



**VCU**

Office of Research and Innovation

## **VCU Faculty Held IND and IDE Procedure Handbook**

### **Contents**

A. Introduction .....	3
B. Purpose of Institutional Oversight.....	3
C. Applicability.....	4
D. University Oversight of Clinical Investigations Being Conducted Under a Sponsor- Investigator IND or IDE Application.....	4
E. General Policy and Procedures .....	5
The Sponsor and Investigator .....	5
IND/IDE Initial Submission .....	6
Documents to be Included with the Initial Submission of an IND Application.....	8
Documents to be Included with the Initial Submission of an IDE Application .....	9
Documents to be Included with Subsequent Submissions to a FDA- accepted IND Application .....	9
Documents to be Included with Subsequent Submissions to a FDA- accepted IDE Application.....	11
F. Conflict of Interest.....	12
IND/IDE Sponsor Responsibilities .....	13
VCU/VCUHS-based Clinical Investigators.....	13
External Clinical Investigators- receiving a sub-award for a study which is PHS or PHS-adherent funded .....	14
External Clinical Investigators- receiving a sub-award for a study which is otherwise federally funded (not PHS or PHS-adherent) .....	14
External Clinical Investigators - study is funded by other than above and sub-recipient entity receives funding .....	14
External Clinical Investigators - external site receives no sub-award.....	15
Reportable Financial Conflicts of Interest on FDA forms 3454 and 3455.....	15
G. Multi-Center (i.e., multiple study sites) Clinical Investigations.....	16
For Multi-Center Clinical Trials LIMITED TO VCU Domestic Study Sites .....	16

For Multi-Center Clinical Investigations INVOLVING EXTERNAL Study Sites .....	17
Standard Operating Procedures for IND/IDE Studies Multiple Study Sites .....	18
H. Sponsor Monitoring of Clinical Investigations Being Conducted Under a Sponsor- Investigator IND or IDE Application.....	22
I. Data and Safety Monitoring Board .....	23
J. Good Clinical Practice (GCP) Compliance in the Conduct of Clinical Trials .....	24
K. Good Laboratory Practices (GLP) Compliance for Supporting Non-clinical Safety Studies .....	25
Use of VCU Laboratories .....	26
Use of External or Contract GLP Facilities.....	26
Financial Responsibility for the Conduct of GLP-compliant Non-clinical Studies .....	27
L. Grant or Contract Proposals to Establish a VCU-Based GLP Laboratory.....	27
M. Compliance for the Manufacturing of Investigational Drugs and Quality System Compliance for the Manufacturing of Investigational Devices (cGMP) .....	27
Specific guidance for cGMP Compliance for the Manufacture of Investigational Drugs .....	28
Use of VCU Facilities .....	29
Use of External or Contract cGMP Facilities .....	29
Financial Responsibility for the cGMP Manufacturing of Investigational Drugs .....	30
Specifics for Quality System (i.e., cGMP) Compliance for the Manufacturing of Investigational Devices .....	30
Use of VCU Facilities .....	30
Use of External Facilities/Contract Facilities.....	30
Financial Responsibility for the Quality System Manufacturing of Investigational Devices.....	31
N. Grant or Contract Proposals to Establish a VCU based cGMP Facility .....	31
O. Control of Investigational Drugs and Biologics.....	31
P. Departure of Sponsor-Investigators from the VCU.....	32
Q. Institutional Disapproval of the Submission or Continuance of Sponsor-Investigator IND and IDE Applications.....	32
APPENDIX 1: Abbreviations.....	33
APPENDIX 2: Quick References .....	34

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## **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. 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. (21 CFR Part 312, Subpart D; 21 CFR Part 812, Subparts C)

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. (21CFR Part 312.3; 21 CFR Part 812.3)

## **B. Purpose of Institutional Oversight**

Proper adherence to the regulations, requirements, and obligations surrounding VCU based IND and/or an IDE 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 VCU on any of its notifications or comments related to VCU based IND or IDE applications unless the Sponsor notifies them that they may communicate. 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. Applicability**

These policies and procedures are applicable to all VCU based (University-based) IND and IDE applications intended for submission to the FDA by VCU faculty and staff as well as Nonsignificant risk IDEs that are submitted to the IRB.

