University of Pittsburgh | Education and Compliance for Human Subject Research | Office of Research Protections

POLICIES AND PROCEDURES

University of Pittsburgh Office of Research Protections
Division of Education and Compliance Support for Human Subject Research: Policies and Procedures - May 24, 2022

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I. General Information

A. Applicability

The Division of Education and Compliance Support for Human Subject Research (ECS-HSR) policies and procedures are applicable to Food and Drug Administration (FDA) regulated Investigational New Drug (IND) and Investigational Device Exemption (IDE) held by qualified University of Pittsburgh faculty members (i.e., University-based).

In addition to traditional IND and IDE applications, these policies and procedures are also applicable to University-based Expanded Access INDs (single patient or intermediate size patient populations), unless an exception is granted by ECS-HSR. These policies and procedures do not apply to Emergency Use INDs or IDEs (refer to University of Pittsburgh IRB guidance for information regarding the submission of Emergency INDs and IDEs. https://www.hrpo.pitt.edu/emergency-use-and-single-patient-expanded-access).

B. Purpose

Although the Sponsor of an IND or IDE is often a drug or device company, the FDA regulations that govern IND and IDE applications and the University of Pittsburgh allow a qualified individual to serve as the Sponsor. The conduct of a clinical investigation under an FDA-accepted IND or IDE application invokes a complex set of FDA regulations, requirements, and obligations. As such, these policies and procedures are intended to educate and inform faculty and staff on the requirements and expectations for conducting a clinical investigation under a University-based IND or IDE application.

Proper adherence to the regulations, requirements, and obligations surrounding University-based IND and IDE applications is critical to managing related risks. Such risks include, but are not limited to, morbidity and mortality of clinical trial participants; tort liability claims; federal citations and sanctions; and the FDA's non-acceptance of accrued clinical trial data submitted in support of subsequent University- or industry-sponsored applications (e.g., INDs, NDAs, IDEs, PMAs).

II. IND and IDE Support Policies and Procedures

A. General Policy

All University-based IND and IDE applications and all documents relevant to such applications must be submitted to the FDA through IND and IDE Support (IIS).

Sponsor: An individual who takes responsibility for and initiates a clinical investigation. The Sponsor does not actually conduct the clinical investigation unless the Sponsor is a Sponsor-Investigator.

Investigator: An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the investigational drug or test article is administered or dispensed to a

subject). In the event an investigation is conducted by a team of individuals, the Investigator is the responsible leader of the team.

Sponsor-Investigator: An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a Sponsor-Investigator under this part include both those applicable to an Investigator and a Sponsor.

1. Sponsor and Investigator are the Same Individual

The Sponsor of the IND or IDE application should be the University of Pittsburgh Investigator who is responsible for the design of the corresponding clinical investigation and who is qualified by training and experience to oversee the conduct of the clinical investigation at the University or UPMC site. When the Sponsor is also acting as the Investigator, they are acting as a Sponsor-Investigator of the IND or IDE application and are subject to compliance with both the FDA regulations governing the responsibilities of the Sponsor and the FDA regulations governing the responsibilities of an Investigator. For INDs, refer to 21 CFR Part 312 Subpart D, and for IDEs 21 CFR Part 812 Subpart C (Sponsor Responsibilities) and Subpart E (Investigator Responsibilities)

2. Sponsor and Investigator are not the Same Individual

In some cases, the Sponsor of the IND or IDE application and the Investigator may be different individuals. This scenario creates certain documented reporting requirements between the Sponsor and the Investigator, even though these two individuals may be located within the same academic unit. Most notably is the commitment by the Investigator not to make any changes to the protocol without first receiving documented approval by the Sponsor.

3. Considerations

Before preparing an IND or IDE application, the Sponsor of the IND or IDE should determine that:

- They have sufficient resources (e.g., facilities, equipment, staff) and an adequate budget to conduct the clinical protocol(s) incorporated into the IND or IDE application and to comply with applicable FDA regulations and institutional requirements; and
- They are fully aware of the regulatory responsibilities of the Sponsor of an IND or IDE application; and
- There are enough eligible research subjects available to meet the statistical requirements for subject accrual as specified in the clinical protocol(s) incorporated into the IND or IDE application.

