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**SECTION:** RESEARCH

**AREA:** RESEARCH ADMINISTRATION

**SUBJECT:** UAMS POLICY ON MULTI-SITE INVESTIGATOR-INITIATED  
CLINICAL TRIALS

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### PURPOSE

The purpose of this policy is to establish the requirements for Investigator-initiated human research multi-site studies where the University of Arkansas for Medical Sciences is Sponsor for Investigational New Drug (IND) or Investigational Device Exemption (IDE) filings.

### SCOPE

This policy shall apply to all UAMS employees and students conducting Investigator-initiated human research studies irrespective of where the research is conducted.

### DEFINITIONS

**Device** – an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory that:

- a. Is recognized in the official National Formulary, the United States Pharmacopeia or any supplement to them.
- b. Is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in humans or other animals.
- c. Is intended to affect the structure or any function of the body of humans or other animals.
- d. Does not achieve any of its primary purposes through a chemical action within or on the body of humans or other animals, and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

**Drug** – An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body.

**External Funding Agency** – Any grantor, private organization, or pharmaceutical company providing funds, drugs, or a device for an Investigator-initiated research study.

**IDE** – An exemption that allows an investigational device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.

**IND** – Investigational New Drug application, a notice of claimed investigational exemption for a new drug.

**Investigational device** – a device, including a transitional device that is the object of an investigation.

**Investigator** – 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.

**Principal Investigator** - The responsible leader of a team in the event of an investigation conducted by a team of individuals. There is only one Principal Investigator per study.

**Monitor** – an appropriately trained individual who oversees an investigation and ensures that the trial is properly conducted and documented in accordance with the protocol, Sponsor’s requirements and applicable laws and regulations.

**Multi-center trial** – these are autonomous study sites located in areas other than the UAMS or Arkansas Children’s Hospital campuses.

**Sponsor** – an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization which takes responsibility for and initiates a clinical investigation. For purposes of this policy, UAMS is the Sponsor.

**Transitional device** – a device subject to section 510(l) of the Food, Drug and Cosmetic Act, as amended (the “Act”), that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

## **POLICY**

UAMS generally discourages the conduct of investigator-initiated multi-center clinical investigations under a UAMS sponsored IND or IDE application. UAMS is not a pharmaceutical or device company and is not structured or adequately supported to routinely conduct multi-center clinical investigations which require routine monitoring of the progress and conduct of the clinical investigation at each of the involved study sites. The investigator is encouraged to contact the Research Support Center for guidance prior to seeking study funding.

Under certain circumstances, there may be a need to include independent study sites in a proposed clinical study (e.g., clinical investigations involving relatively rare diseases or disorders). A process has been put in place to grant exceptions to this policy should an investigator wish to pursue a multi-center study. Investigators must provide adequate documentation and assurances that the proposed study will be conducted in such a manner that IND/IDE Sponsor responsibilities can be upheld in accordance with 21 CFR 312 or 21 CFR 812. Risks to the University and enrolled research participants must be routinely assessed and mitigated as appropriate. An IND/IDE Review Committee shall review requests to pursue multi-site research studies. The decisions of this committee are final; there is no appeal process.

## **PROCEDURE**

The Research Support Center staff shall obtain the following information from the investigator:

- a copy of the research protocol that will be used by all sites;
- UAMS IRB Number, if assigned;
- the number of anticipated external study sites (list the external study sites if known);
- an explanation of why it is necessary to conduct the clinical trial at external study sites;
- an explanation of the reason(s) why the pharmaceutical or device company providing support for the clinical trial does not wish to serve as the sponsor, as that term is defined in the Act, of the corresponding IND/IDE application (if applicable);
- a proposed budget that incorporates sufficient funding to address monitoring of the sites, planned payments to the individual study sites and, if applicable, a copy of the corresponding contract/agreement from the pharmaceutical or device company;