In addition to traditional IND and IDE (both significant risk and nonsignificant risk 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 VCU IRB policies and procedures for information regarding the submission of Emergency INDs or IDEs).

## **D. University Oversight of Clinical Investigations Being Conducted Under a Sponsor- Investigator IND or IDE Application**

All submissions, correspondence, reports, and amendments will be submitted to the CRCO prior to FDA submission utilizing the REDCap database at [go.vcu.edu/submit/indide](http://go.vcu.edu/submit/indide)

The CRCO and the IRB will be in communication regarding VCU Based IND and IDE applications. This communication does not release the Sponsor or Investigator of their reporting responsibilities to the FDA, IRB or the CRCO. The IRB will not issue an approval without verification that the CRCO has received the FDA submission and that it has been approved. The University IRB will notify the CRCO upon its receipt of a modification request for a clinical investigation being conducted under a VCU based IND or IDE application. The Sponsor is responsible for determining if a corresponding Protocol Amendment or Supplemental IDE application of the FDA accepted IND or IDE is required for the protocol amendment. The Sponsor must submit all paperwork and correspondence submitted to the FDA for the amendment.

The VCU IRB will share information with the CRCO 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 CRCO will verify that a corresponding Safety Report has been submitted by the IND or IDE Sponsor to the respective IND or IDE application.

The Sponsor of the IND or IDE application is responsible for notifying the FDA of inactivation, suspension, or withdrawal. The IND or IDE Sponsor must submit all correspondence and documents relevant to the termination or withdrawal of the corresponding IND or IDE

application to the CRCO. The VCU IRB will share information with the CRCO of the termination either by closure or suspension of clinical investigations being conducted under a University-based IND or IDE application.

The Sponsor of the IND or IDE application is responsible for notifying the CRCO and the IRB immediately 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.

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

IND/IDE Protocols will be audited regularly.

All IND/IDE based protocols will be registered in OnCore.

## **E. General Policy and Procedures**

### **The Sponsor and Investigator**

The Sponsor of the IND or IDE application shall be the VCU employee who initiates the IND or IDE and takes responsibility for the clinical investigation. 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.”

The Investigator is the VCU employee who conducts the clinical investigation. 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 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.”

A Sponsor- Investigator is a VCU employee 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 VCU and VCUHS 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 of an IND or IDE application but also with the FDA regulations governing the responsibilities of an Investigator involved in the conduct of a clinical investigation under a FDA-accepted IND or IDE application (i.e., a study site Investigator).

Refer to 21 CFR Part 312, Subpart D (IND applications) and 21 CFR Part 812, Subpart C (IDE applications) for Sponsor and Investigator responsibilities. The regulatory responsibilities of an IND or IDE Sponsor and Investigator are also listed on the VCU Faculty-Held IND or IDE website at [go.vcu.edu/indide](http://go.vcu.edu/indide). For Nonsignificant Risk (NSR) IDEs, the IRB acts as the surrogate for the FDA and a formal IDE is not submitted to the FDA. There are however FDA regulatory requirements for these studies. NSR IDEs must be submitted to the CRCO.

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. When the Sponsor and Investigator are not the same individuals, 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: 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.

## **IND/IDE Initial Submission**

All University-based IND and IDE applications and all documents relevant to such applications shall be submitted to the University's Clinical Research Compliance Officer (CRCO) for Investigator-Sponsored IND or IDE prior to submission to the FDA. The initial submission of a University-based IND or IDE application to the CRCO shall be accompanied by a Certification of IND/IDE Suitability (available on the CRCO 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:

1. The clinical protocol(s) incorporated into the IND or IDE application has been reviewed and approved for scientific merit and quality.
2. The designated study site Investigator(s) for the conduct of the clinical protocol(s) incorporated into the IND or IDE application 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.
3. The IND or IDE Sponsor has adequately assessed feasibility of the protocol submitted with this IND/IDE.
4. The IND or IDE Sponsor has sufficient resources (e.g., facilities, equipment, and staff) as well as an adequate budget to conduct the clinical protocol incorporated into the IND or IDE application and to comply with applicable FDA regulations and institutional requirements.
5. The IND or IDE Sponsor is fully aware of the regulatory responsibilities of the Sponsor of an IND or IDE application.

