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4 **Subject: Responsibilities of Investigators Under FDA Regulations**

5 **PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF RESEARCH SUBJECTS**

6 Investigators have important responsibilities toward research subjects participating in
7 their research investigations. Of paramount importance is protecting the rights, safety, and
8 welfare of research subjects under UAB policy, UAB's Federalwide Assurance with the
9 Department of Health and Human Services, and federal and state laws and regulations.

10 Additionally, if this adverse effect was unexpected, then it should be reported to the IRB.
11 Conversely, IND sponsors must inform investigators about written safety reports of serious and
12 unexpected adverse experiences or results of laboratory animal studies suggesting significant risk
13 for human subjects. Investigators should forward such reports to the IRB when they meet the
14 requirements for reporting in Policy [POL006](#) and Procedure [PRO106](#).

15 **RESPONSIBILITIES OF INVESTIGATORS PERFORMING RESEARCH UNDER AN**
16 **INVESTIGATIONAL NEW DRUG (IND) APPLICATION**

17 Performance of FDA-regulated studies using investigational drugs or biologics (i.e.,
18 agents that require an IND application/number for human use) creates important responsibilities
19 for research investigators. (See [PRO121](#) "Procedure to Ensure Handling of Investigational or
20 Unlicensed Test Articles Meets Organizational Standards Relating to Pharmacy, Inventory
21 Control, and Documentation"; [GUI307](#) "FDA Sponsor Requirements for Investigators Who are
22 Serving as Sponsors of Investigational Drug or Biologic Studies.") In this circumstance the
23 investigator is responsible for the following:

- 24 • Ensuring that an investigation is conducted according to the signed investigator
25 statement, the investigational plan, and applicable regulations;
- 26 • Protecting the rights, safety, and welfare of subjects under the investigator's care; and
- 27 • Controlling the drugs under investigation.
- 28 • Obtaining the informed consent of each human subject to whom the drug is
29 administered, unless there is a specific exception under the FDA regulations (21 CFR
30 §312.60).

1 The investigator statement (Form FDA 1572), once signed, contains a number of
2 commitments by the investigator that generate specific investigator responsibilities. Under these
3 commitments the investigator:

- 4 • Will conduct a study under the relevant current protocol and will only make changes in
5 a protocol after notifying the sponsor, except, when necessary to protect the safety, the
6 rights, or welfare of subjects;
- 7 • Will comply with all the investigator obligations and pertinent requirements in the
8 FDA regulations pertaining to investigational drugs;
- 9 • Will personally conduct or supervise the described investigation;
- 10 • Will inform any potential subjects that the drugs are being used for investigational
11 purposes;
- 12 • Will ensure that the requirements under FDA regulations for obtaining informed
13 consent and IRB review and approval are met;
- 14 • Will report to the sponsor adverse experiences that occur during the course of an
15 investigation in accordance with FDA regulations;
- 16 • Has read and understands the information in the investigator's brochure, including the
17 potential risks and side effects of the drug; and
- 18 • Will assure that all associates, colleagues, and employees assisting in the conduct of
19 the study are informed about their obligations in meeting the above commitments.

20 In addition, the investigator statement expressly commits the investigator to have an IRB
21 that is constituted in accordance with FDA regulations perform the initial and continuing reviews
22 and approvals for any investigation which requires IRB review. This commitment requires the
23 investigator to promptly report to the IRB all changes in the research activity and all problems
24 that require reporting to the IRB under Policy [POL006](#) and Procedure [PRO106](#), and not to make
25 changes in the research without IRB approval, except when necessary to eliminate apparent
26 immediate hazards to the human subjects; see "Protecting the Rights, Safety, and Welfare of
27 Research Subjects" above (21 CFR §312.53 (c) (1); 21 CFR §312.66).