University-based IND or IDE applications should incorporate, into the respective grant or contract application, sufficient funding to address all the regulatory responsibilities associated with being an IND or IDE Sponsor.

B. Compliance for Laboratories Supporting an IND or IDE Application

NOTE: This section of the ECS-HSR policies and procedures only applies to IND or IDE applications where the basis of the Pharmacology Toxicology section is carried out in a University of Pittsburgh laboratory, or the investigational product is being manufactured at the University of Pittsburgh.

1. GLP Compliance for Non-clinical Studies Submitted in Support of an IND or IDE Application

Non-clinical (i.e., animal or laboratory) safety and efficacy studies that support, or are intended to support, IND or IDE applications must, in general, be conducted in compliance with the FDA's Good Laboratory Practice (GLP) regulations at 21 CFR Part 58.

a) Use of University of Pittsburgh or UPMC Laboratories

There are currently no GLP compliant laboratories at the University of Pittsburgh or UPMC. As there are no GLP compliant laboratories, an external lab should be consulted.

b) The Sponsor of the IND or IDE application will assume financial responsibility for the cost of the audits of GLP compliance. Use of External or Contract GLP Facilities

If an external (e.g., contract) facility will be used for the conduct of the GLP-compliant, non-clinical studies, the external facility will be subject to providing written documentation of its GLP certification, FDA registration, or other evidence of GLP compliance.

If the selected external facility is not able to provide written evidence of GLP compliance, it will be subject to a pre-qualification audit of GLP compliance performed by a qualified consultant. The external facility or Sponsor of the IND or IDE application will assume financial responsibility for the cost of the pre-qualification audit of GLP compliance.

The use of an external facility for the performance of the GLP-compliant, non-clinical studies will be described in writing in the IND or IDE application.

(1) Charles River Laboratories

The University of Pittsburgh has entered into a Master Agreement with Charles River Laboratories (CRL). The agreement allows faculty a free consultation with a representative of CRL to discuss the development of GLP studies and a cost estimate. Faculty can contract via the University of Pittsburgh Purchasing Services to have CRL perform the required GLP studies at a cost. Faculty interested in requesting a consult with CRL should contact IIS@pitt.edu.

2. cGMP Compliance for the Manufacture of Investigational Drugs

Drugs being used or evaluated in Phase 2 or 3 clinical investigations being conducted under an IND application must, in general, be prepared (i.e., manufactured) in strict compliance with the FDA's current Good Manufacturing Practice (cGMP) regulations at 21 CFR Parts 210 and 211 (or 21 CFR Part 212 for Positron Emission Tomography drug products).

Drugs being used or evaluated in Phase 1 clinical investigations being conducted under an IND application must be prepared (i.e., manufactured) in accordance with the principles of cGMP.

a) Use of University of Pittsburgh or UPMC Facilities

For University-based IND applications that propose the on-site manufacture of the investigational drug within a University or UPMC facility; compliance with the FDA's cGMP requirements may be subject to pre-qualification and continuing audits performed by a qualified consultant.

The Sponsor of the IND application will assume financial responsibility for the cost of the audit of cGMP compliance.

b) Use of External or Contract cGMP Facilities

For University-based IND applications that propose the cGMP manufacture of the investigational drug by an external facility; either the drug must be currently approved for general marketing by the FDA or the external facility will be subject to providing written documentation of its cGMP certification, FDA registration, or other evidence of cGMP compliance.

In the absence of being able to provide written evidence of its cGMP compliance, the external facility used for the manufacture of the investigational drug will be subject to pre-qualification and continuing audits of cGMP compliance performed by a qualified consultant.

The Sponsor of the IND application will assume financial responsibility for the cost of the audit of cGMP compliance.

The use of an external facility for the cGMP-compliant manufacture of the investigational drug will be described in the initial IND application and/or, if the use of an external manufacturing facility is later selected, will be described in an Information Amendment to the FDA-accepted IND application.