For multisite (external to VCU) studies, a multisite form must be submitted to the CRCO with the IND/IDE External to VCU (Domestic Facilities) Multisite Certification form. This can be found at the VCU Faculty-Held IND or IDE website.

Following receipt, and verification that appropriate documents are included the CRCO will promptly notify the Sponsor that the packet can be submitted to the FDA.

Once the Sponsor has submitted the packet to the FDA, the CRCO must be notified of the date of submission.

All further correspondence with the FDA must be submitted to the CRCO.

All protocols conducted at VCU under a VCU Faculty Held IND/IDE will be managed in OnCore.

**NOTE:** Due to limited staffing, the CRCO is unable to provide editorial services related to University- based IND or IDE applications. If CRCO review of the application is desired prior to its submission to the FDA, the CRCO 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 CRCO review comments.

## 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 CRCO with an electronic copy of all final documents being submitted to the FDA.

1. **Cover letter** that accompanies the IND submission
2. Completed and signed *Investigator's New Drug Application (IND) Form FDA 1571*
3. A completed *Statement of Investigator Form FDA 1572* and **curriculum vitae** of the respective Investigator(s). These must be submitted with the IND application for each study site Investigator.

NOTE: Study site sub-investigators are defined in this form as those individuals that 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) and 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.

4. **IND Application** (See Content and Format of an IND Application) NOTE: The protocol submitted to the FDA and the IRB should always match.
5. A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank (Form FDA 3674)* must be submitted for the clinical protocol that accompanies the initial IND application as well as for new protocols submitted under an IND.

**NOTE:** It is advised that submission to ClinicalTrials.gov occur after the study has been finalized based on input from the FDA and the IRB. On the Form 3674 choose the appropriate statement regarding registration. If this is a new submission of an IND which contains a clinical trial but no participants have been enrolled then choose answer B (I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies). The clinical trial must be registered within 21 days of the first participant enrollment. The updated form noting the registration is then submitted to the FDA as an information Amendment to the IND application. For guidance and regulations, see <https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa>.

## 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 CRCO with an electronic copy of the final packet to be submitted to the FDA.

1. **Cover letter** that accompanies the IDE submission
2. Completed and signed *Application for an Investigational Device Exemption* (See the IDE Template: Application for an Investigational Plan-Feasibility Study or IDE Template: Application for an Investigational Plan-Pivotal Study).
3. Completed and signed *Investigator's Agreement(s)* (See IDE Template: Investigator's Agreement) and **curriculum vitae** of the respective Investigator(s).
6. **IDE application** (See Content and Format of an IDE Application) NOTE: The protocol submitted to the FDA and the IRB should always match.
7. A completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank (Form FDA 3674)* must be submitted for the clinical protocol that accompanies the initial IDE application.

NOTE: 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 by 21 days after the first subject is enrolled. *The Certification of Compliance with the Requirements of the ClinicalTrials.gov Data Bank* should be submitted as an information amendment to the IDE application to commensurate with the submission of the clinical protocol to this Data Bank. See <http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa> for guidance and regulations.

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

For subsequent submissions to an FDA-accepted IND application the Sponsor of the application shall provide the CRCO with an electronic copy of the documents being submitted.

1. **Cover letter** accompanying the subsequent IND submission
2. Completed *Investigational New Drug Application (IND) Form FDA 1571*; with the appropriate reason(s) for the subsequent submission checked under item 11

### 3. **Protocol Amendment** (if Applicable)

A **Protocol Amendment** may be necessary for significant changes to an existing protocol or for the addition of a new investigator to a previously submitted clinical protocol being conducted under a FDA-accepted IND application. An Amendment may also be submitted for new clinical protocols to be conducted under that FDA-accepted IND application. Be sure to state if 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 (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](http://clinicaltrials.gov) is within 21 days after the first subject is enrolled.

### 4. **Information Amendment** (if Applicable)

An **Information Amendment** is for changes to sections of the IND application other than the clinical protocol. This could include changes to the Chemistry, Manufacturing and Control section of the IND application or addition of a new study site.