28 All clinical investigators subject to the IND regulations must provide the sponsor of the
29 study with sufficient accurate information to allow the sponsor to file accurate financial
30 statements with the FDA. There are two types of financial statements: a financial disclosure
31 statement listing prescribed categories of financial interests that could potentially bias a clinical

1 study and a certification stating no such financial interests exist. The investigator must promptly
2 update this information if any relevant changes occur in the course of the investigation or for 1
3 year following completion of the study. The categories of financial interests requiring disclosure
4 include: (1) any financial arrangement between the sponsor and investigator whereby the
5 outcome of the study affects the amount of compensation to the investigator, (2) any proprietary
6 interest in the tested product held by any investigator involved in a study, (3) any significant
7 equity interest in the sponsor of the study held by any clinical investigator involved in the study,
8 (4) any significant payments of other sorts from the sponsor of the study. A significant equity
9 interest generally means any equity interest (e.g., stock, stock options) for non-publicly traded
10 companies and an equity value greater than \$50,000 for publicly traded companies. *Significant*
11 *payments of other sorts* means payments by the sponsor made to the investigator or institution to
12 support the activities of the investigator that have a monetary value of more than \$25,000,
13 exclusive of the costs of conducting the clinical study or other clinical studies (e.g., grants,
14 equipment, retainers, or honoraria) during the time the clinical investigator is carrying out the
15 study and for 1 year after completion of the study. Residual credit balances in grant accounts that
16 meet this definition may constitute significant payments of other sorts if these credit balances are
17 available to support the activities of the investigator (21 CFR §§54.1-54.4).

18 The investigator must maintain control of an investigational study drug. An
19 investigational drug may only be administered to subjects under the personal supervision of the
20 investigator or a designated subinvestigator. An investigator must not supply the drug to anyone
21 not authorized under FDA regulations to receive it (21 CFR §312.61). It is generally and highly
22 preferable to meet this responsibility by arranging for a central pharmacy to receive, store,
23 distribute, and keep proper documentation according to a predefined protocol for investigational
24 drugs.

25 Other responsibilities under FDA regulations on investigational drugs include the
26 following:

- 27 • Keep, maintain, and retain records;
- 28 • Supply reports;
- 29 • Comply with inspections; and
- 30 • Secure controlled substances.

1 A. Records. Investigators must prepare, maintain, and retain records of the investigation.
2 Adequate records are required for drug disposition including dates, times, and amounts
3 administered to subjects. Any unused supplies of drug must go back to the sponsor or be
4 disposed of at the sponsor's direction in accordance with regulation. Again, record requirements
5 for drug disposition are accomplished best by using a central pharmacy to handle the drug.

6 Also, an investigator must prepare and maintain adequate and accurate case histories that
7 record all observations and other data pertinent to the study for each individual receiving an
8 investigational drug or serving as a control. Case histories consist of case report forms and
9 supporting documentation such as copies of progress notes, radiographic interpretations, and
10 laboratory reports. All case histories must document that informed consent was obtained prior to
11 participation in the study or a regulatory exception applied. Under the FDA regulations, records
12 must be retained for at least 2 years following the date of marketing approval of the drug or 2
13 years after an investigation is completed and FDA notified. In most instances this time period
14 will exceed the 3-year retention requirement under DHHS regulations.

15 B. Reports. Besides supplying information for financial statements (see above), an
16 investigator has responsibility to furnish information for or prepare the following:

- 17 • Progress reports,
- 18 • Safety reports, and
- 19 • Final reports.

20 An investigator must furnish to the sponsor all reports required for submission of the
21 annual progress report to the FDA. Also, the investigator must promptly report to the sponsor
22 any adverse effect that may reasonably be regarded as caused by, or probably caused by, the
23 drug. If the adverse effect is alarming, the investigator must report it immediately. Shortly after
24 completion of an investigator's participation in the study, (s)he must provide a final report to the
25 sponsor (21 CFR §312.64).

