University of Pittsburgh O3IS
Policies and Procedures:
University-based IND and IDE Applications

I. Policies and Procedures

Purpose of Policies

University of Pittsburgh O3IS

Policies and Procedures: University-based IND and IDE Applications

(Revised September 2019)

I. Policies and Procedures

A. Applicability

These policies and procedures are applicable to all University of Pittsburgh-based (University-based) IND and IDE applications intended for submission to the FDA by University of Pittsburgh faculty and staff or which involve the use of University of Pittsburgh laboratories or facilities.

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) and Humanitarian Device Exemptions. These policies and procedures do not apply to Emergency INDs or IDEs (refer to University of Pittsburgh IRB policies and procedures for information regarding the submission of Emergency INDs or IDEs.)

B. General Policy and Procedures

1. The Sponsor[1] of the IND or IDE application shall be the University of Pittsburgh Investigator[2] 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 study site(s). Such Sponsor-Investigators of IND or IDE applications are subject to compliance with not only the FDA regulations governing the responsibilities of the Sponsor[3] of an IND or IDE application but also with the FDA regulations governing the responsibilities of an Investigator[4] involved in the conduct of a clinical

[1] FDA regulations governing IND (21 CFR Part 312) and IDE (21 CFR Part 812) applications define the Sponsor of the application as "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."

[2] FDA regulations governing IND (21 CFR Part 312) and IDE (21 CFR Part 812) applications define an Investigator as "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. 'Sub-investigator' includes any other individual member of that team."

[3] Refer to 21 CFR Part 312, Subpart D (IND applications) and 21 CFR Part 812, Subpart C (IDE applications) for Sponsor responsibilities. The regulatory responsibilities of an IND or IDE Sponsor are also listed on the web-site (www.o3is.pitt.edu) of the O3IS.

[4] Refer to 21 CFR Part 312, Subpart D (IND applications) or 21 CFR Part 812, Subpart E (IDE applications) for Investigator responsibilities. The regulatory responsibilities of an IND or IDE Investigator are also listed on the web-site (www.o3is.pitt.edu) of the O3IS.

investigation under a FDA-accepted IND or IDE application (i.e., a study site Investigator).
In certain situations (e.g., the University faculty member responsible for the design of the clinical investigation has a financial conflict-of-interest related to the test article being evaluated in the clinical investigation), the Sponsor of the IND or IDE application and the study site Investigator may be different individuals. Under this scenario, the designated Sponsor of the IND or IDE application is subject to compliance with the FDA regulations governing the responsibilities of the Sponsor of an IND or IDE application and the Investigator is subject to compliance with the FDA regulations governing the responsibilities of a study site Investigator. Note that this latter 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.

2. All University-based IND and IDE applications and all documents relevant to such applications shall be submitted to the FDA **through the University's Office for Investigator-Sponsored IND and IDE Support (O3IS).**[5] (See Purpose of Policies – Institutional Oversight)

   - The initial submission[6] of a University-based IND or IDE application to the O3IS shall be accompanied by a Certification of IND/IDE Suitability (available on the O3IS website) signed by the chairperson of the academic department or director of the institute to which the Sponsor of the application administratively reports. If the Sponsor of the IND or IDE application is the chairperson of an academic department or director of an institute, the Certification of IND/IDE Suitability shall be signed by the dean of the school to which the Sponsor administratively reports. This Certification of IND/IDE Suitability shall affirm that:

     - the clinical protocol(s) incorporated into the IND or IDE application has (have) been reviewed and approved for scientific merit and quality by an appropriately constituted scientific review committee of the academic department or institute (or, if applicable, the school) to which the IND Sponsor administratively reports;

[5]For University-based IND or IDE applications that were submitted to the FDA prior to the date (August, 2007) of the original issuance of these policies and procedures and which remain active, all written correspondence between the Sponsor of the IND or IDE application and the FDA which occurs after this date must be submitted to the FDA through the O3IS and must include the address of the O3IS as the Sponsor's address for subsequent FDA communications.
[6]Note: Due to limited staffing, the O3IS is unable to provide editorial services related to University-based IND or IDE applications. If O3IS review of the application is desired prior to its submission to the FDA, the O3IS should be provided with the final version of the application along with the signed Certification of IND/IDE Suitability. IND or IDE applications of unacceptable editorial quality will be returned to the Sponsor without O3IS review comments.

- the designated study site Investigator(s) for the conduct of the clinical protocol(s) incorporated into the IND or IDE application is (are) aware of and possess the appropriate qualifications and experience so as to be able to comply with the regulatory responsibilities of an IND or IDE Investigator;

- the IND or IDE Sponsor has determined that there are a sufficient number of 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;

- the IND or IDE Sponsor has 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

- the IND or IDE Sponsor is fully aware of the regulatory responsibilities of the Sponsor of an IND or IDE application.

- The academic department or institute to which the Sponsor of an IND or IDE application administratively reports shall incur a one-time charge of $3000 for each protocol to be conducted under an IND or IDE application and a charge of $1500 at the time of each annual report to an existing IND or existing IDE application to address the increased institutional oversight necessary to ensure Sponsor and Investigator compliance with the FDA regulations and standards governing this activity. (Refer to J. Institutional Oversight of Clinical Investigations being Conducted Under an IND or IDE Application.) **NOTE: Expanded Access IND or IDE and Humanitarian Use Device protocols will not be subject to the above fees.**

- All initial University-based IND and IDE applications and all subsequent submissions to a FDA-accepted IND or IDE application shall incorporate the address of the O3IS as the address of the Sponsor on the accompanying FDA Form 1571 (box 3 and box 20); i.e.:

  Name of IND/IDE Sponsor
  Academic Department or Institute
  University of Pittsburgh
  Hieber Building, Suite 303
  3500 Fifth Avenue
  Pittsburgh, PA 15213

  - Following receipt, the O3IS will promptly forward, to the FDA, all University-based IND or IDE applications and all related

communications initiated by the IND or IDE Sponsor (i.e., unless an O3IS review of the application is requested prior to its submission to the FDA).