NOTE: The submission of a completed and signed *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank (Form FDA 3674)* is not required for these Amendment submissions.

### 5. **Safety Report** (if Applicable)

### 6. **Annual Report** (if Applicable)

7. **IND Withdrawal or Discontinuation Notice** (if Applicable)
8. **Request for Reinstatement of an IND** that has been previously withdrawn, inactivated, terminated, or discontinued (if Applicable)
9. Any other report or correspondence concerning the FDA-accepted IND application

For additional guidance and templates, see *Required Amendments and Reports to an FDA-accepted Investigational New Drug (IND) Application* at [go.vcu.edu/indide](http://go.vcu.edu/indide).

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

For subsequent submissions to a FDA-accepted IDE application, the Sponsor of the application shall provide the CRCO with the final packet to be submitted to the FDA.

1. **Cover letter** accompanying the subsequent IDE submission
2. **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: 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 (Form FDA 3674)* must accompany the Supplemental IDE Application if it involves a new clinical protocol submitted to the FDA-accepted IDE application.

3. **Unanticipated Adverse Device Effect Report** (if applicable)
4. **Progress Report** (if applicable)
5. **Withdrawal of IRB Approval Report** (if applicable)
6. **Current Investigator List** (if applicable)
7. **Recall and Device Deposition Request** (if applicable)
8. **Failure to Obtain Informed Consent Report** (if applicable)
9. **Final Report** (if applicable)
10. Any other reports or correspondence concerning the FDA- accepted IDE

For additional guidance, see *Required Amendments and Reports to an FDA-accepted IDE Application* at [go.vcu.edu/indide](http://go.vcu.edu/indide).

## **F. Conflict of Interest**

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.

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 incorporates financial interests of the spouse and each dependent child of the study site Investigator(s) and applicable Sub-investigators.

To address bias, 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 in the drug or device under investigation and/or certain equity or financial interests held by the involved clinical investigators in the company that owns this drug or device. These disclosures are subject to audit by, or submission to, the FDA upon request of the agency.

In addition, **VCU's Conflict of Interests in Research** Policy is directed at ensuring that its reputation and research programs are not compromised by real or perceived conflicts of interest. The policy requires the reporting of any financial interests that the Investigator (i.e., principal investigator) or Sub-investigators (termed 'COI investigators' at VCU) hold with entities outside of VCU, including payments for consulting, travel, fiduciary interests, business ownership and equity interests.

The thresholds for reporting financial interests and for identifying conflicts of interest by the VCU COI Program are substantially lower than for the FDA. As a result, the University COI program may identify and manage conflicts of interest which may not necessarily require reporting on applicable FDA forms, but are, nonetheless, enforceable by VCU.

### **IND/IDE Sponsor Responsibilities**

1. Keep and update records for all Clinical Investigators at all sites. This will include obtaining a *VCU Certification of Financial Interests* and, as applicable, a *VCU Disclosure of Financial Interests* from all Clinical Investigators. These forms will document thresholds for reporting to FDA and allow completion of **Form FDA 3454** and **Form FDA 3455** by the Sponsor.
2. Review the Certification form received from all investigators. An affirmative response to one or more statements triggers the completion of a Disclosure form, which should be accompanied by an institutional management plan.
3. Complete and keep on file **Form FDA 3454** and, as applicable, **Form FDA 3455**.
4. Ensure that all VCU/VCUHS Clinical investigators and external investigators relying on the VCU COI system complete the *Financial Interests Report (FIR)* in the VCU AIRS and update within 30 days per the VCU COI policy.
5. Maintain documentation and comply with any COI management decisions by the VCU COI Committee or sent by external sites.
6. For PHS and PHS-adherent funding associated with sub-awards, assure that the Subrecipient Commitment Form is completed at each external site and maintained in the records.

### **VCU/VCUHS-based Clinical Investigators**

1. Complete the *VCU Certification of Financial Interests* and, as applicable, a *VCU Disclosure of Financial Interests* and submit to the Sponsor of the IND/IDE.
2. In addition, each 'COI investigator' must complete the *Financial Interests Report (FIR)*

in the VCU AIRS and update within 30 days per the VCU COI policy.

