

## Guidance for Investigators Planning the Conduct of a Clinical Investigation at Multi-Center, External Study Sites Under a University-based IND/IDE Application

### I. Background Information:

In accordance with University of Pittsburgh policy (see [www.o3is.pitt.edu](http://www.o3is.pitt.edu), *Policies and Procedures: Sponsor-Investigator IND and IDE Applications*), the conduct of a multi-center clinical trial (i.e., a study involving one or more external study sites<sup>1</sup>) under a University-based IND or IDE application is only permitted upon satisfaction of the requirements set forth in this guidance. Faculty seeking to conduct a multi-site clinical trial under a University-based IND or IDE must have an acceptable plan to meet the Sponsor's obligation to routinely monitor the progress and the conduct of the study at each site and to manage the reporting requirements between site investigators and the Sponsor of the IND or IDE application. As outlined in Section II of this document, trials of this nature require in-depth planning, adequate funding to support the Sponsor's duties, as well as written procedures describing how Sponsor Responsibilities will be fulfilled. The procedures must be submitted to the University's Office for Investigator-Sponsored IND and IDE Support (O3IS) for prior review and approval. **Note that sponsors who are approved to conduct multi-center research under an FDA-accepted IND/IDE application will be required to complete a meeting with the O3IS Director and the ECO-HSR Medical Monitor prior to study implementation.**

Sponsor-investigators are encouraged to explore alternatives for the conduct of their research prior to submitting an approval request to the O3IS. These alternatives are outlined below.

#### A. Does the planned clinical trial, in fact, require the submission and FDA-acceptance of an IND or IDE application?

Note that there are multiple categories of drug and device studies that do not require the submission and FDA-acceptance of an IND or IDE application; provided that certain criteria apply:

---

<sup>1</sup>An *external study site* is defined as a study site external to the University of Pittsburgh and UPMC domestic facilities.

<sup>2</sup>Off-label – when a drug is used in a different way than described in the FDA approved drug label.

*Per 21 CFR § 312.2 Applicability*

*(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;*

*(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;*

*(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;*

*(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and*

*(v) The investigation is conducted in compliance with the requirements of § 312.7.*

**It is recommended that investigators initially contact the University's Office for Investigator-initiated IND and IDE Support (O3IS; 412-383-1502) for guidance regarding the requirement for the submission of an IND or IDE application for their planned clinical trial.** (See also [www.o3is.pitt.edu](http://www.o3is.pitt.edu); *General Requirements for the Submission of IND Applications for Clinical Research* or *General Requirements for the Submission of IDE Applications for Clinical Research*)

**B. If the planned clinical trial does require the submission and FDA-acceptance of an IND or IDE application, would it be possible for each of the external study sites to each submit their own IND or IDE application incorporating the common clinical trial protocol?**

By using this approach, Sponsor and Investigator responsibilities and associated regulatory compliance liabilities are assumed independently by each of the external study sites rather than globally by the University of Pittsburgh. The University of Pittsburgh study site can serve as the coordinating center for the multi-center clinical protocol.

**C. If the planned clinical trial is an “investigator-initiated” evaluation of a FDA-approved drug or device for an “off-label” indication, why is it not being conducted under an IND or IDE application held by the respective pharmaceutical or device company?**

As summarized above, clinical trials directed at evaluating a FDA-approved drug or device for an “off-label” clinical indication may be

exempt from the requirement for the submission of an IND or IDE application provided that certain criteria apply. Investigators should provide a thorough justification for why such a study should proceed under a Sponsor-Investigator held IND or IDE application.

## **II. Requesting O3IS Approval to Include External Study Sites Under a University-based IND or IDE Application**

To request approval to conduct a study at an external study site, the following information should be provided to the O3IS Office. The O3IS Office may approve a request, may ask for additional information or for changes in the monitoring plan, or may reject the request for failure to meet the requirements of this Guidance. Any request that is rejected may be appealed to the Institutional Official, whose decision shall be final.

- A. Cover Letter: Provide a Cover Letter incorporating your request to conduct the clinical trial at one or more external study sites.

Provide within the Cover Letter:

- a. the title of the clinical trial;
  - b. the source of funding for the clinical trial (e.g., NIH or other federal grant number, industry sponsor, or departmental funds);
  - c. the number of anticipated external study sites;
    - Provide a list of the external study sites and corresponding study site Investigators
  - d. a justification for why it is necessary to conduct the clinical trial at external study sites; and
  - e. a justification for why it is not possible for each of the external study sites to file their own sponsor-investigator IND or IDE applications (i.e., via reference to the University of Pittsburgh application); to include the incorporation of a common clinical protocol and the designation of the University of Pittsburgh study site as the data coordinating center.
- B. If the clinical protocol involves an evaluation of the safety and/or effectiveness of a FDA-approved drug or device for a clinical indication that appears in the product labeling or for an “off-label” indication, also provide in the Cover Letter:

1. a justification for why it is necessary to conduct the clinical trial under a sponsor-investigator IND or IDE application; and

C. Attach to the Cover Letter:

1. a copy of the multi-center clinical trial protocol;
2. a copy of the IND/IDE Sponsor's written procedures for addressing the following processes:
  - a. the Sponsor's selection of the external study sites that will be involved in the conduct of the clinical trial.
  - b. the Sponsor's selection of external study site Investigators and criteria for ensuring that these individuals are appropriately qualified by education, training, experience and state licensure to conduct the clinical trial.
  - c. the Sponsor's procurement, from each external study site Investigator, of a curriculum vitae and signed Form FDA 1572 (for IND applications) or Statement of Investigator (for IDE applications).
  - d. the Sponsor's collection and maintenance of current financial disclosure information for each external study site Investigator and for all external study site Sub-investigators who will be involved in the treatment and/or evaluation of research subjects; to include the Sponsor's review of this information for possible financial conflicts-of-interest and the Sponsor's management of identified financial conflicts-of-interest.
  - e. the Sponsor's dissemination of the clinical trial protocol to the external study site Investigators and for ensuring that the these Investigators:
    - i. understand the nature and purpose of the clinical trial and the clinical trial procedures;
    - ii. are capable of conducting or supervising the conduct of the clinical trial; and
    - iii. are aware that any Investigator-recommended changes to the clinical trial protocol must be first communicated to the Sponsor, who is ultimately responsible for making such changes.
  - f. the Sponsor's maintenance of documentation regarding

- i. initial and continuing responsible (i.e., for the external study site) IRB review and approval for the conduct of the clinical trial at each of the external study sites.
- g. the Sponsor's maintenance of the certifications and current normal value ranges for external study site laboratories that will be involved in the performance of clinical trial safety and effectiveness evaluations.
- h. the Sponsor's distribution of the investigational drug or device to the external study sites; to include, if applicable, ensuring accountability of the investigational drug or device at the Sponsor's manufacturing and/or central storage location.
- i. the Sponsor's review of adverse event information received from the external study sites and the Sponsor's reporting of serious and unexpected adverse events (i.e., associated with the investigational drug or device) to the FDA; to include the requisite timeframe for this review and reporting
- j. the Sponsor's reporting, to the external study site Investigators, of new risk information related to the drug(s) or device(s) under investigation; to include the requisite time frame for the prompt dissemination of this information.
- k. the Sponsor's reporting, to the external study site Investigators, of changes to the clinical trial protocol; to include the requisite time frame for the prompt dissemination of this information.
- l. the Sponsor's verification that the external study site Investigators have submitted new risk information and protocol changes to their responsible IRBs and that IRB-approval of respective research protocol/consent form modifications has been obtained.
- m. the Sponsor's plan for independent monitoring, *via a Contract Research Organization*, or *via an approved monitor within the University that is not under direct supervision of the Sponsor*, to evaluate the progress and conduct of the clinical trial at each of the external study sites; to include the frequency of conducting the monitoring, and the reporting of the monitoring outcomes to the Sponsor.

This monitoring should provide assurance for the following:

- The clinical trial is being conducted in accordance with the current version of the clinical trial protocol and applicable regulations and policies
  - The rights, safety and welfare of the research subjects are being adequately protected
  - Adequate and accurate case histories are maintained and that these documents record all observations and other data pertinent to the evaluation of the investigational drug or device; are contemporaneous and original; and that information in the source documents is accurately captured on the case report form
  - The investigational drug or device is being adequately controlled
  - The research records are being maintained in a secure for the retention period specified by FDA regulations, the University of Pittsburgh and the funding entity.
- n. the Sponsor's plan for addressing missing data and data discrepancies identified by the external study site investigator, sub-investigators, research staff or study monitor
- o. the Sponsor's review of monitoring reports, protocol deviations, and other unanticipated problems received from the external study site(s); to include how the Sponsor will respond to identified Investigator and/or external study site non-compliance or other deficiencies.
- p. the Sponsor's preparation of Protocol Amendments (i.e. for IND applications), Supplemental IDE Applications, Annual Reports, Investigator Lists (i.e., IDE application.)
- q. the Sponsor's direct or delegated (e.g., to a Data and Safety Monitoring Board), ongoing review and evaluation of evidence related to the overall safety and effectiveness of the drug(s) or device(s) under investigation; to include, when applicable, discontinuation of those clinical trials that present an unreasonable and significant risk; respective notification of the FDA, the Investigator(s), and the responsible IRB(s); disposition of remaining supplies of the investigational drug or device; and the requisite time frame for these actions.
- r. the Sponsor's preparation of an adequate Final Study Report following completion of the clinical trial and the submission of this report to the FDA.