- Following receipt, the O3IS will promptly transfer all FDA-initiated communications regarding submitted or accepted IND or IDE applications to the responsible IND or IDE Sponsor.

3. Documents to be Included with the Initial Submission of an IND Application

For the initial submission of an IND application to the FDA, the Sponsor of the IND application shall provide the O3IS with a single PDF of the submission sent via email to **o3is@pitt.edu** and include the following:

- cover letter which accompanies the IND submission.
- completed and signed *Investigational New Drug Application (IND)* form (i.e., Form FDA 1571).
- completed and signed *Statement of Investigator* form(s) (i.e., Form FDA 1572) and curriculum vitae / biosketch of the respective Investigator(s).
    - A completed Form FDA 1572 (*Statement of Investigator*) and curriculum vitae must be submitted with the IND application for each study site Investigator. Study site sub-investigators who will make a direct contribution to the clinical data (e.g., individuals who will be directly involved in performance of procedures required by the clinical protocol and/or the collection of data) should be listed under item 6. of the Investigator's Form FDA 1572. A new Form FDA 1572 must be completed by the study site Investigator(s) for each new clinical protocol conducted under the IND application.
- IND application (See Content and Format of an IND Application).

Note: A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank* (i.e., Form FDA 3674) must be submitted for the clinical protocol that accompanies the initial IND application. It is advised that the submission of the clinical protocol (Phase 2 and 3 clinical trials, only) to the ClinicalTrials.gov Data Bank occur after it has been finalized based on input from the FDA and IRB. However, it must be submitted prior to enrollment of the first subject. The *Certification of Compliance with the Requirements of the ClinicalTrials.gov Data Bank* should be submitted as an Information Amendment to the IND application commensurate with the submission of the clinical protocol to this Data Bank

4. Documents to be Included with the Initial Submission of an IDE Application

For the initial submission of an IDE application to the FDA, the Sponsor of the application shall provide the O3IS with

- 2 paper copies (one for the FDA, one for O3IS)
- 2 eCopies

- cover letter that accompanies the IDE submission

- signed *Application for an Investigational Device Exemption* (See IDE Template: Application for an Investigational Plan-Feasibility Study or IDE Template: Application for an Investigational Plan-Pivotal Study)

- completed and signed *Investigator's Agreement(s)* (See IDE Template: Investigator's Agreement) and curriculum vitae of the respective Investigator(s)

- IDE application (See Content and Format of an IDE Application)

- Note: A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank* (i.e., Form FDA 3674) must be submitted for the clinical protocol that accompanies the initial IDE application. It is advised that the submission of the clinical protocol to the ClinicalTrials.gov Data Bank occur after it has been finalized based on input from the FDA and IRB. However, it must be submitted prior to enrollment of the first subject.The *Certification of Compliance with the Requirements of the ClinicalTrials.gov Data Bank* should be submitted as an information amendment to the IDE application commensurate with the submission of the clinical protocol to this Data Bank

5 Documents to be Included with **Subsequent Submissions** to a FDA-accepted IND Application

For subsequent submissions to an FDA-accepted IND application (see Required Amendments and Reports to an FDA-accepted Investigational New Drug (IND) Application), the Sponsor of the application shall provide the O3IS with a single PDF of the submission sent via email to **o3is@pitt.edu** and include the following.

- cover letter accompanying the subsequent IND submission

- completed *Investigational New Drug Application (IND)* form (i.e., Form FDA 1571); with the appropriate reason(s) for the subsequent submission checked under item 11

- Protocol Amendment *(if applicable)*

  - A Protocol Amendment may be necessary for significant changes to a previously submitted clinical protocol being conducted under a FDA-accepted IND application or for a new clinical protocol to be conducted under the FDA-accepted IND application or for the addition of a new investigator. (Note that the IND application is for a certain investigational drug product [or products]. Multiple clinical protocols involving the use or evaluation of this investigational drug product [or products] may be submitted under the same IND application.)

    - If the submission involves a response to an FDA "clinical hold" or other FDA requests for clinical protocol revisions, the submission should include the Sponsor's response to each of the FDA comments; the corresponding marked-up version of the clinical protocol; and a clean version of the revised clinical protocol.

    - If the submission involves changes to a previously submitted clinical protocol; the submission should include a summary of the changes, the corresponding marked-up version of the clinical protocol and a clean version of the revised clinical protocol.

    - Note: A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank* (i.e., Form FDA 3674) must accompany the Protocol Amendment if it involves a new clinical protocol being submitted to the FDA-accepted IND application. The deadline for posting a new clinical protocol on clinicaltrials.gov is within 21 days after the first subject is enrolled.

- Information Amendment *(if applicable)*[7]

  An Information Amendment is for changes to sections of the IND application other than the clinical protocol (e.g., changes to the Chemistry, Manufacturing and Control section of the IND application; addition of a new study site.).

- Safety Report *(if applicable)*

- Annual Report *(if applicable)*

- IND Withdrawal or Discontinuation Notice *(if applicable)*

[7] The submission of a completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank* (i.e., Form FDA 3674) is not required.

- request for reinstatement of an IND that has been previously withdrawn, inactivated, terminated, or discontinued *(if applicable)*

- any other report or correspondence concerning the FDA-accepted IND application

6 Documents to be Included with **Subsequent Submissions** to a FDA-accepted IDE Application

For subsequent submissions to a FDA-accepted IDE application (see Required Amendments and Reports to an FDA-accepted IDE Application), the Sponsor of the application shall provide the O3IS with two paper copies (one for the FDA, one for O3IS) and two eCopies of each of the following:

- cover letter accompanying the subsequent IDE submission

- Supplemental IDE Application *(if applicable)*

  A Supplemental IDE Application may be necessary for changes to a previously submitted clinical protocol being conducted under a FDA-accepted IDE application or for a new clinical protocol to be conducted under the FDA-accepted IDE application. (Note that the IDE application is for a certain investigational device or test article. Multiple clinical protocols involving the use or evaluation of this investigational device or test article may be submitted under the same IDE application.)

