Brief Synopsis of Federal Regulations for Investigators Who Hold an Investigational Device Exemption (IDE)

I. Introduction

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IDE. The federal regulations for IDEs are found under 21 CFR 812. For more information, review the FDA's Center for Devices and Radiologic Health (CDRH) web site http://www.fda.gov/MedicalDevices/default.htm.

Below is a synopsis of requirements specific to sponsor-investigators who hold IDEs. This document is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout this document so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and Washington University policies and procedures. Federal regulations are found in 45 CFR 46, and are available on the Office for Human Research Protections web site. Washington University policies and procedures, along with guidance for human subjects research are available on the Human Research Protection Office's (HRPO) website at http://hrpohome.wustl.edu/.

II. What is a Sponsor-Investigator?

When an Investigator holds an IDE for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a "Sponsor-Investigator." The FDA defines a Sponsor-Investigator as "an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used . . . . The obligations of a sponsor-investigator under this part include those of an investigator and a sponsor." [21 CFR 812.3]

III. What must the Sponsor-Investigator report to the FDA and/or IRB? 21 CFR 812.150(a)

Sponsor-investigators have extensive reporting requirements under FDA regulations. For guidance on reporting requirements and suggested formats for reports see the FDA website: Device Advice

1. Changes in the protocol 21 CFR 812.35

Changes to the investigational plan or manufacturing process must be submitted to the FDA for approval if they significantly affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects. These changes should be

submitted to the FDA as a supplement to the IDE protocol and must be approved by the FDA before being implemented.

- Changes that do not meet the above criteria (e.g., adding follow-up visits, changing secondary endpoints, etc.) should be submitted to the FDA within 5 working days of implementation of the change.
- Minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects can be submitted with the annual report.
- The sponsor-investigator must ensure that all participating investigators notify the sponsor–investigator and the reviewing IRB [21 CFR 56.108(a) (3) and (4)] of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with [21 CFR 812.35(a)].

2. IDE safety/adverse device effects 21 CFR 812.150 and 21 CFR 812.3

The sponsor-investigator must report all unanticipated adverse device effects to the FDA and the IRB within 10 working days of receiving the first notice of the event. An "unanticipated adverse device effect" means 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 a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. For multiple-site studies, the sponsor-investigator must also report all unanticipated adverse device effects to all of the reviewing IRBs and participating investigators.

The sponsor-investigator must have written procedures in place to receive, process, and report to the FDA unanticipated adverse device effects which occur at participating sites. Participating investigators must submit to the sponsor-investigator and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later that 10 working days after the investigator first learns of the effect.

3. Withdrawal of IRB approval 21 CFR 812.150b

The sponsor-investigator must inform the FDA, all reviewing IRBs, and participating investigators of withdrawal of approval of an investigation or any part of an investigation by any reviewing IRB. This notification must occur within 5 working days after receipt of the withdrawal of approval.

4. Withdrawal of FDA approval 21 CFR 812.150b

The sponsor-investigator must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval. This notification must occur within 5 working days after receipt of the withdrawal of approval.

5. **Current investigator list** **21 CFR 812.150b**

   The sponsor-investigator must provide the FDA with a current list of investigators participating in the investigation. This list must be provided to the FDA every 6 months.

- *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

6. **Annual reports** **21 CFR 812.150b**

The sponsor-investigator must submit a progress report to all reviewing IRBs at regular intervals, at least yearly. The first report must be within 60 days of the anniversary date that the IDE went into effect. For IDEs that have been determined to be significant risk, these reports must also be submitted to the FDA.

7. **Recall and device disposition** **21 CFR 812.150b**

   The sponsor-investigator must notify the FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. The notification must occur within 30 working days after the request is made.

8. **Discontinuation of an investigation** **21 CFR 812.150b**

The sponsor-investigator must report the completion or termination of an investigation. These reports should be made by submitting a final report.

- For significant risk devices, the sponsor-investigator must notify the FDA within 30 working days and all reviewing IRBs within 6 months of the completion of the investigation.
- For non-significant risk devices, the sponsor-investigator must notify all reviewing IRBs within 6 months of completion of the study.