*Note: the contract/agreement from the pharmaceutical or device company, if applicable, should address (i.e., in addition to financial arrangements) the company's willingness to indemnify each of the study sites for an injury resulting directly from participation in the clinical trial or, at a minimum, the company's willingness to indemnify each of the study sites for an injury resulting from a defect (i.e., adulteration) in the study drug or device. In the absence of an existing contract/agreement with the pharmaceutical or device company, you should address whether or not the pharmaceutical or device company is willing to provide such indemnification(s).*

The research protocol should address the following issues:

- an explanation of how data received from all sites will be collected and used, what software application(s) (if applicable) will be used to capture the data, and where data will be stored;
- the plan/process/criteria (i.e. should reflect adequate expertise/experience) by which the multi-center principal investigator will evaluate/qualify/select site principal investigators for the clinical trial;
- The plan/process of documenting site principal investigator training on proper administration of the clinical protocol;
- the process by which all sites and Sponsor will be informed of protocol and consent changes;
- the process by which all sites and Sponsor will be informed of Adverse Effects (AE) particularly Life-threatening AEs, Serious AEs, and Unexpected AEs.

The IND/IDE Review Committee shall be comprised of the Vice Chancellor for Research, Vice Chancellor for Institutional Compliance, the Director of the Research Support Center (RSC), and representatives of the Monitoring, Contracts, and Regulatory Affairs Units of the RSC. This committee shall review all documents and shall invite the investigator to present his/her plan in support of multi-site studies to the Committee.

## **.Sponsor Responsibilities for IND Studies as defined in 21 CFR 312 Subpart D**

- A. The Sponsor shall select qualified investigators and provide them with the information they need to conduct the clinical trial properly:
1. Before permitting an Investigator to participate in a clinical trial, the Sponsor shall obtain from the Investigator and retain on file:
    - a. a signed Investigator's Statement (i.e., FDA Form 1572)
    - b. a current Curriculum Vitae
    - c. a signed Certification of Financial Interest of Clinical Investigators and, if applicable, a signed Disclosure of Financial Interest of Clinical Investigators
      - The Sponsor shall describe (i.e., in a written document attached to the corresponding Certification/Disclosure of Financial Interest) any steps taken to minimize the potential for bias resulting from the disclosed reportable financial interest of an Investigator.
  2. The Sponsor shall provide each Investigator with a copy of the current version of the Clinical Protocol and, for external study sites, an Investigator's Brochure, which should incorporate the following:
    - a. A brief description of the drug substance and the formulation, including the structural formula, if known.
    - b. A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
    - c. A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
    - d. A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)
    - e. A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.
    - f. Written procedures to ensure that clinical studies are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practices (GCPs), and applicable regulatory requirements.
    - g. Written procedures for the handling and storage of investigational products and the documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and disposition of unused or expired product.
  3. The Sponsor shall keep each participating Investigator informed of new observations regarding the investigational drug that are reported to the Sponsor, particularly with respect to adverse effects and safe use of the drug.

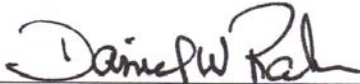
- a. The Sponsor shall copy all IND Safety Reports submitted to the FDA to each participating Investigator.
  - b. The Sponsor shall provide revised Investigator Brochures, Clinical Protocol Amendments, reprints of pertinent published articles, etc. to participating Investigators.
- B. The Sponsor shall ensure proper, periodic monitoring of the progress and appropriate conduct (i.e., in accordance with the clinical protocol) of the clinical trial at each of the study sites.
  1. The Sponsor shall ensure that the auditing of clinical studies/systems is conducted in accordance with the Sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
  2. The Sponsor shall assure that study sites have in place adequate investigational drug accountability records and that the investigational drug is being stored in a secure manner and in accordance with the Sponsor's established storage parameters (e.g., temperature, humidity, avoidance of light exposure, etc.) for stability of the drug.
  3. The Sponsor shall ensure that initial and ongoing IRB approvals have been obtained for the conduct of the clinical trial at each of the study sites.
  4. The Sponsor shall review monitoring/auditing reports of study sites and take appropriate action when warranted.
- C. The Sponsor shall review and evaluate evidence relating to the safety and effectiveness of the investigational drug as it is being obtained from the participating Investigators.
  1. The Sponsor shall have in place a process for ongoing, centralized data collection and analysis.
  2. The Sponsor shall establish a Data and Safety Monitoring Board for conducting ongoing, independent reviews of unblinded data and determining if there are any significant changes to the risk-to-benefit ratio of study participation.<sup>2</sup>
  3. The Sponsor shall promptly review and evaluate adverse event reports submitted by participating Investigators.
  4. The Sponsor shall submit written IND Safety Reports to the FDA and all participating Investigators.
  5. The Sponsor shall submit Annual Reports to the FDA and all participating Investigators.
  6. The Sponsor shall submit, when applicable, Protocol Amendments and IND Amendments in a timely manner to the FDA.
- D. The Sponsor shall establish systems for identifying and shall promptly review all other information relevant to the safety of the investigational drug, including information derived from other clinical investigations, animal investigations, reports in the scientific literature; as well as reports from foreign regulatory bodies.
- E. The Sponsor shall maintain adequate records of the receipt, shipment (e.g., to multi-center study sites), or other disposition of the investigational drug.

