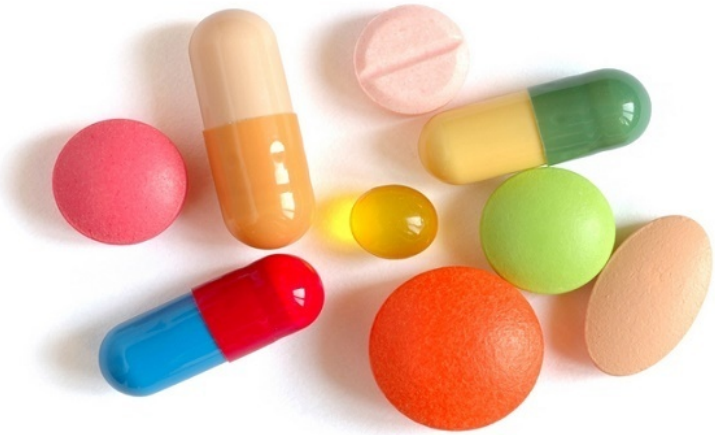
ARE YOU THE HOLDER OF AN IND?

INVESTIGATIONAL NEW DRUG



UNIVERSITY OF
SOUTH ALABAMA

Office of Research Compliance and Assurance

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. USA 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.

DEFINTIONS

Investigator- an individual who actually conducts a clinical investigation (*i.e.* , under whose immediate direction the drug 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. "Subinvestigator" includes any other individual member of that team.

Investigational new drug (IND)- a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Sponsor- a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

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

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.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

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. See 21 CFR 312.2 for a full description of exempt categories. It is the responsibility of the Investigator-Sponsor to justify why a proposed study meetings the requirements for exemption from the IND regulations. Sponsors who are uncertain if their proposed investigator meets the criteria for IND exemption may seek advise from the FDA Review Division responsible for the relevant therapeutic area of the proposed trial. FDA may advise the sponsor to submit a full IND application for the proposed investigation for FDA review.

A reference tool in determining whether an IND is required is the FDA Guidance document, Investigational New Drug Applications – Determining Whether Human Research Studies Can Be Conducted Without an IND.

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".

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

University of South Alabama

Submitters of an IND can learn about the soundness of their study design and study accountability with feedback provided by the Office of Research Compliance and Assurance as well as the Office of Clinical Trials. Investigators should reach out to both departments prior to submitting to the Institutional Review Board or to the FDA.

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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)

USA's Educational Requirements

In addition to federal and state requirements, USA IND holders must comply with applicable USA educational training requirements. Training requirements can be found on the Research Compliance Training webpage as well as the Research Education and Learning Portal.

1. Human Subjects Training

Certification of training on the protection of human research participants is required for all investigators and key personnel involved in the conduct of human subject's research. The Collaborative Institutional Training Initiative (CITI) online platform is utilized to meet this requirement. This training does not expire.

Click **here** for instructions to access the training.

2. Good Clinical Practice (GCP)

All NIH-funded investigations/staff involved in the conduct, oversight, or management of clinical trials are required to complete GCP training, consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2). Training in GCP complements other NIH training requirements on protections for human subjects.

The FDA requires GCP compliance for studies conducted under an investigational new drug application or investigation device exemption. GCP describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials. GCP training must be refreshed at least **every three years** in order remain current with regulations, standards and guidelines.

Acceptable GCP online courses:

* Any GCP modules that have been TransCelerate approved. A list of approved modules can be found Here.

* Collaborative Institutional Training Initiative (CITI) – To access this training, register a new account. Be sure to mark your affiliation with the University of South Alabama in order to receive the training for free. Complete the registration process to access the module title 'CITI Good Clinical Practice Course'.

3. HIPAA in Research

Investigators and key research personnel that obtain/maintain protected health information* (PHI) must complete the USA HIPAA in Research Training. The training is a self-guided training. A certificate of completion is available at the end of the

training document. This training does not expire.