9. **Informed consent** **21 CFR 812.150b**

The sponsor-investigator must report to the FDA any use of the IDE without informed consent. This report must be submitted within 5 working days of receipt of notice of this use.

10. **Significant risk device determinations** **21 CFR 812.150b**

If an IRB determines that a device is significant risk (SR), whereas the sponsor-investigator had proposed it to be a non-significant risk device (NSR), the sponsor-investigator must notify the FDA of this decision within 5 working days after learning of the IRB's determination.

In deciding whether or not a medical device is an SR, the IRB considers if the device:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(1)]
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(2)]
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(3)]; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR 812.3(m)(4)]

The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB considers the nature of the harm that may result from the use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure is considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

To help in the determination of the risk status of the device, the sponsor-investigator is asked to include an assessment of whether or not a device study presents an SR or NSR. The sponsor-investigator must provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor-investigator must inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor-investigator must inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion. [21CFR 812.25 and 21 CFR 812.27]

11. Financial disclosure reports 21 CFR 812.43 (see also 21 CFR 54).

The sponsor-investigator is responsible for ensuring that all participating investigators disclose to the sponsor-investigator sufficient accurate financial information to allow the sponsor-investigator to submit complete and accurate certification or disclosure statements. The sponsor-investigator shall promptly update any changes to financial disclosure information and report it to the FDA during the investigation and for 1 year following completion of the study.

IV. What records must a sponsor-investigator maintain?

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after completion or termination of the investigation or 2 years after the records are no longer needed to support a premarket approval application or a notice of completion of a product development protocol (IRB or other requirements may differ). [21 CFR 812.140d] The sponsor-investigator must make these available to FDA inspectors at their request. For multi-site studies, the sponsor-investigator must ensure that all participating investigators maintain the following records.

1. **Correspondence 21 CFR 812.140**

The sponsor-investigator must maintain copies of all correspondence with other investigators, reviewing IRBs, monitors, and the FDA, including required reports.

2. **Financial interest 21 CFR 812.140**

The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also 21 CFR 54).

3. **Device records 21 CFR 812.140**

The sponsor-investigator must ensure that all participating investigators maintain the following accurate, complete and current records relating to the investigator's participation in an investigation. The sponsor-investigator must maintain, and must ensure that all participating investigators maintain, records relating to the shipment, receipt, use (including adverse effects), and disposition of the device. Additionally, for *nonsignificant risk devices*, the sponsor-investigator must maintain, and must ensure that all participating investigators maintain, the following records:

- the name and intended use of the device (type and quantity of the device, the dates of its receipt, and the batch number or code mark).
- a brief explanation of why the device is not a significant risk.
- the name and address of each investigator and the names of all persons who received, used, or disposed of each device.
- why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- a statement of the extent to which Good Manufacturing Practice (GMP) regulations will be followed in manufacturing the device (see also 21 CFR 820).

4. **Case Histories 21 CFR 812.140**

The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject exposed to the investigational device**.** The case history for each individual shall document that informed consent was obtained prior to participation in the study.

5. **Essential documents ICH E6 S8 and FDA Guidance: Investigator Responsibilities**

The sponsor-investigator must maintain documents included in ICH E6 S8. These documents are considered essential to conducting a clinical trial and are subject to audit by regulatory authorities. Examples of essential documents are signed protocol and amendments, signed and dated informed consent documents, IRB approval notices, and signed, dated, and completed case report forms (CRFs**),** medical records including, for example, progress notes of the physician, the subject's hospital chart(s) and the nurses' notes.

Such records shall include:

- Documents evidencing informed consent and, for any use of a device by the sponsor-investigator or any participating investigator without informed consent, and written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
- All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
- A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates of and the reasons for each deviation from the protocol.
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

For a complete list of essential documents, see ICH E6 S8.

An investigator or sponsor-investigator may withdraw from the responsibility to maintain records for the period required in 21 CFR 812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR 812.140, including the requirements of 21 CFR 812.145 [21 CFR 812.140(e)]. Notice of this transfer shall be given to the FDA not later than 10 working days after transfer occurs.

