ARE YOU THE HOLDER OF AN IND?

...CONSIDER YOUR LEGAL OBLIGATIONS

INVESTIGATIONAL NEW DRUG

USC

Office for the Protection of Research Subjects (OPRS)

This booklet provides researchers with the regulations and responsibilities that apply when they are the holder of an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE). It is intended to be a useful reference for researchers, staff and study teams. USC has accountability obligations for all sponsor-investigator drug, device, or biological research at the University.

In addition, the sponsor-investigator is responsible for compliance with FDA regulations and communications.

Sometimes a faculty member serves as the principal investigator on an IND or IDE, whose sponsor is an outside company, institution, organization, or individual. Under federal law, the outside sponsor, not the University, is responsible for interactions with the FDA. The principal investigator, however, remains subject to all other University policies on clinical research.

What Is An IND Application?

An Investigational New Drug (IND) application is the document submitted to the Food and Drug Administration (FDA) for permission to conduct a clinical study using a drug or biologic that is new or not approved for a given dosage, formulation or indication.

These terms may also be used to describe IND holders:

- Sponsor-investigator*
- Investigator-initiated research
- IND investigator
- Investigator-sponsored IND
- Physician-initiated research

**The terms "sponsor-investigator" and "IND holder" are used interchangeably throughout this pamphlet. Sponsor-investigator is used particularly when the investigator has not yet submitted the IND application to FDA.*

When Do You Need An IND?

An IND is required when the purpose of the investigation *(21CFR 312.2)*:

- is for a product intended to be submitted to FDA by the "sponsor-investigator" in support of a new drug or a new indication for use or significant change in labeling of a marketed drug
- is for a product intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising (i.e., for use in children as well as adults) keep
- involves a different route of administration or dosage level or use in a new, high-risk, and/or different patient population or other factor that significantly increases the risks associated with use of the product – or decreases the acceptability of the risks

When an IND is required, the study must be conducted in compliance with 21 CFR 312.7 which deals with promotion and sale of investigational products.

What If Your Drug Study Is IND Exempt?

If the above do not apply to the investigation, the study is exempt from IND requirements.

Note: At USC, the investigator must select the exemption category in the IRB application Section 17. that demonstrates why the study is exempt.

IND exempt studies must comply with informed consent and IRB approval requirements (21 CFR 50 and 56, respectively). If a study does not require an IND per FDA, the investigator must be able to document this determination, and the Institutional Review Board (IRB) will verify documentation.

Preparing to Submit an IND to FDA?

FDA encourages potential IND holder to utilize the Pre-IND Consultation Program. The focus of the consultation(s) is to discuss preclinical studies needed to support clinical testing, to understand study product chemistry, manufacturing and control (CMC) issues and to preview the proposed clinical studies. Generally, only one pre-IND meeting is granted by FDA per product claim; therefore, it is best to address any issues anticipated in the drug development process. It is important to be well-prepared to utilize this valuable opportunity to obtain FDA feedback and guidance.

To initiate a pre-IND meeting, submit a written request to FDA. An information package must be submitted to FDA at least 4 weeks prior to the meeting.

Detailed contents of the information to be included in the package are found in the "FDA Guidance for Industry Formal Meetings with Sponsors and Applicants for PDUFA Products": www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

After the meeting takes place, FDA will issue written official minutes to the IND applicant within 30 days of the meeting.

USC Scientific Review

Submitters of an IND can learn about the soundness of their study design and study acceptability with feedback provided from scientific review during IRB submission. The USC Clinical Research Support Office of SC CTSI will complete a scientific review of IND submissions. This office is also an available resource for assistance throughout the study process.

SC CTSI Contact Information: info@sc-ctsi.org

How Do You Submit An IND?

What Forms Are Required?

To submit an IND application to FDA, the following are required (21 CFR 312.23):

- IND Application Form FDA 1571 is submitted by the sponsor, or sponsor-investigator.
- Statement of Investigator Form FDA 1572
- Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank Form FDA 3674
  Or
- Dossier (as below) addressing all of the elements outlined in Form 1571

Elements required in an IND Submission Dossier

1. Investigational New Drug Application
    a. Table of Contents
    b. Introductory Statement
    c. General Investigational Plan
    d. Investigator's Brochure
    e. Protocol
        i. Study protocol
        ii. Investigator data or completed Form FDA 1572
        iii. Facilities data or completed Form FDA 1572
        iv. Institutional Review Board data or Form 1572
    f. Chemistry, manufacturing, and control data
    g. Pharmacology and toxicology data
    h. Previous human experience
    i. Additional information
2. Statement of Investigator (Form FDA 1572)
3. Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank (Form FDA 3674)

USC Sponsor-Investigator Agreements

Principal Investigator's Assurance

All investigators must read and agree to the *Principal Investigator's Assurance.* The agreement is located in iStar, and acceptance is required of all Principal Investigator (PI) responsibilities before submitting a completed application for IRB review.

