

## The Carle Foundation IRB Policy 802

<b>Subject</b>	Sponsor Responsibilities				
<b>Approval</b>	Dec 2006	<b>Review</b>	Jun 2009	<b>Revision</b>	Jun 2009
<b>Scope</b>	This policy applies to all research submitted to the Carle IRB.				
<b>Purpose</b>	To describe the responsibilities of the Sponsors of research.				

### Statement of Policy

1. The IRB shall expect and require that the Sponsor adhere to: (i) established ethical and regulatory mandates; (ii) federal, state, and local laws and regulations; (iii) applicable Carle Foundation Hospital policies and procedures; and (iv) Carle IRB policies and procedures. The Sponsor must have the ability to communicate efficiently and effectively with investigators who are participating in the sponsored research in order to communicate its commitment to abide by the above requirements. Sponsor's adherence to the above-cited laws, regulations, policies and procedures, and its communication to the Investigator, shall be demonstrated to the Carle IRB and evidenced via the protocol, clinical trial agreement, consent documents, and an Investigator's brochure.
2. This policy contains Sponsor requirements applicable to: (1) all research studies; (2) research conducted under an IND or NDA; (3) research under an IDE of a significant risk device; and (4) research using non-significant risk devices.

### Specific Policies

1. **All Clinical Trials/Studies.** For any and all types of clinical research, the protocol, clinical trial agreement, consent documents, and Investigator's brochure presented to the IRB for review and approval must evidence the Sponsor's commitment to adhere to and satisfy the requirements, duties and obligations outlined below.
  - a. **General Responsibilities of the Sponsor.** The Sponsor is responsible for selecting a qualified Investigator(s), providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), and ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols.
  - b. **IRB Review of Research.** The Sponsor shall require that clinical research must be reviewed and approved by the Carle IRB before any protocol mandated procedures or activities related to the research are initiated.
  - c. **Informed Consent.** The Sponsor shall require investigators to obtain informed consent from subjects prior to their enrollment into the research. The Sponsor shall require that investigators use the informed consent document approved by the IRB and use the forms only during the period for which they are valid. The Sponsor is expected to communicate serious breaches of the consent process to the IRB if it becomes aware of such breaches.
  - d. **Emergency Research.** The Sponsor shall monitor the progress of all investigations involving an exception to informed consent. The Sponsor also shall monitor such investigations to identify when the Carle IRB determines that it cannot approve the emergency research.
  - e. **Adverse Event Reporting.** During the approval period, the IRB must be immediately informed of any serious or alarming adverse events occurring during an IRB-approved drug/biologic study or any unanticipated adverse device effect caused by, or associated with, an investigational device, occurring during an IRB-approved device study. Reports regarding adverse drug/biologic or device events and reports of serious adverse events will be accepted in any format. Investigators or sponsors must also submit Sponsor-generated reports of adverse events occurring at other investigative sites.
  - f. **Changes in Approved Research.** Changes in approved research, during the period for which approval has already been given, may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to human subjects. If arrangements are made in advance, sponsors may submit amendments that affect the protocol directly to the IRB for review. Any changes that are implemented prior to IRB approval are considered protocol violations. The IRB may arrange for the Sponsor to distribute Approval Letters with the amendment to all sites participating in the protocol.
  - g. **Unanticipated Problems.** The Sponsor must inform investigators that all unanticipated problems must be reported to the IRB. An unanticipated problem is defined as any unforeseen event or events that may affect the safety or welfare of subjects, or that may affect the integrity of the research. Examples of an unanticipated problem include, but are not limited to: higher than expected adverse events, higher than expected subject drop out rate, higher than expected protocol deviation rate, or subject difficulty understanding the informed consent.
  - h. **Periodic Reports.** A research protocol is approved for no more than one year. However, the frequency of continuing reviews depends on the risks involved in the research. Investigators are responsible for requesting renewals before expiration of the approval period. A study may not continue, and an Investigator must cease enrolling participants, if an approval expires. Investigators or their designees and/or Sponsors are required to provide a periodic report regarding their study prior to the end of the approval period, and upon completion of the

## Specific Policies (cont.)

study. If the IRB requires interim reports at a greater than annual frequency, the Investigator is required to submit such interim reports within 14 days of the request.