### **External Clinical Investigators- receiving a sub-award for a study which is PHS or PHS-adherent funded**

This is for agencies using the PHS Financial Conflict of Interests regulations. (See [http://nrc59.nas.edu/pub/fcoi\\_agencies\\_phs\\_regs.html](http://nrc59.nas.edu/pub/fcoi_agencies_phs_regs.html))

1. Complete the *VCU Certification of Financial Interests* and, as applicable, a *VCU Disclosure of Financial Interests* and submit to the Sponsor of the IND/IDE.
2. The *Subrecipient Commitment Form* must be completed by the institutional official signing at the site. The site will certify one of the following: that they have a PHS compliant COI management program and will report to VCU if a managed conflict is identified; that they will develop a compliant program for identification and management; or that they will defer to VCU's policy and process. If deferring to VCU, external Clinical Investigators designated as COI investigators are required to enter their *Financial Interests Report* in the AIRS for further assessment and must update within 30 days as per VCU policy.

### **External Clinical Investigators- receiving a sub-award for a study which is otherwise federally funded (not PHS or PHS-adherent)**

1. Complete the *VCU Certification of Financial Interests* and as applicable a *VCU Disclosure of Financial Interests* and submit to the Sponsor of the IND/IDE.
2. If the site has no COI policy, the clinical investigators designated as COI investigators are required to enter their *Financial Interests Report* in the AIRS for further assessment and must update within 30 days as per VCU policy.

### **External Clinical Investigators - study is funded by other than above and sub-recipient entity receives funding**

1. Complete the *VCU Certification of Financial Interests* and as applicable a *VCU Disclosure of Financial Interests* and submit to the Sponsor of the IND/IDE.
2. If the site has no COI policy, the clinical investigators designated as COI investigators are required to enter their *Financial Interests Report* in the AIRS for further assessment and must update within 30 days as per VCU policy.

## External Clinical Investigators - external site receives no sub-award

1. Complete the *VCU Certification of Financial Interests* and as applicable a *VCU Disclosure of Financial Interests* and submit to the Sponsor of the IND/IDE.

## Reportable Financial Conflicts of Interest on FDA forms 3454 and 3455

In accordance with FDA regulations (21 CFR Part 54) a significant (i.e., reportable, disclosable) financial interest includes one or more of the following:

1. 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.
2. 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.
3. Payments (i.e., a Financial Interest) in excess of \$25,000 (in the aggregate) that may be received by the study site Investigator or an applicable Sub-investigator (including spouses and dependent children of these individuals) from the company (i.e., other than a Sponsor of the study) that owns the drug or device being evaluated under the IND or IDE application during the term of the clinical investigations being conducted under the IND or IDE and/or for one year thereafter; including, but not limited to, grants to fund projects or research (but only if such grants are unrestricted or provide payment in excess [i.e., > \$25,000] of the actual costs for conducting the project or research) or compensation (i.e., > \$25,000) in the form of monetary payments, equipment, or retainers for consultation or honoraria.

See the VCU IND/IDE website for instructions on completing the *VCU Certification of Financial Interests* and the *VCU Disclosure of Financial Interests*. Form FDA 3454 and Form FDA 3455 can be found on the FDA website at

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090301.htm>

## **G. Multi-Center (i.e., multiple study sites) Clinical Investigations**

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. The difficulty of addressing these requirements increases substantially when the study sites are external to the VCU. 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, while University policies do not totally preclude the conduct of clinical investigations at external study sites under a VCU faculty based IND or IDE application; the Sponsor must certify that he/she understands the responsibilities, budget and resource requirements, and has appropriate policies in place.

### **For Multi-Center Clinical Trials LIMITED TO VCU Domestic Study Sites**

University policy does not place restrictions on the conduct of a clinical investigation at multiple VCU 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 VCU 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 Sponsors of University-based IND or IDE applications should consider appointing a separate study site Investigator for each of the involved VCU study sites.

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.

Investigators planning the conduct of a multi-center (i.e., involving multiple VCU study sites)

clinical investigation under a VCU 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. For additional guidance, see *Investigational New Drug Applications: Sponsor and Investigator Responsibilities or Investigational Device Exemptions: Sponsor and Investigator Responsibilities* at [go.vcu.edu/indide](http://go.vcu.edu/indide).