  - If the submission involves a response to a FDA "clinical hold" or other FDA requests for clinical protocol revisions, the submission should include the Sponsor's response to each of the FDA comments; the corresponding marked-up version of the clinical protocol; and a clean version of the revised clinical protocol.

  - If the submission involves changes to a previously submitted clinical protocol,the submission should include a summary of changes, the corresponding marked-up version of the clinical protocol and a clean version of the revised clinical protocol.

  - Note: A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank* (i.e., Form FDA 3674) must accompany the Supplemental IDE Application if it involves a new clinical protocol submitted to the FDA-accepted IDE application.

- Unanticipated Adverse Device Effect Report *(if applicable)*

- Progress 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 *(if applicable)*
- any other reports or correspondence concerning the FDA-accepted IDE

C. Conflict of Interest

The Sponsor of the IND or IDE application shall obtain and maintain on file completed and signed certifications and disclosures, (if applicable), of financial interests (see Certification/Disclosure of Financial Interests of Clinical Investigators) for each study site Investigator and for all Sub-investigators who may be involved in the treatment and/or evaluation of research subjects under the direction of the study site Investigator (i.e., for all Sub-investigators who will contribute significantly to the research data). (See Purpose of Policies – Conflict of Interest Declarations) **Note that these are specific FDA requirements in addition to University of Pittsburgh's requirements.**

The Sponsor of the IND or IDE application 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 associated with an identified, significant (i.e., disclosable) financial conflict of interest. In accordance with FDA regulations (21 CFR Part 54) a significant (i.e., disclosable) financial interest includes any:

- ownership interest, stock options, or other financial interest (i.e., an *Equity Interest*) that the study site Investigator or an applicable Sub-Investigator (including spouses and dependent children of these individuals) has in a non-public company that owns the drug or device being evaluated under the IND or IDE application, or equity worth more than $50,000 in any public company that owns the drug or device under evaluation.

- property or other financial interest (i.e., a *Proprietary Interest*) that the study site Investigator or an applicable Sub-investigator (including spouses and dependent children of these individuals) has in the drug or device being evaluated under the IND or IDE application; including, but not limited to, a patent or patent interest, trademark, copyright, licensing agreement, or any arrangement tied to a current or future

right to receive royalties associated with the development or eventual commercialization of the drug or device.

- Significant payments of other sorts in excess of $25,000 made by the sponsor of an IND or IDE application to the study site investigator or an applicable sub-investigator (including the spouse and each dependent child of these individuals) during the time that the investigator / sub-investigator is carrying out a clinical study under the respective sponsor's IND or IDE application and for one year following completion of the clinical study. Significant payments of other sorts include payments made to the investigator / sub-investigator (e.g., grants to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria) or to the University to support activities of the investigator / sub-investigator (e.g., individually designated Research Gifts) that have a monetary value of more than $25,000, exclusive of the cost of conducting the clinical study.

D. Multi-Center (i.e., multiple study sites) Clinical Investigations

1. For multi-center clinical investigations involving external study sites[8]:

   The proposed conduct of a clinical investigation at an external study site under a University-based IND or IDE application requires prospective approval by the O3IS.
   For assistance in addressing the issue, refer to the University's guidance document entitled *Guidance to University Departments, Institutes and Schools - Planning the Conduct of a Multi-Center (External Study Site) Clinical Investigation Under a University-based IND/IDE Application*.[9]

   Investigators planning the conduct of a multi-center (i.e., involving one or more external study sites) 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 (see Investigational New Drug Applications: Sponsor and Investigator Responsibilities or Investigational Device Exemptions: Sponsor and Investigator Responsibilities). The IND or IDE Sponsor must also establish appropriate processes and corresponding written

[8] *External study sites* are defined as study sites external to the University of Pittsburgh and UPMC domestic facilities.
[9] This guidance document is posted on the O3IS web-site (www.o3is.pitt.edu)

procedures directed at addressing these responsibilities.[10] 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.

For clinical investigations involving a University based IND or IDE protocol conducted at external study sites, standard operating procedures (SOPs) must be developed to address the following:

a. the Sponsor's selection of the external study sites and investigators who will be involved in the conduct of the clinical trial. This should address the criteria for ensuring that:
    - these individuals are appropriately qualified by education, training, experience and state licensure to conduct the clinical trial; and
    - the site has appropriate resources to conduct the clinical trial.

b. the Sponsor's procurement, from each external study site investigator, of a CV and signed FDA Form 1572 (for IND applications) or Statement of Investigator (for IDE applications).

c. the Sponsor's collection and maintenance of up-to-date 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.

d. the Sponsor's dissemination of the clinical trial protocol to the external study site Investigators and for ensuring that these investigators:

    - understand the nature and purpose of the clinical trial and the clinical trial procedures;
    - are capable of conducting or supervising the conduct of the clinical trial; and
    - 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.

e. the Sponsor's maintenance of documentation regarding initial and continuing responsible (i.e., for the external study site) IRB review

[10] Refer to *Guidance to University Departments, Institutes and Schools - Planning the Conduct of a Multi-Center (External Study Site) Clinical Investigation Under a University-based IND/IDE Application*.

and approval for the conduct of the clinical trial at each of the external study sites.

f. 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.

g. the Sponsor's oversight of the test article to include:

   - maintenance at the central storage location
   - distribution of the investigational drug or device to the external study sites; including shipment, receipt, accountability, labeling and return of test article

h. 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 time frame for this review and reporting.

i. the Sponsor's reporting, to the external study site Investigators, of new risk information related to the drug or device under investigation; to include the requisite time frame for the prompt dissemination of this information.

j. the Sponsor's reporting, to the external study Investigators, of changes to the clinical trial protocol; to include the requisite time frame for the prompt dissemination of this information

k. the Sponsor's verification that the external study site Investigators have submitted new risk information and protocol changes to their responsible IRB's and that IRB approval of respective research protocol/consent form modifications has been obtained.