- i. **Monitoring Reports.** As sponsors are required to monitor research sites, they are in a unique position to uncover information to which the IRB may not otherwise be privy. The IRB requires that the Sponsor provide the IRB, via the Investigator, with any information that may affect the rights and welfare of participants, or their willingness to continue participation. Such information may be contained within a monitoring report, or may be a summary of the Sponsor's assessment. The IRB will then work with the Investigator and Sponsor to rectify the situation.
2. **Research conducted using an investigational drug or biologic, or conducted under an IND or NDA.** In addition to the above requirements for all clinical research, the following requirements shall apply to clinical research conducted under an IND or an NDA:
    - a. **General Responsibilities of Sponsor.** The Sponsor is responsible for selecting a qualified Investigator(s), providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in an IND or IDE and protocol, maintaining an effective IND or IDE with respect to the investigations, and ensuring that FDA and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug. For studies conducted under an IND or IDE, the Sponsor must insure that the Investigator completes, signs and submits an investigators statement (Form FDA-1572). Before the Investigator begins conducting an investigation, the Sponsor (other than a Sponsor-Investigator) shall give each participating clinical Investigator an Investigator brochure and shall, as the overall investigation proceeds, keep the Investigator informed of new observations discovered by or reported to the Sponsor on the drug or device, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised Investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. The Sponsor shall require that investigators present all such information to the Carle IRB.
    - b. **Emergency Research.** The Sponsor shall monitor the progress of all investigations involving exceptions to informed consent under 21 CFR 50.24. When the Sponsor receives from the Carle IRB information concerning the public disclosures required by 21 CFR 50.24(a)(7)(ii) and (a)(7)(iii), the Sponsor promptly shall submit this to the IND file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852, copies of the information that was disclosed, with the IND number.

The Sponsor also shall monitor investigations even when the Carle IRB determines that it cannot approve the emergency research because it does not meet the criteria in the exception in 21 CFR 50.24(a) or because of other relevant ethical concerns. The Sponsor shall promptly provide this information in writing to FDA, Investigators who participate in this or a substantially equivalent clinical investigation, and other IRBs that are asked to review this or a substantially equivalent investigation.

- c. **Review of Ongoing Investigations.** The Sponsor shall monitor the progress of all clinical investigations being conducted under its IND or IDE.

A Sponsor who discovers that an Investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug or device to the Investigator and end the Investigator's participation in the investigation. If the Investigator's participation in the investigation is ended, the Sponsor shall require that the Investigator return the investigational drug or device in accordance with applicable regulations and shall notify FDA.

The Sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug or device as it is obtained from the Investigator. The Sponsors shall make such reports to FDA regarding information relevant to the safety of the drug or device. The Sponsor shall make annual reports on the progress of the investigation.

A Sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall: discontinue those studies, notify the FDA, notify all institutional review boards, notify all other Investigators who have at any time participated in the study of the drug, assure the disposition of all stocks of the drug outstanding, and furnish the FDA with a full report of the Sponsor's actions. The Sponsor shall discontinue the study as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a Sponsor on the need to discontinue a study.

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- d. **Recordkeeping.** A Sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the Investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

A Sponsor shall maintain complete and accurate records showing any payments made to clinical investigators by the Sponsor of the covered study. A Sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators.

A Sponsor shall retain the records and reports required herein for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

A Sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies, and release the reserve samples to the FDA upon request.

A Sponsor shall upon request from any properly authorized officer or employee of the FDA, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation.

- e. **Disposition of Unused Drug.** The Sponsor shall ensure the return of all unused supplies of the investigational drug from each individual Investigator whose participation in the investigation is discontinued or terminated. The Sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The Sponsor shall maintain written records of any disposition of the drug.

3. **Research conducted under an IDE.** In addition to the above requirements for all clinical research, the following requirements shall apply to clinical research conducted under an IDE.

a. **Responsibilities of Sponsors for Significant Risk Device Studies**

- **General Responsibilities.** Sponsors are responsible for selecting qualified investigators and providing them with the information that they need to conduct the investigation properly. They must also ensure proper monitoring of the investigation and IRB review and approval, submit an IDE application to the FDA for significant risk device studies, and inform the Carle IRB and the FDA promptly of any significant new information about the investigation.
- **FDA and IRB Approval.** A Sponsor cannot begin an investigation or any part of an investigation until an IRB and the FDA have both approved the application or supplemental application.
- **Selecting Investigators.** A Sponsor is responsible for selecting investigators qualified by training and experience to investigate the device.
- **Selecting Monitors.** A Sponsor must select monitors qualified by training and experience to monitor the investigational study in accordance with the IDE and other applicable FDA regulations.
- **Device Control.** A Sponsor can ship investigational devices only to qualified investigators participating in the investigation.
- **Investigator Agreements.** A Sponsor must obtain a signed agreement from each participating Investigator that includes;
  - The Investigator's curriculum vitae,
  - A statement of the Investigator's relevant experience, including the dates, location, extent, and type of experience, where applicable,
  - An explanation of the circumstances that led to termination of a study if the Investigator was involved in an investigation or other research that was terminated,
  - A statement of the Investigator's commitment to:
    - \* Conduct the investigation in accordance with the agreement, the investigational plan, the IDE and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA,
    - \* Supervise all testing of the device involving human subjects, and
    - \* Ensure that the requirements for obtaining informed consent are met.
  - Sufficient accurate financial disclosure information to allow the Sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. The Sponsor shall also obtain a commitment from the clinical Investigator to

## Specific Policies (cont.)

promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. (The financial certification or disclosure is submitted in the PMA or Premarket Notification 510(k) application. It should not be submitted in the IDE application.)