26 C. Inspections. An investigator must permit, at reasonable times, an authorized FDA
27 official or employee to have access to, and copy, and verify any records or reports made by the
28 investigator pertaining to case histories and drug disposition. The names of the subjects do not
29 have to be divulged unless the records of particular individuals require more detailed study or
30 unless there is reason to believe the records do not represent actual case histories or actual results
31 obtained (21 CFR §312.68).

1 D. Controlled Substances. An investigator must take adequate precautions to prevent
2 theft or illegal diversion of investigational drugs that are controlled substances. Such precautions
3 include maintaining security of the drugs with controlled access and a locked sturdy repository
4 when such drugs are maintained for some reason outside a central pharmacy (21 CFR §312.69).

5 **RESPONSIBILITIES OF INVESTIGATORS PERFORMING RESEARCH UNDER A**
6 **DEVICE EXEMPTION**

7 Clinical studies evaluating unapproved FDA devices for safety and effectiveness are
8 governed by a separate and distinct set of regulations from investigational drugs. Under the
9 device regulations, a study device must attain an approved exemption before use of the device
10 may proceed lawfully. Two types of exemptions are common: investigational device exemption
11 (IDE) and humanitarian device exemption (HDE). As in the case of the investigational drug
12 regulations, the investigational device regulations specify responsibilities for investigators during
13 conduct and review of research involving investigational devices. (See also: [PRO141](#) "Procedure
14 to Ensure Handling of Investigational or Unlicensed Test Articles Meets Organizational
15 Standards Relating to Devices, Inventory Control and Documentation"; [GUI306](#) "FDA Sponsor
16 Requirements for Investigators Who are Serving as Sponsors of Investigational Device or Test
17 Article Studies.")

18 A. Investigator responsibilities for studies involving an investigational device exemption
19 (IDE). Investigational device exemptions are approved in two different ways depending on
20 whether the study involves a significant risk device or not. Investigations of significant risk
21 devices require the sponsor to submit a separate application for an IDE approval along with its
22 application for pre-market approval to the FDA. Investigations of non-significant risk devices
23 have abbreviated requirements for an IDE. One of these requirements calls for the sponsor,
24 generally through the investigator, to present information explaining why the device should be
25 categorized as a non-significant risk device as part of the IRB review. When all of the
26 abbreviated requirements are met, including IRB approval, the investigation is considered to
27 have an approved IDE without need for filing a separate IDE application to FDA.

28 By definition, a significant risk device is an investigational device that: (1) is intended as
29 an implant and presents a potential for serious risks to the health, safety, and welfare of a subject;
30 (2) is purported or represented to be for a use in supporting or sustaining human life and presents
31 a potential for serious risk to the health, safety, and welfare of a subject; (3) is for a use of

1 substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise
2 preventing impairment of human health and presents a potential for serious risk to the health,
3 safety, and welfare of a subject; or (4) otherwise presents a potential for serious risk to the
4 health, safety, and welfare of a subject (21 CFR §812.3(m)).

5 The responsibilities for investigators conducting investigations on devices are analogous
6 to those for investigators conducting studies on drugs. Generally, the investigator is responsible
7 for ensuring that an investigation is conducted according to the signed written agreement, the
8 investigational plan and applicable FDA regulations; for protecting the rights, safety, and welfare
9 of subjects under the investigator's care; and for control of the devices under investigation. Also,
10 an investigator is responsible for obtaining informed consent in accordance with regulations (21
11 CFR §812.100). These general requirements translate into the following specific responsibilities:

- 12 • An investigator must not request the written informed consent of any subject to
13 participate, and must not allow any subject to participate before obtaining IRB and
14 FDA approval. (However, an investigator may determine whether potential subjects
15 would be interested in participating in an investigation.)
- 16 • An investigator must conduct the investigation in accordance with the signed
17 agreement with the sponsor, the investigational plan, any applicable FDA regulations,
18 particularly those on investigational devices, and any conditions of approval imposed
19 by an IRB or FDA.
- 20 • An investigator must permit an investigational device to be used only with subjects
21 under the investigator's supervision. An investigator must not supply an investigational
22 device to any person unauthorized under the regulations to receive it.
- 23 • A clinical investigator must disclose to the sponsor sufficient, accurate financial
24 information to allow the applicant to submit complete and accurate financial disclosure
25 statements under the regulations (see pg. 4).
- 26 • Upon completion or termination of a clinical investigation or the investigator's part of
27 the investigation, or at the sponsor's request, an investigator shall return to the sponsor
28 any remaining supply of the device or dispose of the device in accordance with the
29 sponsor's directions (21 CFR §812.110).

30 In addition, the regulations require participating investigators to discharge obligations
31 with regard to:

- 1 • Records,
- 2 • Inspections, and
- 3 • Reports.

4 i. Records.

5 (a) Investigators records. Participating investigators must maintain the following
6 accurate, complete, and current records relating to the investigator's
7 participation in an investigation:

8 (1) All correspondence with another investigator, an IRB, the sponsor, a
9 monitor, or FDA, including required reports.

10 (2) Records of receipt, use, or disposition of a device that relates to:

11 a. The type and quantity of the device, the dates of its receipt, and the
12 batch number or code mark.

13 b. The names of all persons who received, used, or disposed of each
14 device.

15 c. Why and how many units of the device have been returned to the
16 sponsor, repaired, or otherwise disposed of.

17 (3) Records of each subject's case history and exposure to the device. These
18 records must contain:

19 a. Documentation of informed consent and, for any use of a device
20 without informed consent, the written concurrence of a licensed
21 physician and brief description of the circumstances justifying the
22 failure to obtain informed consent.

23 b. All relevant observations, including records of anticipated and
24 unanticipated adverse device effects; information and data on the
25 condition of each subject upon entering, and during the course of, the
26 investigation, including information about relevant past medical
27 history and results of all diagnostic tests.

28 c. A record of exposure of each subject to the investigational device,
29 including the date and time of each use, and any other therapy.

30 (4) The protocol, with documents showing the dates of and reasons for each
31 deviation from the protocol.

1 (5) Any other records that FDA requires to be maintained by regulation or
2 specific requirement for a category of investigations or a particular
3 investigation (21 CFR §812.140).

4 (b) Retention and Custody.

5 (1) An investigator or sponsor must retain the records and reports required
6 under the device regulations during the investigation and for 2 years after
7 the latter of the following two dates: The date on which the investigation
8 is terminated or completed, or the date that the records are no longer
9 required for purposes of supporting a premarket approval or a notice of
10 completion of a product development protocol.

11 (2) An investigator or sponsor may withdraw from the responsibility to
12 maintain records for the periods stated in (1) above and transfer custody to
13 any other person who will accept responsibility for them under the
14 investigational device regulations including the inspection requirements.
15 Notice of transfer must be given to FDA not less than 10 days after transfer
16 occurs (21 CFR 812.140).

17 ii. Inspections. Authorized FDA personnel have jurisdiction to inspect facilities
18 and records as listed below:

19 (a) Entry and inspection of facilities. An investigator with authority to grant
20 access must permit authorized FDA employees, at reasonable times and in a
21 reasonable manner, to enter and inspect any facility where devices are
22 installed, used, or implanted or where records of results from use of devices
23 are kept.

24 (b) Records inspection. An investigator, or any other person acting on the
25 investigator's behalf with respect to an investigation, must permit authorized
26 FDA employees, at reasonable times and in a reasonable manner, to inspect
27 and copy all records relating to an investigation.

28 (c) Records with subjects' identity information. An investigator must permit
29 authorized FDA employees to inspect and copy records that identify subjects,
30 after receiving notice that FDA has reason to suspect that adequate informed
31 consent was not obtained, or that reports required to be submitted by the

1 investigator to the IRB or sponsor have not been submitted or are incomplete,
2 inaccurate, false, or misleading (21 CFR §812.145).