3. Quality System (i.e., cGMP) Compliance for the Manufacturing of Investigational Devices

Devices being evaluated for safety and effectiveness under an IDE application must, in general, be manufactured in accordance with the Design Controls section of the FDA's Quality System regulations at 21 CFR Part 820.

a) Use of University of Pittsburgh or UPMC Facilities

For University-based IDE applications that propose the on-site manufacture of the investigational device within a University or UMPC facility; compliance with the FDA's Quality System/Design Control requirements and will be subject to pre-qualification and continuing audits performed by a qualified consultant.

The Sponsor of the IDE application will assume financial responsibility for the cost of the audit of Quality System/Design Control requirements.

b) Use of External or Contract cGMP Facilities

For University-based IDE applications that propose the cGMP manufacture of the investigational device by an external facility; either the device must be currently approved for general marketing by the FDA or the external facility will be subject to providing written documentation of its Quality System/Design Control certification, FDA registration, or other evidence of Quality System/Design Control compliance.

In the absence of being able to provide written evidence of its Quality System/Design Control certification, the external facility used for the manufacture of the investigational device will be subject to pre-qualification and continuing audits of Quality System/Design Control requirements performed by a qualified consultant.

The Sponsor of the IDE application will assume financial responsibility for the cost of the audit of Quality System/Design Control requirements.

The use of an external facility for the Quality System/Design Control compliant manufacture of the investigational drug will be described in the initial IDE application and/or, if the use of an external manufacturing facility is later selected, will be described in a Supplement to the FDA-accepted IDE application.

C. Funding for Laboratories

1. Grant or Contract Proposals to Establish a University- or UPMC- Based GLP Facility

All grant, contract, or other proposals or agreements directed at establishing a University- or UPMC-based GLP facility for the performance of non-clinical (i.e., animal or laboratory) studies should be discussed with the University's Office of Sponsored Programs (OSP) and Office of Research Protections (ORP) leadership well in advance of submission to the funding agency.

2. Grant or Contract Proposals to Establish a University- or UPMC- based cGMP Facility

All grant, contract, or other proposals or agreements directed at establishing a University- or UPMC-based GMP or Quality System facility for the manufacturing of investigational

drugs or devices for use under IND or IDE applications should be discussed with the University's OSP and ORP leadership well in advance of submission to the funding agency.

D. Procedures

1. Procedures for FDA Submissions

All University-based IND and IDE applications and all documents relevant to such applications must be submitted to the FDA through IIS. Additionally, all requests for a Pre-IND meeting or Pre-submission for IDEs must be submitted to the FDA through IIS.

- **Initial IND applications** are to be sent by e-mail to IIS@pitt.edu and should include a single merged PDF including the following:
  - Cover letter
  - Completed Form FDA 1571
  - Completed Form FDA 1572
  - Completed Form FDA 3674
  - IND application (to include Chemistry, Manufacturing, and Control information, Pharmacology and Toxicology information, and Clinical Protocol)
  - Sponsor-Investigator CV
  - Other appendices as needed

  Please refer to the IIS webpage for IND application templates and FDA Forms https://www.ecshsr.pitt.edu/ind-ide-support.

- **Subsequent submissions to an FDA-accepted IND application** are to be sent by e-mail to IIS@pitt.edu merged as a single PDF. Subsequent submissions include:
  - Annual Reports
  - Protocol Amendments (Change in Protocol, New Protocol, New Investigator)
  - Informational Amendments
  - Change in Sponsor only
  - Change in Sponsor-Investigator
  - IND Safety reports
  - Inactivation requests
  - Withdrawal requests

  Please refer to the IIS webpage for IND templates https://www.ecshsr.pitt.edu/ind-ide-support/investigational-new-drug-ind-templates.