### **For Multi-Center Clinical Investigations INVOLVING EXTERNAL Study Sites**

VCU places certain restrictions on the conduct of clinical investigations at external study sites under a University-based IND or IDE application. External study sites are defined as study sites external to the VCU domestic facilities. The proposed conduct of a clinical investigation at an external study site under a University-based IND or IDE application requires the sponsor complete the *IND/IDE External to VCU (Domestic Facilities) Multisite Certification* form and submit to the CRCO prior to submission to the FDA.

The conduct of a University-based, Investigator-Initiated clinical investigation at an external study site is only permitted only under one of the following circumstances:

1. The clinical investigation does not require the submission of a corresponding, University-based IND or IDE application; **OR**
2. The clinical investigation requires the submission of a corresponding University- based IND or IDE application, **AND**:
  - a. The CRCO has received the completed *IND/IDE External to VCU (Domestic Facilities) Multisite Certification* form. This form certifies the Sponsor is aware and has procedures in place to meet the additional Sponsor responsibilities. **OR**
  - b. Each of the involved external study sites has filed its own IND or IDE application incorporating the same (i.e., common) clinical protocol; **OR**
  - c. The University has accepted a contract/agreement with a qualified industry partner leading to the conduct of the clinical investigation at the external study site(s) under a respective Industry-Sponsored IND or IDE application.

If you are planning a multisite IND/IDE as the Sponsor please contact the CRCO and complete the *IND/IDE External to VCU (Domestic Facilities) Multisite Certification* form. This form is also posted on the CRO website at [go.vcu.edu/indide](http://go.vcu.edu/indide).

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. The IND or IDE Sponsor must also establish appropriate processes and corresponding written procedures directed at addressing these responsibilities. See *Investigational New Drug Applications: Sponsor and Investigator Responsibilities* or *Investigational Device Exemptions: Sponsor and Investigator Responsibilities* for additional details at [go.vcu.edu/indide](http://go.vcu.edu/indide).

## **Standard Operating Procedures for IND/IDE Studies Multiple Study Sites**

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

1. The Sponsor's selection of the external study sites and investigators that 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.
2. 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)
3. 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 (See *Conflict of Interest*)
4. The Sponsor's dissemination of the clinical trial protocol to the external study site Investigators and for ensuring that these investigators:
  - a. Understand the nature and purpose of the clinical trial and the clinical trial procedures;
  - b. Are capable of conducting or supervising the conduct of the clinical trial; and
  - c. 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.

5. The Sponsor's maintenance of documentation regarding initial and continuing responsible (i.e., for the external study site) IRB review and approval for the conduct of the clinical trial at each of the external study sites
6. 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
7. The Sponsor's oversight of the test article to include:
  - a. Maintenance at the central storage location; and
  - b. Distribution of the investigational drug or device to the external study sites; including shipment, receipt, accountability, labeling and return of test article
8. 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
9. 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
10. 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
11. 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.
12. The Sponsor's plan for independent monitoring, (can be via a *Contract Research Organization*), 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:
  - a. The clinical trial is being conducted in accordance with the current version of the clinical trial protocol and applicable regulations and policies;

- b. The rights, safety and welfare of the research subjects are being adequately protected;
  - c. 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(s);
  - d. The investigational drug or device is being adequately controlled; and
  - e. The research records are being maintained in a secure manner for the retention period specified by FDA regulations and by the funding entity.
13. 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.
14. 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.
15. The Sponsor's preparation and maintenance of an effective IND or IDE:
- a. IND- Protocol Amendments, Annual Reports, Safety Reports and Final Reports
  - b. IDE- Supplemental IDE Applications, Progress Reports, Investigator Lists, Safety Reports and Final Reports
16. 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,
- a. Discontinuation of those clinical trials that present an unreasonable and significant risk;
  - b. Respective notification of the FDA, the Investigators, and the responsible IRBs;
  - c. Disposition of remaining supplies of the investigational drug or device; and
  - d. The requisite time frame should be specified for these actions.

NOTE: In lieu of a SOP, this can be accomplished via the *Data and Safety Monitoring*

*Plan* described in the protocol.