V. What are the sponsor-investigator's responsibilities *as a sponsor*?

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. General responsibilities of sponsors 21 CFR 812.40

The sponsor-investigator is responsible for:

- selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
- ensuring proper monitoring of the investigation. For more information on monitoring guidelines, see Section 5.18 of the ICH Guidance.
- ensuring that IRB review and approval are obtained.

- submitting an IDE application to the FDA.
- ensuring that any reviewing IRB, FDA, and participating investigators are promptly informed of significant new information about an investigation.

2. **Selecting and monitoring investigators 21 CFR 812.43 – 812.46**

The sponsor-investigator is responsible for:

- selecting qualified investigators and monitors.
- ensuring that the investigational device is shipped only to participating investigators.
- obtaining investigator agreements.
- obtaining statements from participating investigators attesting to their commitment to the proper conduct of the investigation.
- obtaining accurate financial disclosure statements from participating investigators.
- providing participating investigators with the investigational plan.
- informing co-investigators of new observations with regard to the investigational device and progress of the study.
- reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational device, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

3. **Adverse device effects and study termination 21 CFR 812.46**

The sponsor-investigator must immediately evaluate any unanticipated adverse device effect. If the sponsor-investigator determines that the device presents an unreasonable risk to subjects, the sponsor-investigator must terminate the study within 5 working days after making this determination, but not later than 15 working days after first receiving notice of the adverse effect.

- If the device is significant risk, the sponsor-investigator may not resume a terminated investigation without IRB and FDA approval.
- If the device is nonsignificant risk, the sponsor-investigator may not resume a terminated investigation without IRB approval.

4. **Recordkeeping and record retention 21 CFR 812.140**

The sponsor-investigator is responsible for maintaining study records, as described above in part IV of this document.

5. **Inspection of sponsor's records and reports 21 CFR 812.145**

The sponsor-investigator must allow FDA employees access to all records and reports at their request.

- A sponsor-investigator and all participating investigators who have authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [21 CFR 812.145(a)].
- A sponsor-investigator and all participating investigators shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [21 CFR 812.145(b)].
- A sponsor-investigator and all participating investigators shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the participating investigator to the sponsor-investigator or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR 812.145(c)].

VI. What are the sponsor-investigator's responsibilities *as an investigator*?

As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. General responsibilities of investigators 21 CFR 100

The sponsor-investigator is responsible for

- ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable FDA regulations.
- protecting the rights, safety, and welfare of subjects under the investigator's care
- ensuring the control of devices under investigation.

2. Compliance with protocol 21 CFR 812.110b

The sponsor-investigator must conduct the investigation in accordance with the signed agreement, the investigational plan, FDA regulations, and IRB conditions. [21 CFR 812.110] The signed agreement should include:

- the investigator's curriculum vitae;
- where applicable, a statement of the investigator's relevant experience (including the dates, location, extent and type of experience);
- if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination; and
- a statement of the investigator's commitment to:
- conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA;
- supervise all testing of the device involving human subjects; and
- ensure that the requirements for obtaining informed consent are met

- the nvestigator's commitment to provide sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study.

3. **Device use and disposition 21 CFR 812.110c**

The sponsor-investigator shall permit the use of an investigational device only with subjects under the sponsor-investigator or participating investigator's supervision. An investigator shall not supply an investigational device to any person not authorized to receive it. Upon completion or termination of a clinical investigation or the participating investigator's part of an investigation, or at the sponsor-investigator's request, a participating investigator shall return to the sponsor-investigator any remaining supply of the device or otherwise dispose of the device as the sponsor-investigator directs. [21 CFR 812.110]

4. **Investigator record keeping and record retention 21 CFR 812.140a**

The sponsor-investigator is responsible for maintaining study records, as described above in Part IV of this document.

5. **Investigator reports 21 CFR 812.150**

The sponsor-investigator must provide reports to the FDA as described above in Part III of this document.

6. **Inspection of investigator's records and reports 21 CFR 812.145**

The sponsor-investigator must allow FDA employees access to all records and reports at their request.

VII. Additional References

For additional information, refer to the following links:

- Premarket Approval of Medical Devices 21 CFR 814
- Medical Device Classification Procedures 21 CFR 860