3 iii. Reporting. An investigator must prepare and submit the following reports in a
4 timely, accurate, and complete manner:

- 5 (a) Unanticipated adverse device effects. An investigator must submit to the
6 sponsor and to the reviewing IRB a report of any unanticipated adverse device
7 effect occurring during an investigation as soon as possible, but in no event
8 later than 10 working days after the investigator learns of the effect.
- 9 (b) Withdrawal of IRB approval. An investigator must report to the sponsor,
10 within 5 working days, a withdrawal of a approval by the reviewing IRB of
11 the investigator's part of an investigation.
- 12 (c) Progress. An investigator must submit progress reports on the investigation to
13 the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no
14 event less than annually.
- 15 (d) Deviations from the investigational plan. An investigator must notify the
16 sponsor and the reviewing IRB of any deviations from the investigational plan
17 to protect the life or physical well-being of a subject in an emergency. This
18 notice must be given as soon as possible but in no event later than 5 working
19 days after the emergency occurred. Except in such emergency, prior approval
20 by the sponsor is required for changes in a deviation from a plan, and if these
21 changes or deviations may affect the scientific soundness of the plan or the
22 rights, safety, or welfare of human subjects, approval from FDA and the IRB
23 in accordance with FDA regulations.
- 24 (e) Informed Consent Process. If an investigator uses a device without obtaining
25 informed consent, the investigator must report such use to the sponsor and the
26 reviewing IRB within 5 working days after initiating the use.
- 27 (f) Final Report. An investigator must, within 3 months after termination or
28 completion of the investigation or the investigator's part of the investigation,
29 submit a final report to the sponsor and reviewing IRB.

1 (g) Other. An investigator shall, upon request by a reviewing IRB or FDA,
2 provide accurate, complete, and current information about any aspect of the
3 investigation (21 CFR §812.150).

4 **FACULTY RESPONSIBILITIES FOR STUDIES INVOLVING A HUMANITARIAN**
5 **USE DEVICE (HUD)**

6 Occasionally, faculty wish to engage in clinical activities involving a HUD. In general
7 separate regulations from the IDE regulations apply to HUDs. These regulations allow pre-
8 marketing approval of an HUD through special application procedure termed a humanitarian
9 device exemption (HDE). HDE regulations require HUDs to be used only in facilities that have
10 an IRB constituted in accordance with FDA regulations and the proposed uses of the device to
11 undergo initial and continuing review by that IRB or by another IRB to which the facility's IRB
12 deferred. In the case of HUDs, IRBs are being asked to review non-research activity under the
13 FDA regulations for clinical investigation. Informed consent process requirements under the
14 HUD regulations do not apply, but the IRB may impose this as an additional request. Because
15 the HUD regulations are not research regulations per se, no investigator responsibilities are
16 explicitly listed. There are numerous responsibilities, such as reporting requirements, placed on
17 the holder of the HDE; however, many of these requirements will have to be met through the
18 HUD users actions. To further complicate matters, HUDs may be involved in clinical
19 investigations, in which case IRB approval of the clinical investigation under human protections
20 regulations must be obtained. UAB faculty members using HUDs should be aware of the
21 following obligations under the HUD regulations:

- 22 • Use of HUD must undergo initial and continuing review and approval.
- 23 • Any emergency use of a HUD to prevent serious harm or death to a patient without
24 prior local IRB approval must be reported by the physician to the IRB within 5 days
25 after the use of the device.
- 26 • Any withdrawal of approval for use of a HUD by an IRB must be reported promptly to
27 the holder of the HDE.
- 28 • All correspondence with the IRB must be submitted to the approved HDE holder.
- 29 • All medical device reports (MDRs) submitted to FDA by the approved HDE holder
30 must also be submitted to the IRB.

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- Any MDRs listing reportable events sent to the user of the HUD must be forwarded to the IRB.