l. the Sponsor's plan for independent monitoring, *via a Contract Research Organization, or via the University of Pittsburgh Center for Research on Healthcare*, 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 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 manner for the retention period specified by FDA regulations and by the funding entity

It is expected that monitoring visit reports will be issued within four weeks of the visit. O3IS must be prospectively copied on the monitoring visit reports and responses, and additional actions.

m. 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.

n. the Sponsor's review of monitoring reports, protocol deviations and other unanticipated problems received from the external study sites; to include how the Sponsor will respond to identified Investigator and/or external study site non-compliance or other deficiencies.

o. the Sponsor's preparation and maintenance of an effective IND or IDE:

   - IND - Protocol Amendments, Annual Reports, Safety Reports and Final Reports
   - IDE - Supplemental IDE Applications, Progress Reports, Investigator Lists, Safety Reports and Final Reports

p. the Sponsor's ongoing review and evaluation of evidence related to the overall safety and effectiveness of the drug or device under investigation; to include, when applicable,

   - discontinuation of those clinical trials that present an unreasonable and significant risk;
   - respective notification of the FDA, the Investigators, and the responsible IRB's;
   - disposition of remaining supplies of the investigational drug or device; and
   - the requisite time frame should be specified for these actions. In lieu of a SOP, this can accomplished via the Data and Safety Monitoring Plan described in the protocol.

q. the Sponsor's oversight of external study site procedures for verification that the external study sites investigators have processes in place for the following:

- obtaining IRB review and approval of the clinical trial 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.

- maintaining an up-to-date, clinical trial-specific list of appropriately qualified Sub-investigators and research staff to whom the Investigator has delegated significant clinical trial tasks. This list should describe the delegated tasks, identify 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. The list should also include signatures of the respective Sub-investigators and research staff as documentation that these individuals have knowledge of and have accepted their delegated tasks.

- 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.)

- 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 external study site IRB's review of new risk information provided to the site by the Sponsor; and, notifying the Sponsor of the responsible IRB's approval of research protocol and consent changes necessary to reflect the new risk information

- the preparation of external study site Progress Reports and of a 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 responsible IRB.

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 Associate Director prior to study implementation.

It is highly recommended that enrollment begin at the University of Pittsburgh site. Upon completion of the first monitoring visit of enrolled subjects without identified issues, then, the other sites may be activated.

2. **For multi-center clinical trials limited to University and/or UPMC study sites:**

University policy does not place restrictions on the conduct of a clinical investigation at multiple University and/or UPMC (University/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 or device is administered or dispensed to the 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 University/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.[11] Sponsors of University-based IND or IDE applications should consider appointing a separate study site Investigator for each of the involved UPMC or University study sites.

[11] Refer to the FDA guidance document, *Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Participants*, at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

The Sponsor of the IND or IDE application may be requested to provide written SOPs that are directed at ensuring the regulatory responsibilities of the Sponsor and the Investigator are being adequately addressed in this situation.

Investigators planning the conduct of a multi-center (i.e., involving multiple University or UPMC study sites) 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 (see Investigational New Drug Applications: Sponsor and Investigator Responsibilities or Investigational Device Exemptions: Sponsor and Investigator Responsibilities).

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

Non-clinical (i.e., animal or laboratory) safety[12] studies that support, or are intended to support, IND or IDE applications must, in general[13], be conducted in compliance with the FDA's Good Laboratory Practice (GLP) regulations at 21 CFR Part 58. (See Purpose of Policies – GLP Regulations)

1. Use of University of Pittsburgh or UPMC Laboratories[14]

   If a University or UPMC laboratory will be used for the conduct of GLP-compliant, non-clinical studies, the laboratory will need to undergo pre-qualification and continuing audits of GLP compliance performed by a qualified consultant selected or prospectively approved by the University's Office of Research Protections.[15]

   - The department, institute, or school to which the Sponsor of the IND or IDE application administratively reports and/or the academic department, institute, or school that is administratively responsible for the laboratory performing the non-clinical studies shall assume financial responsibility for the cost of the audits of GLP compliance.

2. Use of External or Contract GLP Facilities

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[12] In general, the FDA's Good Laboratory Practice (GLP) regulations at 21 CFR Part 58 apply only to non-clinical safety (i.e., pharmacology/toxicology) studies submitted in support of an IND or IDE application. However, for certain types of investigational drugs or devices, it may not be possible to evaluate directly the effectiveness of the investigational drug or device in humans; in which case the FDA will need to base its approval of the drug or device primarily on the results of effectiveness studies conducted on animal models (i.e., the "Animal Rule"). Such non-clinical studies of effectiveness conducted in support of the Animal Rule are also subject to compliance with the GLP regulations at 21 CFR Part 58.

[13] The FDA may accept safety data from non-clinical studies that were not conducted in full compliance with the GLP regulations at 21 CFR Part 58. This will require that the Sponsor of the IND or IDE application formally petition the FDA for the acceptance of such studies and describe, in detail, all differences between the practices actually used and those required in the GLP regulations. This will necessitate the involvement of an individual with GLP expertise, and there is no guarantee that the FDA will, in fact, accept the data submitted.

[14] **Note: There are currently no University or UPMC laboratories or facilities that are certified as operating in compliance with the GLP regulations at 21 CFR Part 58.**

[15] The requirement for a pre-qualification audit of GLP compliance and the frequency of continuing audits shall be determined by the University's Office of Research Protections based on, but not limited to, factors such as the length of time since previous certification of GLP compliance, the extent of ensuing facility and personnel changes, and the extent of usage of the facility for the conduct of GLP-compliant non-clinical studies.

If an external (e.g., contract) facility will be used for the conduct of the GLP-compliant, non-clinical studies, the external facility shall 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 shall be subject to a pre-qualification audit of GLP compliance performed by a qualified consultant. The department, institute, or school to which the Sponsor of the IND or IDE application administratively reports and/or the selected external facility shall 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 shall be described in writing in the IND or IDE application.