USC Sponsor-Investigator Agreement

For investigator-initiated drug studies, in which the PI is the IND holder, the investigator must upload a signed *USC Sponsor-Investigator Agreement form* on the iStar application. By signing this form, the investigator agrees to comply with both sponsor and investigator responsibilities and assure compliance with regulations. A copy of the *USC Sponsor-Investigator Agreement form* can be found at:

https://oprs.usc.edu/files/2016/11/Sponsor-Investigator-Agreement-Form.pdf

USC Educational Requirements

In addition to federal and state requirements, USC IND holders must comply with applicable USC educational training requirements. All trainings are online.

1. **Human Subjects Training**
   All investigators and key personnel conducting human subjects research at USC, whether IND holders or not, must complete the CITI human subjects training. The mandatory training is a condition of IRB study approval. For CITI access, FAQs: https://oprs.usc.edu/education/citi/.

2. **Good Clinical Practice (GCP)**
   Good Clinical Practice training is required for all principal investigators and key personnel conducting full board clinical trials (not applicable to personnel who conduct expedited or exempt studies exclusively). More information can be found at: https://oprs.usc.edu/education/citi/ .

3. **HIPAA**
   All USC faculty, staff, employees, students, volunteers and agents with access to patient protected health information (PHI) from USC providers must complete the online HIPAA compliance program: http://ooc.usc.edu/hipaa-privacy-regulations.

Maintaining Regulatory Compliance

In studies sponsored by a pharmaceutical or device company, study monitors, provided by the sponsors, visit sites on a regular basis to ensure regulatory compliance. However, when investigators act as their own sponsors, they normally do not have study monitors to verify that the study is conducted in compliance with the protocol, IRB application, and applicable regulations. IND holders must ensure that all federal, state and institutional regulations are being met. The monitoring

functions may be delegated to a contract research organization.

The monitoring plan should include the following:

- The protocol/investigational plan is being followed
- Changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB
- Records are accurate, current, and complete
- Informed consent has been documented in accordance with 21 CFR Parts 50 and 56

In order to encourage and understand self-monitoring, the relevant excerpts from FDA guidance and regulations are provided at:
http://oprs.usc.edu/files/2013/01/IND_IDE_monitoring.pdf

A self-audit checklist is also provided:
http://oprs.usc.edu/files/2013/01/Audit_Checklist_42010_HSIRB.pdf

Products Manufactured in California

If an IND product is manufactured in California, the following requirements must be met:

1. **License and Inspection**

   A license application (one per place of manufacture) must be submitted to the Food and Drug Branch (FDB) of the California Department of Health Care Services for IND products manufactured in California. The license depends on a successful audit from Good Manufacturing Practice (GMP) facilities to determine ownership, adequacy, and personnel qualifications for the product in question, and will be effective for two years from date of issue unless it is revoked.

Thereafter, renewal depends on an audit every two years. A license renewal application should be filed before its expiration date to maintain compliance and avoid penalties.

2. Drug Manufacturing Requirements

When a drug or device is manufactured in the state of California, IND holders must abide by additional requirements according to the CA Sherman Food, Drug, and Cosmetic Law, click here: www.cdph.ca.gov/services/Documents/fdbSFDCA.pdf

IND Reporting Requirements

Protocol Amendments (21 CFR 312.30)

- Any changes to existing protocols must be submitted to FDA for review as well as to the Institutional Review Board (IRB) for approval before the protocol changes are implemented.

IND Safety Reports (21 CFR 312.32)

- Adverse events that are **unexpected and fatal or life-threatening** whether or not they can be causally associated with a drug or placebo must be reported to FDA within 7 calendar days after an IND holder is notified of the event
- Adverse events **associated with use of the drug that are both serious and unexpected** or any **finding from tests in laboratory animals that suggests a significant risk for human subjects** must be reported to FDA within 15 calendar days after the IND holder is informed of the incident.
- Follow up information to safety reports should be submitted as soon as the information is available.

Annual Reports (21 CFR 312.33)

A brief progress report of the investigation must be submitted to FDA within 60 days of the IND anniversary date.

