving risks to subjects or others, (b) any serious or continuing noncompliance with HHS policy or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval. (45 CFR 46.103(a) and (b)(5)).
- An incident, experience or outcome that meets the three criteria set forth in the definition of Unanticipated Problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Illustrations of corrective actions or substantive changes that might need to be considered by the IRB in response to an Unanticipated Problem 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 participants when such information may relate 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

## Specific Policies (cont.)

- \* Monitoring of the research or the consent process
- \* Modification of protocol and research activities, including the monitoring process to ensure patient safety
- Following initial HSP-staff review of those events that potentially meet the criteria for Unanticipated Problems, the Chair (or designee) is provided with the Carle Foundation IRB *Prompt Reporting to the IRB* 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.
- The Chair (or designee) considers whether the event meets the criteria for an Unanticipated Problem. After reviewing the materials, the Chair (or designee) documents the results of the review and all determinations on the Unanticipated Problem Review Guide. This is added to the protocol file, communicated to the investigator, and reported to the IRB via the agenda for convened IRB review at the next meeting.
- 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 before making a determination that the event is an Unanticipated Problem that requires further review by the convened IRB; **Referral to the HSP staff occurs to acquire additional needed information;**
  - 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 the IRB that risks to subjects are minimized and that risks to subjects (and others) are reasonable in relation to anticipated benefits, if any, to subjects. (44 CFR 46.111 (a).);
  - The event likely represents an Unanticipated Problem **and** the event **does** have the potential to modify the prior determination by the IRB that risks to subjects are minimized and that risks to subjects (and others) are reasonable in relation to anticipated benefits, if any, to subjects.
  - **Referral to the convened IRB occurs for the 3 previous statements above.**
- Subject complaints, including those that are Unanticipated Problems, protocol violations, changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, and allegations of non-compliance also require referral by the Chair to the convened IRB.
- For events that are to be referred to the convened IRB, the Chair (or designee) will 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]. Actions may also include an emergency convening of the IRB by the Chair.
- 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 problem to the convened IRB.
- The IRB members of the convened IRB receive and review at a minimum:
  - Prompt reporting form;
  - Supplementary or follow-up information provided about the event;
  - Protocol summary (with all members provided access to the complete protocol file);
  - Current approved research protocol (primary reviewer(s) only);
  - Current approved consent document; and
  - Previous reports of Unanticipated Problems in the approved research study.
- For reports involving changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, the IRB will include a review and determination as to (a) whether the change was necessary to eliminate apparent immediate hazards to the subject, and (b) whether there was insufficient time for IRB review. If both of these conditions are not met, the incident also represents a protocol violation.
- 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 the IRB that risks to subjects are minimized and that risks to subjects (and others) are reasonable in relation to any anticipated benefits to subjects. (44 CFR 46.111 (a). Actions accompanying this final determination by the convened IRB will

## Specific Policies (cont.)

include documentation in the minutes and follow-up report with the investigator, and any other actions deemed appropriate by the IRB. Reporting by the IRB to the Institutional Official and by the Institutional Official to HHS/OHRP is required.

- A determination that an event represents an Unanticipated Problem **and** that the event **does** modify the prior determination by the IRB that risks to subjects are minimized and that risks to subjects (and others) are reasonable in relation to anticipated benefits, if any, to subjects. (44 CFR 46.111 (a)). If this determination is made, actions taken by the IRB will include documentation in the minutes and follow-up report with the investigator, and 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 participants when such information may relate 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.

Reporting by the IRB to the Institutional Official and by the Institutional Official to HHS/OHRP is required.

- The determinations and any IRB stipulated actions are noted in the protocol file and meeting minutes, and are communicated to the investigator.
  - The IRB also makes the determinations and, where it deems appropriate, stipulates actions for subject complaints that are not related to Unanticipated Problems, protocol violations, changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, and allegations of non-compliance. As described in Section I.H1, additional reporting by the IRB may be required to the Institutional Official and by this official to HHS and OHRP.
- i. **Events determined by the IRB to constitute (a) Unanticipated Problems, (b) the suspension or termination of approval, or (c) which represent serious non-compliance are reported to the Institutional Official and regulatory agencies, including HHS and OHRP, as required [45 CFR 46.103(a)].**
- The IRB will carry out all required reporting of IRB determinations to the Institutional Official.
  - The Institutional Official, or designee, will carry out all required reporting to regulatory agencies, including HHS and OHRP.
2. **Specific policies regarding Unanticipated Problems, including those that are adverse events, related to clinical studies that are subject to FDA regulations.**
- a. **Definitions:**
- **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 of information described in the investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed. (21 CFR 312.32)
  - **Unanticipated Adverse Device Effect (UADE)** – Any serious adverse effect on health or safety or 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 investigational plan or application (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects. (21 CFR 812.3(s))
  - **Unanticipated Problems** – Unanticipated Problems may be adverse events or other types of problems, i.e., certain adverse events are a subset of unanticipated problems. Unanticipated Problems are further defined below.
  - **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. (21 CFR 312.32)

