SPONSOR REQUIREMENTS

This is an overview of the FDA sponsor requirements contained in 21 CFR 812 for research with investigational devices. This overview is intended to assist the sponsors in identifying and complying with their responsibilities in connection with the conduct of clinical investigations of medical devices that are deemed "significant risk" by the reviewing IRB or by the FDA. Other FDA regulations for sponsors include, but are not limited to, 21 CFR Parts 11, 54, 814, and 820. Please review the federal regulations before performing any sponsor duties. If you are the sponsor and the investigator for the device, you must meet the requirements for the sponsor and the investigator. In addition, sponsors should be aware that a clinical investigation must be conducted in accordance with any requirements imposed by the reviewing IRB, by institutional policies, or by state law. Additional information can be found on the FDA’s web site: http://www.fda.gov/cdrh/mdr

General Duties (21 CFR 812.40):

- Selects qualified investigators;
- Provides investigators with information they need to properly conduct the investigation;
- Ensures proper monitoring;
- Ensures IRB review and approval are obtained;
- Submits the IDE application to the FDA;
- Ensures that any reviewing IRB and FDA are promptly informed of significant new information about an investigation;
- Does not begin an investigation or part of an investigation until an IRB and the FDA have both approved the application or supplemental application relating to the investigation or part of the investigation.
Selection of Investigators (21 CFR 812.43):

- Selects investigators qualified by training and experience to investigate the device;
- Ships the investigational device only to participating qualified investigators;
- Obtains a signed investigator's agreement from each participating investigator that includes:
  - investigator's curriculum vitae
  - statement of investigator's relevant experience, including dates, location, extent, and type of experience, where applicable;
  - if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination
  - statement of the investigator's commitment to:
    - conduct the investigation in accordance with the agreement, the investigational plan, Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA
    - supervise all testing of the device involving human subjects
    - ensure that the requirements for informed consent are met (21 CFR Part 50)
- Supplies investigators participating in the investigation with copies of the:
  - investigational plan
  - report of prior investigations

Monitoring (21 CFR 812.46)

- Selects monitor(s) qualified by training and experience to monitor the progress of the investigation;
- Secures prompt compliance or discontinues shipments of the device to the investigator and terminates the investigator’s participation in the investigation, upon discovery that an investigator is not complying with the signed agreement, the investigational plan, the requirements of applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or the FDA;
- Requires any investigator terminated from participation in an investigation to dispose or return the device, unless this action would jeopardize the rights, safety, or welfare of the subject;
• Conducts immediately an evaluation of any unanticipated adverse device effect and terminates all investigations or parts of investigations whenever the sponsor determines that an unanticipated device effect presents an unreasonable risk to subjects.

Termination shall occur:

- Not later than 5 working days after the sponsor makes this determination; and
- Not later than 15 working days after the sponsor first received notice of the effect.

• Resumes terminated investigations as follows:
  - If the device is a significant risk device, only after both FDA and IRB approvals are obtained;
  - If the device is a non-significant risk device, only after IRB approval and FDA approval if the termination was due to an unanticipated adverse device effect.

**Controlling Distribution and Disposition of Devices**

Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (see 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (§ 812.43(b)). Sponsors must also maintain complete, current, and accurate records pertaining to the shipment and disposition of the investigational device (§ 812.140(b)). Records of shipment shall include the name and address of the consignee, type, and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

To ensure further compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at § 812.140(a). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (§ 812.110(c)).
Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

- Promotion or test marketing of the investigational device;
- Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;
- Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,
- Representing that the device is safe or effective for the purposes for which it is being investigated.

Supplemental Applications [21 CFR 812.35(a) and (b)]

Supplemental applications are required to be submitted to, and approved by the FDA in the following situations:

- Changes in the investigational plan: FDA approval is required for any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety, or welfare of the subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.
- Addition of new institutions: IRB approval is also required for new institutions. The investigation at the new institution(s) may not begin until both FDA and IRB approval(s) are obtained, and certification of IRB approval is submitted to FDA.