17. The Sponsor's oversight of external study site procedures for verification that the external study sites investigators have processes in place for the following:
- a. 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
  - b. 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
  - c. 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.

- d. 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: This 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

- e. 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

- f. 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
- g. 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

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

FDA regulations (21 CFR Part 312, Subpart D; 21 CFR Part 812, Subpart C) and GCP 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 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, the Sponsor shall provide the CRCO with copies of all monitoring reports and subsequent correspondence.

The CRCO will audit these IND/IDE protocols at VCU sites. These audits will be entered into the OnCore Audit Console.

## **I. Data and Safety Monitoring Board**

A Data and Safety Monitoring Board (DSMB) 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. (21 CFR 50.24) 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 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. (21 CFR 56.111)
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 (21 CFR 56.108).
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; (21 CFR 56.108) 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. (21 CFR 56.108)

NOTE: The FDA regulations (21 CFR Part 312.56; 21 CFR Part 812.46) 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 VCU 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 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.

## **J. Good Clinical Practice (GCP) Compliance in the Conduct of Clinical Trials**

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.

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.

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

ICH GCP is an international standard for the design, conduct, monitoring and reporting of clinical trials research. It provides assurance that the rights, safety, and well-being of participants are protected and respected and ensures the integrity of the research data.

As of February 15, 2015, mandatory Good Clinical Practice (GCP) training is required for all study personnel listed on a new or continuing review IRB protocol involved in executing a drug,

device, biologic and/or behavioral intervention that meets the NIH Definition of Clinical Trial. It reads that a clinical trial is “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

VCU requires the GCP module to be retaken ever three (3) years.

## **K. Good Laboratory Practices (GLP) Compliance for Supporting Non-clinical Safety Studies**

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. ([WHO Technical Report Series. No. 927, 2005](#))

Establishment of a University-based, GLP laboratory requires 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.

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.

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.

Non-clinical (i.e., animal or laboratory) safety Purpose of Policies – GLP Regulations) 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.

### **Use of VCU Laboratories**

If a VCU or VCUHS 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 Clinical Research Compliance Officer (CRCO). The requirement for a pre-qualification audit of GLP compliance and the frequency of continuing audits shall be determined by the CRCO 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.

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.

### **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 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 selected or prospectively approved by the Clinical Research Compliance Officer.

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.

### **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.

### **L. Grant or Contract Proposals to Establish a VCU-Based GLP Laboratory**

All grant, contract, or other proposals or agreements directed at establishing a VCU-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 Vice President for Research and Innovation or his/her designee. (See *Purpose of Policies – GLP Regulations*)

The CRCO and OSP 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 for VCU held IND/IDE.

Note: The University's Office of Research and Innovation will not process a grant or contract proposal directed at establishing a GLP facility to be used on a VCU based IND/IDE unless the proposal is accompanied by a letter of approval signed by the VPR or his/her designee.

### **M. Compliance for the Manufacturing of Investigational Drugs and Quality System Compliance for the Manufacturing of Investigational Devices (cGMP)**

The FDA regulations, entitled *Current Good Manufacturing Practice for Finished Pharmaceuticals* (21 CFR Part 210; 21 CFR Part 211; 21 CFR Part 212), define a quality system that addresses the 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* (21 CFR Part 820), 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).

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 are 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.

Devices being evaluated under University-based IDE applications are exempt from the FDA's Quality System regulations except for the requirements for Design Control ( 21 CFR Part 820, Subpart C).

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 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.

### **Specific guidance for 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.

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.

### **Use of VCU Facilities**

For University-based IND applications that propose the on-site preparation (i.e., “manufacture”) of the investigational drug within a VCU 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 CRCO. 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.

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.

### **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 of cGMP compliance performed by a qualified consultant selected or prospectively approved by the CRCO. 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 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.

## **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.

## **Specifics for 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 and labeled 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*)

### **Use of VCU Facilities**

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

### **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 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<sup>22</sup> of compliance with the FDA's Quality System/Design Control requirements performed by a qualified consultant selected or prospectively approved by the CRCO. 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, it shall be described in a Supplemental IDE Application submitted to the FDA-accepted IDE.