Potential Conflicts of Interest

The University of Southern California defines Conflict of Interest (COI) as "*a situation in which financial or other personal considerations compromise, or have the appearance of compromising an individual's professional judgment in proposing, conducting, supervising or reporting research*" (*USC Conflict of Interest in Research: Policy and Procedure*). USC Conflict of Interest reporting requirement are found at: http://ooc.usc.edu/conflict-interest

diSClose

Researchers who are proposing or have received support from the US Department of Health and Human Services (including NIH, CDC, HRSA, and AHRQ) must also make an annual disclosure of all financial interests related to their USC institutional responsibilities, regardless of whether any of these interests give rise to a conflict of interest related to their research.

Link: diSClose

Investigators must disclose Conflicts of Interest (COI) in the iStar application.

An IND holder must disclose COIs as a sponsor and as an investigator. If the IND holder does not have an identifiable disclosable financial arrangement to report, an FDA 3454 Form (Certification: Financial Interests and Arrangements of Clinical Investigators) must be completed and submitted to FDA. However, if an identifiable disclosable financial arrangement will be reported, an FDA 3455 Form (Disclosure: Financial Interest and Arrangement of Clinical Investigators) must be submitted to FDA to disclose the financial arrangement.

Note: if the IND holder is the only investigator for the study, only one form is submitted to FDA. If other investigators are involved in the study, the IND holder can attach a list of all investigators without a disclosable financial arrangement to report to FDA 3454 Form. However, an individual FDA 3455 Form must be completed by each investigator in the study reporting a disclosable financial arrangement

Federal Resources

Food and Drug Administration

IND Application:
www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

Draft Guidance on IND Applications:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf

Pre-IND Consultation Program:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm

Expanded Access to Investigational Drugs and Biologics:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm

Regulations for Clinical Trials:
www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm

Guidance on Formal Meetings with Sponsors and Applicants for PDUFA Products:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

NIH Clinical Trials Registry
ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

https://clinicaltrials.gov/

Office of Human Research Protections (OHRP)
www.hhs.gov/ohrp/

State Resources

California Dept. of Health for Manufacturers, Processors, and Distributors
www.cdph.ca.gov/certlic/manfprocdistrib/Pages/default.aspx

California Food and Drug Branch
www.cdph.ca.gov/programs/Pages/FDB%20Food%20and%20Drug%20Branch.aspx

Whom to Contact at USC

Health Sciences Institutional Review Board
General Hospital, Suite 4700
1200 North State Street
Los Angeles, CA 90033
Tel: (323) 223.2340 Fax: (323) 224.8389 E-mail: irb@usc.edu
Web: https://oprs.usc.edu/hsirb/

University Park Campus Institutional Review Board
Credit Union Building (CUB), Suite 301
3720 S. Flower Street
Los Angeles, CA 90089 Tel:(213) 821.5272 E-mail: upirb@usc.edu
Web: https://oprs.usc.edu/upirb/

Office for the Protection of Research Subjects (OPRS)
3720 South Flower Street, Third Floor
Los Angeles, CA 90089-0706
Tel: (213) 821.1154 Fax: (213) 740.9299 E-mail: oprs@usc.edu
Web: https://oprs.usc.edu/
https://oprs.usc.edu/hsirb/biomedical/investigator-initiated-trials/

USC Office of Compliance
University Gardens Building, Room 105
3500 Figueroa Street
Los Angeles, CA 90089-8007
Tel: (213) 740.8258 E-mail: complian@usc.edu
Web: www.usc.edu/compliance/

USC Clinical Trials Office
2011 North Soto Street, 2nd Floor
Los Angeles, CA 90032
Tel: (323) 442-7218 E-mail: clinicaltrialsoffice@med.usc.edu
Web: http://clinicaltrials.usc.edu

iStar Helpdesk: istar@usc.edu (323)276-2238

CITI Helpdesk: citi@usc.edu (213)821-5272

Additional Resources at Other Institutions

Partners Research Management
Provides various comprehensive checklists including the "FDA Sponsor & Investigator Responsibility Checklist" to ensure that all IND/INDE responsibilities have been fulfilled. They also offer a personalized study binder to achieve and maintain regulatory compliance. For more information, go to: http://navigator.partners.org/Pages/IDE.aspx

Virginia Commonwealth University IND Flowchart
http://research.vcu.edu/IND_IDE/IND_flowchart.pdf

University of Minnesota
IND /IDE programs provide assistance with determination of product classification (i.e. drug, device, biologic), applicability of an IND or IDE, preparation, coordination, facilitation, and attendance at FDA meetings, preparation for and regulatory support during FDA inspections of investigator-sponsored clinical trials, and regulatory support for IRB applications. This information can be found at:
www.policy.umn.edu/Policies/Research/INDIDE.html