## Specific Policies (cont.)

- **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. (21 CFR 312.32)
  - The Investigational New Drug (IND) regulations use the term *adverse effect* (21 CFR 312.64) and **adverse experience** (21 CFR 312.32). These terms are interchangeable with **adverse event**.
- b. **In clinical investigations of drugs and biologics conducted under an FDA-approved Investigational New Drug application (IND):**
- Investigators must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by the drug. If the adverse event is alarming, the investigator shall report the adverse effect immediately. (21 CFR 312.64(b)). The timing of prompt reporting is usually explicitly specified by the Sponsor in the investigational plan;
  - Sponsors must notify all participating investigators (and FDA) in a written IND safety report of “any adverse experience associated with the use of the drug that is both serious and unexpected” and “any finding from tests in laboratory animals that suggests a significant risk for human subjects. (21 CFR 312.32(c)(1)(i)(A),(B));
  - Sponsors must keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. (21 CFR 312.55(b));
  - Investigators must promptly report to the IRB all unanticipated problems involving risks to human subjects or others including adverse events that should be considered unanticipated problems. (§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66). For purposes of this Policy, such events will be termed Unanticipated Problems.
- c. **In clinical investigations of medical devices conducted under an FDA-approved Investigational Device Exemption application (IDE), or under an *abbreviated IDE for a not significant risk device*:**
- Investigators must report to the sponsor and to the reviewing IRB a report of any **unanticipated** adverse device effect (which is deemed to constitute an Unanticipated Problem) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a)).
  - Investigators must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator’s part of an investigation.
  - Investigators must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
  - Investigators must report use of the device when used without obtaining informed consent to the sponsor and IRB within 5 working days after use. No further such use may occur at the institution.
  - Investigators must notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Investigator must provide such notice to sponsor and IRB in no event later than 5 working days after the emergency occurred; in addition, further reporting may be required to the sponsor, FDA and IRB under this regulation. (21 CFR 812.150(a)(4)).
  - Investigators must, within 3 months after termination of the investigation or the investigator’s part of the investigation, submit a final report to the sponsor and the IRB.
  - Among other requirements, sponsors must conduct an evaluation of an unanticipated adverse device effect (UADE) and report the results to FDA and to all IRBs and investigators within 10 working days after receiving notification of the event. (21 CFR 812.150(b)).
- d. **For clinical investigations of drugs and biologics conducted under an IND, adverse events that are also Unanticipated Problems must be reported to the IRB.** Adverse events, including serious adverse events that are not Unanticipated Problems, do not require reporting to the IRB. Based on current FDA guidance, only those adverse events that meet one of the following 6 criteria should be considered Unanticipated Problems that are to be reported to the IRB.
- Single occurrence of a **serious**, unexpected, and uncommon event that is strongly associated with drug exposure;
  - A single or small number of a **serious**, unexpected event that is not commonly associated with drug exposure but is uncommon in the study population;

## Specific Policies (cont.)

- Multiple occurrences of an adverse event that, based on *aggregate* analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups in the drug treatment arm versus a control);
  - An adverse event that is described in the investigator's brochure, protocol, or informed consent documents, but occurs at a *specificity* or *severity* that is inconsistent with prior observations;
  - A **serious** adverse event that is described in the investigator's brochure, protocol, or informed consent documents, but for which there is a clinically significant increase in the *expected rate of occurrence* (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison);
  - Any other adverse event or safety finding, including those based on animal or epidemiologic data that would cause the sponsor to modify the investigator's brochure, protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.
- e. **How to Report Unanticipated Problems to the IRB in FDA-regulated drug, biologic product, and device studies**
- An investigator participating in a **multi-center study** may rely on the sponsor's assessment that an event is an Unanticipated Problem. The investigator may provide to the IRB a report of the Unanticipated Problem prepared by the sponsor and provided to the investigator;
  - The investigator, sponsor, and IRB may make an explicit agreement for the sponsor to report any Unanticipated Problem **directly** to the IRB. Such agreement must be incorporated into the IRB's written procedures. (21 CFR 56.108(b)(1), 56.115(a)(6)). If the investigator was copied on the report from the sponsor to the IRB, the investigator is not expected to provide the IRB with a duplicate copy of the report.
  - IRBs must follow written procedures to ensure that there is prompt reporting to the IRB, appropriate institutional officials, and FDA of any Unanticipated Problems, serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB, or any suspension or termination of IRB approval. (21 CFR 56.108(b)).
3. **Studies Subject to Both FDA and HHS Regulations**
- a. The FDA regulations regarding the protection of human subjects are separate from the HHS policy, also known as the Common Rule. The HHS regulations, which apply to non-exempt human subjects research conducted or supported by HHS that is subject to HHS regulations (45 CFR 46), do not supersede FDA regulatory obligations.
  - b. If the research project is non-exempt human subjects research conducted or supported by HHS **and** also subject to FDA regulations, both sets of regulatory obligations are applicable.

## Reference

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (01/15/07)  
45 CFR 46  
FDA Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs - Improving Human Subject Protection. Final. (01/2009)  
21 CFR 56 (Institutional Review Boards)  
21 CFR 312 (Investigational New Drug Application)  
21 CFR 812 (Investigational Device Exemptions)

## Approval On File

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