3. Financial Responsibility for the Conduct of GLP-compliant Non-clinical Studies

   The department, institute or school to which the Sponsor of the IND or IDE application administratively reports shall assume financial responsibility for the cost of performing the respective GLP-compliant, non-clinical laboratory study.

F. 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.[16] (See Purpose of Policies – cGMP Requirements)

1. Use of University of Pittsburgh or UPMC Facilities[17]

[16]The manufacture of investigational drugs being used or evaluated in Phase 1 clinical trials is not subject to strict compliance with the cGMP regulations at 21 CFR Parts 211 or 212; rather the manufacture of investigational drugs for use in Phase 1 clinical trials will be subject to complying with the manufacturing procedures and processes specified in the corresponding, FDA-accepted IND application.

[17] Note: There are currently two University/UPMC facilities that are certified as operating in compliance with the cGMP regulations at 21 CFR Part 211; the Immunologic Monitoring and

For University-based IND applications that propose the on-site preparation (i.e., "manufacture") of the investigational drug within a University or UMPC facility; compliance with the FDA's cGMP requirements may be subject to pre-qualification and continuing audits performed by a qualified consultant selected or prospectively approved by the University's Office of Research Protections.[18]

- The department, institute or school to which the Sponsor of the IND application administratively reports and/or the academic department, division, center or institute that is administratively responsible for the selected drug manufacturing facility shall assume financial responsibility for the cost of the pre-qualification and continuing audits of cGMP compliance.

2. 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 shall 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 shall be subject to pre-qualification and continuing audits[19] of cGMP compliance performed by a qualified consultant selected or prospectively approved by the University's Office of Research Protections.

     - The department, institute or school to which the Sponsor of the IND application administratively reports and/or the selected external manufacturing facility shall assume financial responsibility for the cost of the pre-qualification audit of cGMP compliance.

   - The use of an external facility for the cGMP-compliant manufacture of the investigational drug shall be described in the initial IND

Cellular Products Laboratory (IMCPL; Lisa Butterfield, Ph.D., Director) and the Human Cells, Tissues and Cellular- and Tissue-Based Products Laboratory (Albert Donnenberg, Ph.D., Director)

[18] The requirement for a pre-qualification audit of cGMP compliance and the frequency of continuing audits shall be determined by the University's Research Conduct and Compliance Office based on, but not limited to, factors such as the length of time since previous certification of cGMP compliance, the extent of ensuing facility and personnel changes, and the extent of usage of the facility for the cGMP preparation of investigational drug products.

[19] It is anticipated that requirement for continuing audits of cGMP compliance would apply only if the manufacture of the investigational drug for use under a University-based IND application would extend over multiple years. In this circumstance, the frequency of continuing audits shall be determined by the University's Office of Research Protections.

application and/or, if the use of an external manufacturing facility is later selected, shall be described in an Information Amendment to the FDA-accepted IND application.

3. Financial Responsibility for the cGMP Manufacturing of Investigational Drugs

   The department, institute or school to which the Sponsor of the IND application administratively reports shall assume financial responsibility for the cost of manufacturing the investigational drug in accordance with the FDA's cGMP requirement.

G. 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. (See Purpose of Policies – cGMP Requirements)

1. Use of University of Pittsburgh or UPMC Facilities[20]

   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 may be subject to pre-qualification and continuing audits performed by a qualified consultant selected or prospectively approved by the University's Office of Research Protections.[21]

   - The department, institute or school to which the Sponsor of the IDE application administratively reports and/or the academic department, division, center or institute that is administratively responsible for the selected device manufacturing facility shall assume financial responsibility for the cost of the pre-qualification and continuing audits of compliance with the FDA's Quality System/Design Control requirements.

2. Use of External Facilities/Contract Facilities

   For University-based IDE applications that propose the manufacture of the investigational device by an external facility; either the device must

[20] **Note: There are currently no University or UPMC laboratories or facilities that are certified to operate in full compliance with the FDA's Quality System regulations.**

[21] The requirement for a pre-qualification audit of Quality System/Design Control compliance and the frequency of continuing audits shall be determined by the University's Office of Research Protections based on, but not limited to, factors such as the number of investigational devices that will be manufactured for use under the IDE application, the length of time since previous certification of Quality System/Design Control compliance, the extent of ensuing facility and personnel changes, and the extent of usage of the facility for the Quality System (i.e., GMP) manufacturing of investigational devices.

be currently approved for general marketing by the FDA or the external facility shall be subject to providing written documentation of its Quality System certification, FDA registration, or other evidence of Quality System/Design Control compliance.

- In the absence of being able to provide documentation of its Quality System/Design Control compliance, the external facility selected for the manufacture of the investigational device shall be subject to pre-qualification and continuing audits[22] of compliance with the FDA's Quality System/Design Control requirements performed by a qualified consultant selected or prospectively approved by the University's Office of Research Protections.

    - The department, institute, or school to which the Sponsor of the IDE application administratively reports and/or the selected external manufacturing facility shall assume financial responsibility for the cost of the pre-qualification audit of compliance with the FDA's Quality System/Design Control requirements.

- The use of an external facility for the manufacture of the investigational device shall be described in the initial IDE submission and/or, if the use of an external manufacturing facility is later selected, shall be described in a Supplemental IDE Application submitted to the FDA-accepted IDE.

3. Financial Responsibility for the Quality System Manufacturing of Investigational Devices

   The department, institute or school to which the Sponsor of the IDE application administratively reports shall assume financial responsibility for the cost of manufacturing the investigational device in accordance with the FDA's Quality System/Design Control requirements.

H. GCP Compliance in the Conduct of Clinical Trials

The conduct of a clinical investigation under a FDA-accepted IND or IDE application shall be in compliance with the Good Clinical Practice (GCP) standards adopted by the FDA (See Purpose of Policies – GCP Compliance).

- University/UPMC-based study site Investigators and, if applicable, multi-center, external study site Investigators who conduct clinical investigations under a University-based IND or IDE application shall be

[22] It is anticipated that requirement for continuing audits of Quality System/Design Control compliance would apply only if the manufacture of the investigational device for use under a University-based IDE would extend over multiple years. In this circumstance, the frequency of continuing audits shall be determined by the University's Office of Research Protections.

required to complete prospectively a University-accepted education program on GCP standards.