- **Informing Investigators.** A Sponsor must supply all investigators participating in the investigation with copies of the investigational plan and a report of prior investigations of the device.
- **Securing Compliance.** A Sponsor who discovers that an Investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or the FDA, must promptly either secure compliance, or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation. A Sponsor must also require that the Investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of subjects.
- **Unanticipated Adverse Device Effects.** The Sponsor must immediately conduct an evaluation of any unanticipated adverse device effects. A Sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first received notice of the effect.
- **Resumption of Terminated Studies.** For significant risk device investigations, a Sponsor may not resume a terminated investigation without IRB and FDA approval. For a nonsignificant-risk device investigation, a Sponsor may not resume a terminated investigation without IRB approval. If the nonsignificant-risk device study was terminated for unanticipated adverse device effects, the Sponsor must also obtain FDA approval.
- **Sponsor Records.** The Sponsor must maintain accurate and complete records relating to the investigation. These records include:
  - All correspondence including required reports,
  - Records of shipment of the device,
  - Records of disposition of the device,
  - Signed Investigator agreements including financial disclosure information,
  - Records concerning complaints and adverse device effects whether anticipated or not,
  - Any other records that the FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- **Sponsor Reports.** The Sponsor must provide the following reports in a timely manner to the FDA, the IRBs, and/or the investigators.
  - Unanticipated Adverse Device Effects
  - Withdrawal of IRB Approval
  - Withdrawal of FDA Approval
  - Current List of Investigators
  - Progress Reports
  - Recalls and Device Disposition
  - Final Report
  - Informed Consent
  - Significant Risk Device Determination
  - Other Reports
- **Labeling.** An investigational device or its immediate package must bear a label with the following information:
  - The name and place of business of the manufacturer, packer, or distributor;
  - The quantity of contents, if appropriate; and
  - The statement, "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

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The Sponsor should provide detailed information on device labeling in the investigational protocol. This information may vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.

- b. **Responsibilities of Sponsors of Nonsignificant Risk Device Studies.** Sponsors of nonsignificant risk device studies must comply with the abbreviated IDE requirements set forth in 21 CFR §812.2(b).
- **Label the Device in Accordance with 21 CFR §812.5**
    - The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
    - The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.
    - The Sponsor should provide detailed information on device labeling in the investigational protocol. This information may vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.
  - Obtain IRB approval of the investigation as a nonsignificant risk device study after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintain such approval.
  - Ensure that each Investigator participating in an investigation of the device obtains informed consent under 21 CFR 50 for each subject under the Investigator's care and documents the consent, unless documentation is waived by an IRB.
  - Comply with the requirements of 21 CFR §812.46 with respect to monitoring investigations.
    - **Securing Compliance.** A Sponsor who discovers that an Investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or the FDA must promptly either secure compliance, or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation. A Sponsor must also require that the Investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.
    - **Unanticipated Adverse Device Effects.** The Sponsor must immediately conduct an evaluation of any unanticipated adverse device effect. A Sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first received notice of the effect.
    - **Resumption of Terminated Studies.** For significant risk device investigations, a Sponsor may not resume a terminated investigation without IRB and FDA approval. For a nonsignificant risk device investigation, a Sponsor may not resume a terminated investigation without IRB approval. If the nonsignificant risk study was terminated for unanticipated adverse device effects, the Sponsor must also obtain FDA approval.
  - **Maintain Certain Records and Submit Required Reports.** The following records must be maintained in one location and available for FDA inspection:
    - The name and intended use of the device;
    - The objectives of the investigation;
    - A brief explanation of why the device is not a significant risk device;
    - The name and address of each Investigator;
    - The name and address of each IRB;
    - A statement of the extent to which the good manufacturing practices (21 CFR 820) were followed in manufacturing the device.
    - Any other information required by FDA
- The Sponsor must maintain records concerning complaints and adverse device effects. The Sponsor must provide the following reports in a timely manner to the FDA, the IRBs, and/or the investigators:
- Unanticipated Adverse Device Effects
  - Withdrawal of IRB Approval

## Specific Policies (cont.)

- Withdrawal of FDA Approval
- Progress Reports
- Recalls and Device Disposition
- Final Report
- Informed consent
- Significant Risk Device Determination
- Other Reports
- Ensure that participating investigators maintain the records of each subject's case history and exposure to the device and ensure that participating investigators make the following required reports:
  - Unanticipated Adverse Device Effects
  - Withdrawal of IRB Approval
  - Informed consent
  - Other reports requested by a reviewing IRB or the FDA
- Comply with the prohibitions in 21 CFR §812.7 against promotion and other practices
  - A Sponsor, Investigator, or any person acting for or on behalf of a Sponsor or Investigator cannot:
    - \* Promote or test market an investigational device, until after the FDA has approved the device for commercial distribution.
    - \* Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
    - \* Unduly prolong an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the Sponsor must promptly terminate the investigation.
    - \* Represent that an investigational device is safe or effective.
  - The Sponsor may advertise for research subjects to solicit their participation in a study. Appropriate advertising methods include but are not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects.
  - Advertisements must be reviewed and approved by the Carle IRB to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device.

## Reference

21 CFR 312, 21 CFR 812, 21 CFR 50, FDA Form 1572

## Approval On File

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