- **Initial IDE applications** are to be sent by e-mail to IIS@pitt.edu and will include the following:
  - Cover letter
  - IDE application (to include Report of Prior Investigations, Investigational Plan, and Methods, Facilities and Control information)
  - Sponsor-Investigator CV
  - Informed Consent Document
  - Other appendices as needed

  Please refer to the IIS webpage for IDE templates https://www.ecshsr.pitt.edu/ind-ide-support/investigational-device-exemption-ide-templates

- **Subsequent submissions to an FDA-accepted IDE application** are to be sent by e-mail to IIS@pitt.edu. Subsequent submissions include:
  - Reports:
    - Progress Report
    - Unanticipated Adverse Device Effect Report (if applicable)
    - Withdrawal of IRB Approval Report (if applicable)
    - Current Investigator List (if applicable)
    - Recall and Device Deposition Request (if applicable)
    - Failure to Obtain Informed Consent Report (if applicable)
    - Final Report
  - IDE Supplements
  - 5-Day Notifications

  Please refer to the IIS webpage for IDE templates https://www.ecshsr.pitt.edu/ind-ide-support/investigational-device-exemption-ide-templates

III. Monitoring and Compliance Policies and Procedures

The Sponsor of the IND or IDE application needs to fulfill required monitoring as specified in 21 CFR Part 312.56 and 21 CFR Part 812.46.

A. ECS-HSR Monitoring of Clinical Trials under a University-based IND or IDE

Unless other acceptable arrangements are made, the Education and Compliance Support (ECS) Coordinators will provide local monitoring as described in the monitoring plan. The monitoring services assist the Sponsor in fulfilling their requirement to monitor the progress of the clinical investigation(s). The Sponsor is ultimately responsible for ensuring protocol compliance and the integrity of the study data.

There are three types of monitoring visits: initial, interim, and close-out visits. A report summarizing each monitoring visit is generated by the ECS Coordinator and provided to the appropriate parties. All monitoring visit reports are reviewed by the Compliance Activity Reviews (CARs) Committee and may also be reviewed by the IRB Executive Committee.

B. Non ECS-HSR Monitoring of Clinical Trials under a University-based IND or IDE

If the Sponsor has contracted with an independent monitoring Agency (e.g., a CRO), or the University of Pittsburgh Center for Clinical Trials and Data Coordination (CCDC), the Sponsor will provide the IIS with copies of all monitoring reports and subsequent correspondence within four weeks of the site visit. All monitoring visit reports are reviewed by the CARs Committee and may also be reviewed by the IRB Executive Committee.

The Sponsor of the IND or IDE application will assume responsibility for the costs of monitoring the progress and appropriate conduct of the clinical investigation at each of the involved study sites.

C. Fees

The ECS-HSR does charge a moderate fee for its routine monitoring services. If the funding agency, Sponsor or ORP leadership, requires additional monitoring visits than routinely provided by the ECS-HSR, a supplemental monitoring fee may be required. Please refer to https://www.ecshsr.pitt.edu/ for the current fee structure.

D. Procedures

The ECS-HSR standard operating procedures can be found at https://www.ecshsr.pitt.edu/standard-operating-procedures.

IV. Clinical Trials Registration & Transparency Support Policies and Procedures

A. Policies for ClinicalTrials.gov

1. **Determining whether to register:** The study initiator/sponsor (responsible for overall study preparation, planning and control; when applicable, the FDA IND/IDE holder) is responsible for determining whether to register the study, per guidance provided at https://www.ecshsr.pitt.edu/ct/registration.
2. **Determining Sponsor Organization**: Only studies initiated by an individual primarily affiliated with the University of Pittsburgh or UPMC should be registered in the University of Pittsburgh account.
3. **Determining Responsible Party**
   a) The Responsible Party of an FDA-regulated study is the Sponsor-Investigator. If the Sponsor is not also the Investigator, the Sponsor may designate the Investigator as Responsible Party, so long as: the Investigator is responsible for conducting the study, has access to and control over the data from the study, has the right to publish the results of the study, and has the ability to meet all of the requirements for the submission of clinical study information.

b) The Responsible Party of a study that is not FDA-regulated is the IRB approved Principal Investigator.

B. Procedures for ClinicalTrials.gov

Responsible Parties should follow the guidance and procedures specified at https://www.ecshsr.pitt.edu/ct governing registration, record maintenance, summary results information submission, and study document submission.