I. Sponsor Monitoring of Clinical Investigations Being Conducted Under a Sponsor-Investigator IND or IDE Application

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

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

When the Sponsor has contracted with an independent monitoring Agency (i.e., PPD), or the University of Pittsburgh Center for Research on Healthcare, the Sponsor shall prospectively provide the O3IS with copies of all monitoring reports and subsequent correspondence within four weeks of the site visit.

J. University Oversight of Clinical Investigations being Conducted Under a University-based IND or IDE Application

1. The University's Institutional Review Board (University IRB) shall notify the O3IS and ECO-HSR upon its initial receipt, initial approval or renewal of a clinical investigation being conducted under a University-based IND or IDE application and the O3IS shall verify respective compliance with these University policies and procedures.

2. The University IRB shall notify the O3IS upon its receipt of a modification request for a clinical investigation being conducted under a University-based IND or IDE application. The O3IS shall 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 University IRB shall notify the O3IS of reportable events and determinations of serious non-compliance and or continuing non-compliance reported to the University IRB for clinical investigations being conducted under a University-based IND or IDE application. The O3IS shall ensure that a corresponding Safety Report has been submitted by the IND or IDE Sponsor to the respective IND or IDE application.

4. The University IRB shall inform the O3IS of the termination of clinical investigations being conducted under a University-based IND or IDE application. The O3IS shall advise the IND or IDE Sponsor of the need

for termination or withdrawal of the corresponding IND or IDE application.

5. The O3IS shall promptly notify the University IRB 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 O3IS shall 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 O3IS shall submit, 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 shall 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 shall 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 shall be determined by the ECO-HSR.

8. The University's O3IS shall determine the acceptability of the procedures developed by the IND or IDE Sponsor in response to the University's guidance document entitled Guidance to University Departments, Institutes and Schools – Procedures to be Established when Conducting a Clinical Investigation Under a University-based IND or IDE Application.

K. IND/IDE Sponsor – Data Safety and Monitoring Board Interactions

Note that the FDA regulations[23] 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 (see Purpose of Policies - Data and Safety Monitoring Board), it shall serve in an advisory capacity to the IND or IDE Sponsor regarding

[23] 21 CFR Sec. 312.56 (for IND applications); 21 CFR Sec. 812.46 (for IDE applications)

identified changes to the risk-to-benefit ratio of the clinical investigation, continuation of the clinical investigation, and other pertinent issues. I.e., 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.

L. Departure of the Sponsor of an IND or IDE Application from the University of Pittsburgh

Upon departure from the University of Pittsburgh, the Sponsor (or Sponsor-Investigator) of an active IND or IDE application is required to 1) notify the O3IS, and 2) transfer sponsorship of the IND or IDE application to another appropriately qualified University faculty member. The O3IS will assist with the respective processes and procedures to be followed.

M. Institutional Disapproval of University-based IND and IDE Applications

The Vice Chancellor for Research Protections shall have the right to disapprove the submission, to the FDA, of a University-based IND or IDE application and/or to terminate or withdraw a FDA-accepted, University-based IND or IDE application. (See Purpose of Policies – Institutional Oversight)

N. 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 to be submitted in support of IND or IDE applications shall be prospectively approved by the Institutional Official.

1. The O3IS shall be notified at a minimum of 3 months in advance of the initial submission of a grant or contract proposal to establish a GLP facility.

2. Note: The University's Office of Sponsored Programs will not process a grant or contract proposal directed at establishing a GLP facility unless the proposal is accompanied by a letter of approval signed by the Senior Vice Chancellor for Health Sciences.

O. 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 cGMP or Quality System facility for the manufacturing of investigational drugs or devices for use or evaluation under IND or IDE applications shall be prospectively approved by the Senior Vice Chancellor for the Health Sciences. (See Purpose of Policies – cGMP Requirements)

1. The O3IS shall be notified at a minimum of 3 months in advance of the initial submission of a grant or contract proposal to establish a cGMP facility.

2. Note: The University's Office of Sponsored Programs will not process a grant or contract proposal directed at establishing a cGMP or Quality System facility unless the proposal is accompanied by a letter of approval signed by the Vice Chancellor for Research Protections or his/her designee.

II. Purpose of Policies

A. Introduction

The conduct of a clinical investigation (i.e., clinical trial) under a FDA-accepted IND or IDE application invokes a complex set of FDA regulations, requirements, and obligations; to include the submission of initial and supplemental IND or IDE applications; continuing oversight (i.e., monitoring) of the manufacture of the investigational drug or device; routine monitoring of the conduct of the clinical trial at all involved study sites; and the requisite reporting, at specified times, of clinical trial outcomes. The FDA holds the "Sponsor" of the IND or IDE application responsible for ensuring that all of these regulations, requirements and obligations are being met.[24]

Although Sponsors of IND and IDE applications are typically pharmaceutical and device companies, the FDA regulations governing IND and IDE applications do permit the Sponsor to be an individual, governmental agency, academic institution, private organization, or other organization.[25]

[24] 21 CFR Part 312, Subpart D; 21 CFR Part 812, Subparts C
[25] 21CFR Sec. 312.3; 21 CFR Sec. 812.3

B. Institutional Oversight

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).

The FDA communicates directly with the Sponsors of IND and IDE applications and holds these communications confidential. Hence, the FDA does not include or copy the University on any of its notifications or comments related to University-based IND or IDE applications. However, the University is potentially liable for the actions of its faculty members; thus necessitating that the University be engaged in the communications between the FDA and University-based Sponsors of IND or IDE applications. In addition, the University must assume certain oversight of the manufacturing of investigational drugs and devices being used or evaluated under University-based IND or IDE applications and must also ensure appropriate monitoring of the progress and appropriate conduct of respective clinical trials.