Maintaining Records [21 CFR 812.140(b)]

A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

- All correspondence (including reports) with another sponsor, monitor, investigator, IRB or the FDA;
- Records of shipment must include:
  - name and address of consignee;
• type and quantity of device;
• date of shipment;
• batch numbers or code marks.

• Records of disposition must describe:
  • batch number or code mark of any devices;
    ▪ returned to the sponsor;
    ▪ repaired, or
    ▪ disposed of by the investigator or another persons; and
    ▪ reasons for and method of disposal.

• Signed investigator agreements, including the financial disclosure information required by 21 CFR Part 54;
• Adverse device effects (whether anticipated or unanticipated) and complaints;
• Any other records that the FDA requires by regulation or by specific requirement for a category of investigation or a particular investigation;
• For each investigation of a device other than a significant risk device subject to abbreviated requirements of 21 CFR 812.20(b)(1), maintains the following records consolidated in one location and available from FDA inspection and copying:

The table below shows the responsibilities for record maintenance by Investigator and Sponsor:

<table>
<thead>
<tr>
<th>Records</th>
<th>Maintained by Investigator</th>
<th>Maintained by Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Correspondence Pertaining to the Investigation</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shipment, Receipt, Disposition</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Device Administration and Use</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Subject Case Histories</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Protocols and Reasons for Deviations from Protocol</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Adverse Device Effects and Complaints</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Signed Investigator Agreements</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Membership/Employment/Conflicts of Interest</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Minutes of Meetings</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Submitting Reports [21 CFR 812.150(b)]:
A sponsor shall prepare and submit the following complete, accurate, and timely reports:

- Unanticipated adverse device effects (with evaluation) to the FDA, all IRBs, and investigators within 10 working days after notification by the investigator;
- Follow-up reports on the effect, as required by FDA;
- Withdrawal of IRB approval;
- Withdrawal of FDA approval;
- Current 6month investigator list;
- Annual progress report (see format for IDE progress report);
- Recall and device disposition (within 30 working days after the request was made);
- Final report (see format for progress reports);
- Use of device without obtaining patient informed consent;
- Significant risk determinations by the IRB when proposed to be nonsignificant risk;
- Other reports requested by the IRB or FDA.

The table below describes the responsibilities for investigators and sponsors for preparing and submitting reports:

<table>
<thead>
<tr>
<th>Type of Report</th>
<th>Prepared by Investigators for</th>
<th>Prepared by Sponsors for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Effect Evaluation</td>
<td>Sponsors and IRBs</td>
<td>FDA, IRBs and Investigators</td>
</tr>
<tr>
<td>Withdrawal of IDE Approval</td>
<td>Sponsors</td>
<td>FDA, IRBs, and Investigators</td>
</tr>
<tr>
<td>Progress Report</td>
<td>Sponsors, Monitors and IRBs</td>
<td>FDA and IRBs</td>
</tr>
<tr>
<td>Final Report</td>
<td>Sponsors and IRBs</td>
<td>FDA, IRBs, and Investigators</td>
</tr>
<tr>
<td>Withdrawal of FDA Approval</td>
<td>N/A</td>
<td>IRBs and Investigators</td>
</tr>
<tr>
<td>Current Investigator List</td>
<td>N/A</td>
<td>FDA</td>
</tr>
<tr>
<td>Recall and Device Disposition</td>
<td>N/A</td>
<td>FDA and IRBs</td>
</tr>
<tr>
<td>Records Maintenance Transfer</td>
<td>FDA</td>
<td>FDA</td>
</tr>
<tr>
<td>Significant Risk Determinations</td>
<td>N/A</td>
<td>FDA</td>
</tr>
</tbody>
</table>
Inspections [21 CFR 812.145]

Sponsors are required to permit FDA to enter and inspect (at reasonable times and in a reasonable manner) any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records or results from use of devices are kept). The FDA may also inspect and copy all records relating to an investigation including, in certain situations, records which identify subjects.

There are other sponsor responsibilities beyond the scope of this summary (e.g., quality system regulation (21 CFR 820)). If you have questions, contact UAB Office of Counsel.