V. General ECS-HSR Policies

A. Conflict of Interest

Note that there are specific FDA requirements in addition to University of Pittsburgh's requirements. The Sponsor of the IND or IDE application will obtain and maintain completed and signed certifications and disclosures (if applicable) of financial interests for each study site Investigator and for Sub-investigators who may be involved in the treatment and/or evaluation of research subjects under the direction of the study site Investigator. These completed forms should be kept within the regulatory binder. It is the investigator's responsibility to ensure that these forms are updated and are consistent with information submitted to the MyDisclosures System.

Conflicts reported to or discovered by the ECS-HSR will be managed through the Conflict of Interest (COI) Office. The COI management plan will be kept in the regulatory binder.

B. Multi-center Clinical Trials

1. Multiple University of Pittsburgh or UPMC Sites

University policy does not place restrictions on the conduct of a clinical investigation at multiple University of Pittsburgh and/or UPMC (Pitt/UPMC) study sites under a University-based IND or IDE application. However, if such is being planned, it must be recognized that the FDA regulations governing IND and IDE applications define an Investigator as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject)."

Thus, consideration should be given as to whether a single Investigator can adequately direct or supervise the conduct of the clinical investigation at multiple Pitt/UPMC study sites. Sponsors of University-based IND and IDE applications should also be aware that the FDA has placed certain limitations on what the agency regards as "adequate Investigator supervision" of the clinical investigation. Refer to the FDA Guidance document, Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Participants, at https://www.fda.gov/media/77765/download. Sponsors of University-based IND or IDE applications should consider appointing a separate study site Investigator for each of the involved Pitt/UPMC study sites.

2. Multiple External Sites

The conduct of a multi-center clinical trial (i.e., a study involving one or more external study sites) under a University-based IND or IDE application is only permitted upon satisfaction of the requirements set forth by the ECS-HSR.

Sponsors 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, as outlined in the federal regulations, to 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.

Sponsors planning the conduct of a multi-center clinical investigation under a University-based IND or IDE application should incorporate, into the respective grant or contract application, sufficient funding to address all of the regulatory responsibilities associated with being an IND or IDE Sponsor. The IND or IDE Sponsor must also establish appropriate processes and procedures directed at addressing these responsibilities. The existence of these processes and procedures and the adequacy of available funding to support these processes will be the major considerations in the decision to permit the involvement of external study sites under a University-based IND or IDE application.

Please refer to https://www.ecshsr.pitt.edu/multicenter-guidance-content for additional information and required application.

C. GCP Training and Requirements in the Conduct of Clinical Trials

All Investigators and research team members who are engaged in the conduct, oversight, or management of clinical trials (as defined by the NIH) are required to complete the CITI GCP for Clinical Trials with Investigational Drugs and Medical Devices (US FDA focused) training course before they participate in any research activities. The University has extended this requirement to all research studies that meet the definition of a clinical trial regardless of the funding source.

It is the responsibility of the Sponsor-Investigator to ensure that all members of the research team who meet this requirement (see guidance below) complete FDA GCP training requirements and maintain certification during the course of the study.

Those required to take FDA GCP training include those who:

1. Manage participant recruitment and enrollment, including obtaining consent
2. Perform research procedures or evaluations
3. Contribute significantly to the collection and recording of research data or
4. Contribute significantly to data management
5. Have more than minimal contact with the research subjects or their identifiable study records or specimens

Those not required to take GCP training include:

Hospital staff (including nurses, residents, fellows, or office staff) who provide ancillary or intermittent care but do not make a direct and significant contribution to the study or administrators or individuals who perform routine or supportive tasks related to the research.

To assist with conducting the investigation under the principles of GCP, Sponsor-investigators should follow the University of Pittsburgh Guideline: Study Documentation for FDA Regulated Research and Clinical Trials found at https://www.ecshsr.pitt.edu/monitoring-compliance/good-clinical-practice-gcp-toolbox.