C. Conflict-of-Interest Declarations

In making its decision as to whether a product can be approved for commercial marketing, the FDA reviews the data generated from clinical trials of the investigational drug or device to determine if the product is safe and effective for the clinical indication specified in the proposed product labeling. FDA may consider a clinical trial and the resulting data to be inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the study to minimize bias. One potential source of bias in the conduct of clinical trials is a financial interest of the involved clinical investigators in the outcome of the investigation. To address this, the FDA has issued regulations (21 CFR Part 54) which require the Sponsor of the IND or IDE application to obtain and maintain on file disclosures of any proprietary interest that the involved clinical investigators[26] may have in the drug or device under investigation and/or if the clinical investigator has certain equity or financial interests in the company that owns this drug or device. (See

[26] The FDA's conflict of interest regulations at 21 CFR Part 54 define a "clinical investigator" to include the study site Investigators and any Sub-investigators who are involved in the treatment and/or evaluation of the research subjects under the overall direction or supervision of the study site Investigator. The term also includes the spouse and each dependent child of the study site Investigator(s) and applicable Sub-investigators.

Certification/Disclosure of Financial Interests of Clinical Investigators) These disclosures are subject to audit by, or submission to, the FDA upon request of the agency.

In addition, the University has policies in place (www.coi.pitt.edu) directed at ensuring that its reputation and research programs are not compromised by real or perceived conflicts of interest. These institutional policies also mandate the disclosure of any proprietary interest that the Investigator (i.e., principal investigator) or Sub-investigators may have in the drug or device under clinical investigation and/or certain equity and financial interests that the Investigator or Sub-investigators may have in the company that owns this drug or device.

D. Multi-Center Clinical Trials: External Study Sites

The FDA regulations governing IND and IDE applications invoke a complex set of reporting requirements between study site Investigators and the Sponsor of the IND or IDE application, and the difficulty of addressing these requirements increases substantially when the study sites are external to the University and UPMC. Moreover, the Sponsor of the IND or IDE application is obligated, by FDA regulation, to routinely monitor the progress and conduct of the clinical investigation(s) at each of the external study sites and is held ultimately responsible for any uncorrected, inappropriate actions on the part of the external study site Investigators.

It must also be recognized that the conduct of a multi-center clinical trial under a University-based IND or IDE application extends the research subject injury and regulatory compliance liabilities of the University to each of the involved, external study sites. The involvement of external study sites further necessitates complicated contract negotiations between the University and the parent organization for the external study site. Hence, in summary, while University policies do not totally preclude the conduct of clinical investigations at external study sites under a University-based IND or IDE application; the University must and should be involved centrally in making this decision.

E. GLP Regulations

1. General Requirements

   The FDA's regulations, entitled *Good Laboratory Practice for Non-clinical Laboratory Studies* (21 CFR Part 58), are applicable to non-clinical laboratory studies that support or are intended to support applications for research (e.g., IND or IDE applications) or marketing permits for products regulated by the FDA; including human and animal drugs, medical devices for human use, biological products, and electronic products. "Non-clinical laboratory studies" are defined within these regulations as:

"*in vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article."

These GLP regulations define a quality system that addresses the organizational process and the conditions under which non-clinical laboratory studies are planned, performed, monitored, recorded, and reported. Compliance with these GLP regulations is intended to assure the quality, reliability and integrity of the laboratory studies; the reporting of respective, verifiable conclusions; and the traceability of study data.[27]

2. Current University GLP-Certified Laboratories:

There is currently no University laboratory or research group that has been pre-qualified or is certified to conduct non-clinical laboratory or animal studies in compliance with the FDA's GLP regulations. Moreover, the University has committed to notifying potential external sponsors of non-clinical laboratory studies that the University will conduct the research in accordance with generally accepted academic standards, but will not operate at the GLP level. Furthermore, the Sponsor must agree, in writing, that any data generated from the sponsored laboratory studies will not be submitted as part of any regulatory application or filing that requires certification of GLP compliance.

The above statements do not preclude the potential establishment of a University-based, GLP laboratory at some future date. However, substantial facility, equipment, and personnel resources and related expertise are required in order to meet the GLP standard. Thus, any grant, contract or other proposal or agreement to establish a GLP-compliant laboratory must be reviewed, in advance, to determine if the corresponding plans and budget are appropriate and adequate.

F. cGMP Requirements

1. General Requirements

The FDA regulations, entitled Current Good Manufacturing Practice for Finished Pharmaceuticals,[28] define a quality system that addresses the

[27] World Health Organization. WHO Technical Report Series. No. 927, 2005.

[28] 21 CFR Part 210; 21 CFR Part 211 (21 CFR Part 212 for Positron Emission Tomography drug products)

methods used in, and the facilities and controls used for the manufacturing, processing, packaging, labeling, holding and distribution of drug products intended for administration to humans or animals. Likewise, the FDA regulations, entitled Quality System Regulation,[29] define a quality system that addresses the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. These current Good Manufacturing Practice (cGMP) and Quality System regulations are intended to ensure that drug products and devices intended for use in humans are of appropriate and consistent specifications and quality so as to be inherently safe and effective and to provide scientifically valid clinical trial data. Drug products being used or evaluated under University-based IND applications are subject to compliance with the FDA's cGMP regulations at 21 CFR Parts 210 and 211 (or 21 CFR Part 212 for Positron Emission Tomography drug products).[30] Devices being evaluated under University-based IDE applications are exempt from the FDA's Quality System regulations; except for the requirements for Design Control (i.e., 21 CFR Part 820, Subpart C).