3. a copy of the IND/IDE Sponsor's Investigator's Brochure, which will be distributed to each of the external study sites. The Investigator's Brochure should contain the following information:
  - a. A brief description of the investigational drug or investigational device; to include, for investigational drugs, the structural formula and the formulation.
  - b. A summary of the safety evaluations of the investigational device in animals and, to the extent known, in humans; or a summary of the pharmacokinetics, pharmacological and toxicological effects of the investigational drug in animals and, to the extent known, in humans.
  - c. A summary of information relating to the safety and effectiveness of the investigational device or investigational drug in humans obtained from prior clinical studies.
  - d. A description of possible risks and side effects to be anticipated on the basis of prior experience with the device or drug under investigation or with related devices or drugs; and of precautions or special monitoring to be done as part of the experimental evaluation or use of the investigational device or drug.
  - e. External study site procedures for:
    - i. maintaining appropriate accountability of investigational drug(s) or device(s) at the external study site.
    - ii. obtaining responsible IRB approval for the conduct of the clinical trial at the external study site; to include notifying the Sponsor of any IRB-requested changes to the clinical trial protocol (i.e., as a condition of obtaining IRB approval) and providing the Sponsor with a copy of the final IRB approval notification and IRB-approved consent form.
    - iii. maintaining an up-to-date, clinical trial-specific list of appropriately qualified Sub-investigators and research staff to whom the external study site Investigator has delegated significant clinical trial tasks.
      - This list should describe the delegated tasks, identify (e.g., curriculum vitae) the training that these individuals have received which qualifies them to perform their delegated tasks, and specify the dates of these individuals' involvement in the clinical trial.

- Sign-off signatures of the respective Sub-investigators and research staff should be obtained as documentation that these individuals have knowledge of and have accepted their delegated tasks.
- iv. providing the Sponsor with appropriate certifications and current normal value ranges for external study site laboratories that will be involved in the performance of clinical trial safety and effectiveness evaluations.
- v. maintaining adequate and accurate case histories (i.e., completed case report forms) that record all observations and other data pertinent to the evaluation of the investigational drug(s) or device(s).
- vi. ensuring that source data are accurate, contemporaneous and original; and that information in source documents is accurately captured on the case report form.
- vii. addressing missing data and data discrepancies identified by the external study site Investigator, Sub-investigators, research staff or study monitor.
- viii. maintaining research records in a secure manner for the retention period specified by FDA regulations and by the funding entity.
- ix. permitting access of the IND/IDE Sponsor, or his/her representatives, to the private information/protected health information of research subjects who participate in the clinical trial at the external study sites. (Note: Access of the IND/IDE Sponsor, or his/her representatives, to the private/protected information of research study participants must also be addressed in the respective informed consent document and in the sub-award contract executed with the parent organization for each of the external study sites.)
- x. reporting, to the Sponsor, of current financial disclosure information for the external study site Investigator and for all external study site Sub-investigators who will be involved in the treatment and/or evaluation of research subjects.
- xi. the prompt or immediate (i.e., if the adverse event is alarming) reporting, to the Sponsor, of adverse events identified by or reported to the external study site Investigator; to include the requisite time frame for this reporting.

- Note that the process for the reporting of adverse events to the external study site Investigator and subsequently to the Sponsor must ensure that such reporting occurs within a time frame that permits the Sponsor and the Investigator to be compliant with the requirements for the reporting, if applicable, of serious and unexpected adverse events to the FDA and reviewing IRB.
  - reporting, to the Sponsor, of protocol deviations and other unanticipated problems (e.g., medical and ethical issues that may arise during the course of the clinical trial) identified by or reported to the external study site Investigator; to include the requisite time frame for this reporting.
  - notifying the Sponsor of the responsible (i.e., for the external study site) IRB's review of new risk information provided to the external study site Investigator by the Sponsor, and notifying the Sponsor of the responsible IRB's approval of research protocol changes provided to the Investigator by the Sponsor and/or in response to the IRB's review of the new risk information provided by the Sponsor.
  - the preparation of external study site Progress Reports and of an adequate Final Study Report (i.e., following completion of the clinical trial at the external study site) and the submission of these reports to the Sponsor and the responsible IRB.
- 4. a copy of the Case Report Form(s) that will be utilized for the planned clinical trial.
- 5. a copy of the budget corresponding to the Sponsor responsibilities described under B.2., above, and evidence of the availability of adequate financial resources (i.e., from current grants or department funding) to address this budget. (Note: the availability of adequate financial resources may be addressed by providing a letter of respective financial support from the IND/IDE Sponsor's department chair.)
- 6. a Biosketch of the Sponsor of the IND or IDE application (Note: This biosketch should reflect adequate expertise/experience to serve as the Sponsor of a multi-center clinical trial.)