D. Data and Safety Monitoring Board

The FDA regulations governing IND and IDE applications specify that it is the Sponsor's responsibility to review and evaluate the evidence relating to the safety and effectiveness of the investigational drug or device as it is being obtained from the Investigators. These regulations further specify that it is the Sponsor's responsibility to discontinue those clinical investigations that present an unreasonable and significant risk to subjects and to notify the FDA, the responsible IRBs, and all currently or previously involved Investigators of the discontinuance.

Should a Data Safety Monitoring Board (DSMB) be established for a clinical investigation being conducted under a University-based IND or IDE application, it will serve in an advisory capacity to the IND or IDE Sponsor regarding identified changes to the risk-to-benefit ratio of the clinical investigation, continuation of the clinical investigation, and other pertinent issues. Any discussions of the role of the DSMB within the clinical protocol or other sections of the IND or IDE application should recognize the regulatory responsibilities of the Sponsor of the IND or IDE application as they relate to the review of safety and effectiveness information and the decision to discontinue any clinical investigation that presents an inordinate risk to research subjects. Such reviews and decisions should not be made directly and solely by the DSMB.

E. Compliance with 21 CFR Part 11

The Sponsor of the IND or IDE application should maintain compliance with 21 CFR Part 11 when using electronic records in place of paper copies. Regulations apply to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations.

F. University Oversight

1. The University's Human Research Protections (HRP) Division's Pitt Protocol Review Online (PittPRO) system automatically notifies the ECS-HSR upon its initial receipt and initial approval of a clinical investigation being conducted under a University-based IND or IDE application.

2. The PittPRO system automatically notifies the ECS-HSR upon its receipt of a modification request for a clinical investigation being conducted under a University-based IND or IDE application. The IIS will review the proposed modification(s) and advise the IND or IDE

Sponsor of the requirement, if applicable, to submit prospectively a corresponding Protocol Amendment or Supplemental IDE application to the FDA-accepted IND or IDE application.

3. The PittPRO system automatically notifies the ECS-HSR of reportable new information reported to the University IRB for clinical investigations being conducted under a University-based IND or IDE application. The IIS will ensure that a corresponding Safety Report has been submitted by the IND or IDE Sponsor to the respective IND or IDE application.

4. The PittPRO system automatically notifies the ECS-HSR of the termination of clinical investigations being conducted under a University-based IND or IDE application. The IIS will advise the IND or IDE Sponsor of the need for termination or withdrawal of the corresponding IND or IDE application.

5. The IIS will promptly notify the University HRP of a "clinical hold" issued by the FDA for a clinical investigation being conducted under a University-based IND and IDE application and/or of any other FDA actions or determinations (e.g., FDA '483' citations, FDA warning letters) that may impact the ethical and safe conduct of such clinical investigations.

6. The IIS will maintain an active database of University-based IND and IDE applications; to include the date of initial FDA receipt and/or final acceptance of the application. The IIS will send to IND or IDE Sponsors timely reminders of the requirement to submit Annual Reports to the FDA-accepted IND or IDE application.

7. The ECO-HSR will monitor the research oversight programs of Sponsors of IND or IDE applications wherein ongoing clinical investigations are being conducted under the application. These monitoring visits will include an assessment of Sponsor and Investigator compliance with applicable FDA regulations, applicable University of Pittsburgh policies and the IRB-approved protocol and consent document. The frequency of these monitoring visits will be outlined in a monitoring plan.

G. Institutional Disapproval of University-based IND or IDE Applications

The Vice Chancellor for Research Protections (i.e., Institutional Official) has the right to disapprove the submission of a University-based IND or IDE application and/or require the Sponsor to terminate or withdraw an FDA-accepted, University-based IND or IDE application.

H. Departure of Sponsor-Investigator from the University of Pittsburgh

Prior to departure from the University of Pittsburgh, the Sponsor should review the Checklist for Departing Investigators. The Sponsor-Investigator of an active IND or IDE application is required to notify the ECS-HSR to discuss the plans for the disposition of the IND or IDE, which may include withdrawal of the IND or IDE, transferring the IND or IDE to another appropriately qualified University faculty member or transferring the IND or IDE to their new institution.