2. Current University cGMP-Certified Facilities:

   University facilities that have been pre-qualified and/or are currently certified to be cGMP compliant are listed below:

Facility	Responsible Faculty	Applicable Drug Products
Immunological Monitoring and Cell Products Laboratory	Lisa Butterfield, Ph.D.	Immunological Cell-Based Products
Cells, Tissues and Cellular and Tissue-Based Products Laboratory	Al Donnenberg, Ph.D.	Other Cell and Tissue-Based Products

A review of the FDA's cGMP regulations for the manufacture of investigational drug products or the FDA's Quality System/Design Control regulations for the manufacture of investigational devices intended for human use will reveal that substantial facility, equipment, and personnel resources and related expertise are required in order to comply with these federal standards. Thus, any grant, contract or

[29] 21 CFR Part 820

[30] FDA regulations specify that investigational drugs being used or evaluated in Phase 2 or 3 clinical trials must be manufactured in strict accordance with the FDA's cGMP regulations at 21 CFR Part 211. The manufacture of investigational drugs being used or evaluated in Phase 1 clinical trials is not subject to strict compliance with the cGMP regulations at 21 CFR Part 211; rather the manufacture of investigational drugs for use in Phase 1 clinical trials will be subject to the manufacturing procedures and processes specified in the corresponding, FDA-accepted IND application.

other proposal or agreement to establish a cGMP- or Quality System-compliant facility must be reviewed, in advance, to determine if the corresponding plans and budget are appropriate and adequate.

G. GCP Compliance

The ICH Good Clinical Practice (GCP) guidelines are an international ethical and scientific quality standard (See ICH Harmonized Tripartite Guideline for Good Clinical Practice) for designing, conducting, recording and reporting investigations that involve the participation of human subjects. Compliance with these guidelines provides public assurance that the rights, safety and well-being of research participants are protected and that the resulting clinical investigation data are credible. Adherence to the components of these GCP guidelines adopted by the FDA is required when generating clinical research data that are intended to be submitted to the FDA; and is subject to audit by the FDA.

H. Clinical Trial Monitoring

FDA regulations[31] specify that the Sponsor of the IND or IDE application is responsible for ensuring proper monitoring of the progress of the clinical investigation(s) and for ensuring that the clinical investigation(s) is (are) being conducted in accordance with the general investigational plan and the clinical protocol(s) contained in the IND or IDE application. Deviations from the clinical protocol are only permitted after notifying the Sponsor and responsible IRB, except when necessary to protect the safety, the rights, or the welfare of the research subject(s). A Sponsor who discovers that an Investigator is not complying with the general investigational plan or the clinical protocol(s) contained in the IND or IDE application must promptly either secure compliance or end the Investigator's participation in the clinical investigation. Identified clinical protocol deviations involving a potential risk to the research subject are required, by FDA regulation, to be reported to the responsible IRB as an "unanticipated problem involving risks to human subjects or others". The responsible IRB is required, by FDA regulation, to report "unanticipated problems involving risks to human subjects or others" to the FDA. The individual(s) selected by the Sponsor to monitor the clinical investigation must be qualified by training and experience to perform this function.

The Education and Compliance Office for Human Subject Research (ECO-HSR), Office of Research Protections, has extensive experience in the auditing and monitoring of clinical investigations for compliance with GCP standards and IND or IDE commitments. To ensure appropriate institutional oversight of University-based IND and IDE applications, the ECO-HSR will periodically monitor the research oversight programs of IND/IDE Sponsors, which will include compliance of the Sponsor and Investigator with applicable FDA regulations, applicable

[31] 21 CFR Part 312, Subpart D (IND applications); 21 CFR Part 812, Subpart C (IDE applications)

University of Pittsburgh policies and the IRB-approved protocol and consent document. The frequency of these monitoring visits shall be determined by the ECO-HSR.

I. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB)[32] is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more clinical investigations. The DSMB advises the Sponsor of the respective IND or IDE application regarding the continuing safety of clinical trial participants and those yet to be recruited into the trial, as well as the continuing validity and scientific merit of the trial.

The FDA regulations governing IND and IDE applications do not require the use of DSMBs; except for research studies of emergency procedures wherein an exception for the requirement for written informed consent may be applicable.[33] (See *FDA Guidance for Clinical Trial Sponsors – Establishment and Operation of Clinical Trial Data Monitoring Committees*.[34]) However, certain governmental agencies, such as the National Institutes of Health (NIH) and Veteran's Administration (VA), may require the use of DSMBs for certain clinical trials. In addition, the responsible institutional review board (IRB) may require the use of a DSMB consistent with the IRB's obligations to (1) ensure that risks to subjects are minimized by using procedures (e.g., statistically valid endpoints for early study termination) that are consistent with sound research design[35]; (2) to determine which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review[36]; (3) to ensure that the IRB is made aware of any significant new information that may affect the subject's decision to participate or to continue participation in the clinical trial[37]; and (4) to ensure, where appropriate, that the research plan makes adequate provision for the monitoring of data collected to ensure the safety of subjects[38]. (See University IRB Guidance – Data and Safety Monitoring Plans)

IND or IDE Sponsors planning the involvement of a DSMB in the review of clinical investigations should be aware that the University's Office of Clinical Research, Health Sciences (OCR-HS) has in place processes and procedures for the establishment and operation of independent DSMBs. Moreover, use of a DSMB established or accepted by the OCR-HS helps

[32] DSMBs may also be called Data and Safety Monitoring Committees (DMSCs) or Data Monitoring Committees (DMCs).
[33] 21 CFR 50.24(a)(7)(iv)
[34] http://www.fda.gov/cber/guidelines.htm
[35] 21 CFR 56.111(a)(1)(i)
[36] 21 CFR 56.108(a)(2)
[37] 21 CFR 56.108 (b)(1)
[38] 21 CFR 56.111 (a)(6)

to ensure objective review of interim data for any emerging concerns and provides for appropriate institutional oversight of this function and its associated responsibilities.

J. Departure of the IND/IDE Sponsor from the University of Pittsburgh

An IND or IDE application developed and submitted to the FDA by a University faculty member during her/his tenure at the University of Pittsburgh is the intellectual property of the University. Likewise, research data accrued in a clinical investigation being conducted under a University-based IND or IDE application is the intellectual property of the University. Thus, the Sponsor (or Sponsor-Investigator) of an active, University-based IND or IDE application is required to transfer the sponsorship of the application to another qualified faculty member of the University upon his or her departure from the University. This also serves to ensure the continued involvement and safety of research subjects who are currently participating in clinical investigations being conducted under the University-based IND or IDE application.