## **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.

### **N. Grant or Contract Proposals to Establish a VCU based cGMP Facility**

All grant, contract or other proposals or agreements directed at establishing a VCU-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 VPR or his/her designee. (See Purpose of Policies – cGMP Requirements)

The CRCO and OSP 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.

NOTE: The University's Office of Research and Innovation 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 VPR or his/her designee.

### **O. Control of Investigational Drugs and Biologics**

The Investigational Drug Pharmacy will be used for all protocols utilizing a drug or biologic at a VCU site. If the Investigational Drug Pharmacy cannot be utilized for logistical reasons, a waiver must be obtained from the Director of the Investigational Pharmacy or his/her designee. Drug handling and accountability will be audited by the Investigational Pharmacy.

The department, institute or school to which the Sponsor of the IND application administratively reports shall assume financial responsibility for the cost of the Investigational Pharmacy utilization or monitoring.

For multisite studies other than VCU domestic sites, the Sponsor of the IND Application must assure that the procedures for drug handling and accountability are established prior to the conduct of the study and are monitored throughout the study.

## **P. Departure of Sponsor-Investigators from the VCU**

An IND or IDE application developed and submitted to the FDA by a University faculty member during her/his employment at the VCU is the intellectual property of the University. See VCU's Intellectual Property Policy. 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. (See VCU policy on *Research Data Ownership, Retention, and Access*) 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 must be ensured.

Prior to departure from Virginia Commonwealth University, the Sponsor (or Sponsor-Investigator) of an active IND or IDE application is required to:

1. Notify the CRCO, and
2. Transfer sponsorship of the IND or IDE application to another appropriately qualified VCU faculty member, or
3. Obtain approval from the Vice President for Research and Innovation to take the IND or IDE with them.

The CRCO will assist with the respective processes and procedures to be followed. If the faculty sponsor, intends on transferring the IND or IDE to another institution, this will need to be approved by the Vice President for Research or his/her designee and all agreements between VCU and the new institution finalized before transfer. If the Sponsor is transferring the IND or IDE Application but there is an active protocol being done at a VCU site, the Sponsor must appoint an Investigator and assure that all Sponsor and Investigator responsibilities are addressed. Changes to sponsors of an IND or IDE require notification of the FDA and IRB.

## **Q. Institutional Disapproval of the Submission or Continuance of Sponsor-Investigator IND and IDE Applications**

The Vice President for Research and Innovation, in consultation with the Senior Associate Vice President for Research Administration and Compliance and the CRCO will have the authority to disapprove a VCU based IND or IDE Application.

## **APPENDIX 1: Abbreviations**

<b>CFR</b>	Code of Federal Regulations
<b>COI</b>	Conflict of Interest
<b>CRCO</b>	Clinical Research Compliance Officer
<b>DSMB</b>	Data and Safety Monitoring Board
<b>FDA</b>	U.S. Food and Drug Administration
<b>GCP</b>	Good Clinical Practice
<b>GLP</b>	Good Laboratory Practice
<b>GMP</b>	Good Manufacturing Practice
<b>ICH</b>	International Conference on Harmonisation
<b>IDE</b>	Investigational Device Exemption
<b>IND</b>	Investigational New Drug
<b>IRB</b>	Institutional Review Board
<b>NSR</b>	Nonsignificant Risk
<b>OSP</b>	Office of Sponsored Programs
<b>SOP</b>	Standard Operating Procedures
<b>SR</b>	Significant Risk
<b>VCU</b>	Virginia Commonwealth University
<b>VCUHS</b>	Virginia Commonwealth University Health System
<b>WHO</b>	World Health Organization

## **APPENDIX 2: Quick References**

### **Code of Federal Regulations Title 21, Part 312**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312>

### **Code of Federal Regulations Title 21, Part 812**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=812>

### **FDA Device Advice: Investigational Device Exemption (IDE)**

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/default.htm>

### **Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions - Statement of Investigator (Form FDA 1572)**

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>

### **Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring**

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>

### **Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07122.pdf>

### **ICH GCP (E6)**

<http://ichgcp.net/>

### **VCU Faculty-Held IND or IDE website**

[go.vcu.edu/indide](http://go.vcu.edu/indide)

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