PHI obtained/maintained within the USA Health Systems Covered Entity must comply with HIPAA privacy and security training requirements. USA Covered Entities include: USA Hospitals, USA Physician's Group Clinics, Mitchell Cancer Institute, Speech and Health Center, and Psychology Clinic.

* List of 18 PHI identifiers

4. Biohazardous Packaging and Shipping

Any personnel that will be handling and shipping biohazards (including dry ice) require this training. The online CITI module "Shipping and Transport of Regulated Biological Materials" is designed as initial training and periodic retraining for employees who package or ship diagnostic and clinical human or animal specimens, human or animal pathogens, and other regulated biohazards. The course is designed to meet requirements of the International Air Transport Association (IATA) and the U.S. Department of Transportation (DOT).

The Biohazardous Packaging and Shipping training expires every two years.

WHAT IF I WANT TO RUN A MULTI-SITE STUDY WITH THE IND?

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 if the budget allows.

The Office of Research Compliance and Assurance may be utilized for certain monitoring functions. It is important to discuss the monitoring plan with ORCA prior to submitting to IRB or FDA.

The monitoring plan should include the following:

- How subject eligibility will be confirmed
- Verification of documentation of informed consent
- Verification of protocol adherence
- Quality of data collected
- Source document verification
- Accountability of study drug(s)
- Adverse event review and compliance
- Compliance of sponsor-investigator obligations

IND REPORTING REQUIREMENTS

IND safety reports are required to ensure timely communication of significant new information about experiences with the investigational drug. Findings suggest a significant risk would typically result in a safety-related change in the protocol, inform consent, investigator brochure or the conduct of the study. (e.g., result in a protocol amendment)

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 lifethreatening 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. This is the date the FDA permitted the study to begin and can be found on the FDA IND Acknowledgement Letter. The expected contents of the progress report are outlined in 21 CFR 312.33.

If the due date of the annual report does not coincide with the date of the IRB continuing review, the research site should describe in the IRB continuing review application that the annual report is not yet due, but will be provided at the time of the next continuing review cycle.

ClinicalTrials.gov reporting and results (FDAAA801)

The responsible party should update their records within 30 days of a change to the recruitment status, or completion date. Other changes or updates to the record, such as protocol amendments, must be made at least every 12 months.

In general, results of an applicable clinical trial of a drug or biologic that is approved, licensed, or cleared by FDA must be submitted by the sponsor no later than 12 months after the primary completion date.

Withdrawal of an IND (21 CFR 312.38)

Sponsor-investigators must inform the FDA of the desire to withdraw an IND. All clinical investigations conducted under the IND must cease, all current investigators must be notified and all of the study drug must be returned to the sponsor or otherwise disposed of at the request of the sponsor per 21 CFR 312.58.

SPONSOR RECORDKEEPING

The sponsor is responsible for maintain the following records.

Drug accountability [21 CFR 312.57a]

Accurate records documenting the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

Financial interest [21 CFR 312.57b]

Documentation of any financial interests of any of the participating investigators involved in the study (see also 21 CFR 54). The sponsor-investigator is responsible for ensuring all participating investigators provide the Investigator with sufficient accurate financial information to allow him/her to submit complete and accurate certification or disclosure statements. The Investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

POTENTIAL CONFLICTS OF INTEREST

A conflict of interest exists when an employee's financial or personal considerations may compromise, or have the appearance of compromising, an employee's personal judgment in administration, management, instruction, research, and other professional and academic activities.

An IND holder must disclose conflict of interests 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

All University Conflict of Interest policies and procedures must be followed and can be found on the USA Conflict of Interest webpage.

Resources

Food and Drug Administration

IND Application:

https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

Draft Guidance on IND Applications:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be

Pre-IND Consultation Program:

https://www.fda.gov/drugs/investigational-new-drug-ind-application/pre-ind-consultation-program

Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use:

https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use

Regulations for Clinical Trials:

https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

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/

Whom to Contact at USA

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