## **Sponsor Responsibilities for IDE Studies as defined in 21 CFR 812 Subparts C and G**

- A. The Sponsor shall select qualified investigators and provide them with the information they need to conduct the clinical trial properly:
1. Before permitting an Investigator to participate in a clinical trial, the Sponsor shall obtain from each participating Investigator a signed agreement that includes:
    - a. a Statement of the investigator's relevant experience, including the dates, location, extent, and type of experience
    - b. the investigator's Curriculum Vitae
    - c. If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination
    - d. a Statement of the investigator's commitment to:
      - i. Conduct the investigation in accordance with the agreement, the investigational plan, 21 CFR 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
      - ii. Supervise all testing of the device involving human subjects; and
      - iii. Ensure that the requirements for obtaining informed consent are met.
    - e. 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. The Sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
  2. The Sponsor shall supply all Investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.
- B. Sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of 21 CFR 812 or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. The Sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.
- C. Sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.
1. The Sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 days after the Sponsor first received notice of the effect.

2. If the device is a significant risk device, the Sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, the Sponsor may not resume a terminated investigation without IRB approval, and if the investigation was terminated under 21CFR 812.46(b)(2), FDA approval.
- D. The Sponsor shall maintain the following accurate, complete, and current records relating to an investigation:
1. All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.
  2. Records of shipment and disposition of the device in accordance with 21 CFR 812.140..
  3. Signed investigator agreements including the financial disclosure information required to be collected under 21CFR 812.43(c)(5) in accordance with 21 CFR 54.
  4. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints
  5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- E. The Sponsor shall prepare and submit the following complete, accurate, and timely reports:
1. Unanticipated adverse device effects
  2. Withdrawal of IRB approval
  3. Withdrawal of FDA approval
  4. Current Investigator list
  5. Progress reports
  6. Recall and device disposition
  7. Final report
  8. Use of device without informed consent
  9. Significant risk device determinations. If an IRB determines that a device is a significant risk device, and the Sponsor had proposed that the IRB consider the device not to be a significant risk device, the Sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the Sponsor first learns of the IRB's determination.
- F. Sponsor Responsibilities as defined in 21 CFR 812.2(b) *Abbreviated requirements apply to investigations of* a device other than a significant risk device, if the device is not a banned device and the Sponsor:
1. Labels the device in accordance with 21CFR812.5;
  2. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
  3. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care informed consent under 21 CFR 50 and documents it, unless documentation is waived by an IRB under Part 21CFR56.109(c)
  4. Complies with the requirements of 21CFR812.46 with respect to monitoring investigations;

5. Maintains the records required under 21CFR812.140(b) (4) and (5) and makes the reports required under 21CFR812.150(b) (1) through (3) and (5) through (10).
6. Ensures that participating investigators maintain the records required by 21CFR812.140(a)(3)(i) and make the reports required under 21CFR812.150(a)(1), (2), (5), and (7); and
7. Complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

Signature: 

Date: August 4, 2011