

Guidance and Procedures: Use of Drugs and Biologics in Clinical Research and Treatment (last updated June 9, 2016)

- [Brief Overview](#)
- [Investigational New Drug Applications \(INDs\)](#)
 - [When Is an IND Required for Clinical Research?](#)
 - [When is an IND Not Required for Clinical Research?](#)
 - [What Is the Difference Between a “Sponsor” and a “Sponsor-Investigator” IND?](#)
 - [How Should an Investigator Time the Request for an IND?](#)
- [Situations and Methods that Allow for Expanded Access to Unapproved Drugs for Treatment](#)
- [IRB Requirements](#)
 - [What Is Required for IRB Review of the Study Application?](#)
 - [What Are the Consent Form Requirements?](#)
- [Control of Investigational Drugs and Biologics](#)
- [Reporting Requirements](#)
 - [Post Approval Reporting \(Adverse Events and Beyond\)](#)
 - [Reporting Obligations for Investigators](#)
 - [Additional Reporting Obligations for Sponsors and Investigator-Sponsors](#)
- [References and Regulations](#)

Brief Overview

This guidance is intended to assist UCLA investigators in meeting the various Food and Drug Administration (FDA) requirements as well as UCLA requirements when using unapproved drugs or biologics in clinical research and an in treatment. Food and Drug Administration (FDA) regulations [21 CFR 312](#) contain procedures and requirements governing the use of unapproved drugs and biologics. All clinical research projects or treatments involving drugs or biologics which are not FDA-approved for marketing must be reviewed by the FDA and the IRB. This is done by filing an IND with the FDA and submitting a protocol for review by the IRB.

Investigational New Drug Applications (INDs)

When is an IND required? An IND is required for:

- Any use of a drug or biologic ***not approved for marketing by the FDA***, even if no study is being conducted.
- Studies involving a drug or biologic that is ***not approved by the FDA***.
- Studies involving an approved (i.e., commercially available) drug or biologic that is being ***tested to support a new indication or significant change in labeling of the drug or biologic***.

- Studies involving an approved drug or biologic that is being **tested to support a significant change in advertising for the drug or biologic**.
- Studies involving an approved drug or biologic that is being used or **tested in a new route of administration, new dosage level, or new patient population** that may increase the risk of the drug or biologic.

When is an IND *not* required?

Please review the OHRPP information sheet, [Exemptions from IND Requirements](#) for a complete list of all types of investigations involving drugs that are exempt from FDA IND requirements, according to [21 CFR 312.2](#).

- **Clinical Studies:** Any clinical investigation of an approved, marketed drug or biologic requires UCLA Institutional Review Board (IRB) review and approval. An IND is **not** required if **all** of the following conditions are met:
 - It is **not intended to be reported to the FDA** in support of a new indication for use or to support any other significant change in the labeling; **and**
 - It is **not intended to support a significant change in the advertising** for the product; **and**
 - It **does not involve a route of administration or dosage level, use in a subject population, or other factor** that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; **and**
 - It is conducted in compliance with the FDA requirements for **IRB review** ([21 CFR part 50](#)) **and informed consent** ([21 CFR part 56](#)); **and**
 - It is conducted in compliance with the FDA requirements concerning the **promotion and sale of drugs** ([21 CFR 312.7](#)).

IMPORTANT NOTES:

1. When the **principal intent** of the clinical investigation is to **develop information about the safety or efficacy of a drug or biologic**, the UCLA IRB may require that the PI submit an IND request to the FDA.
2. Even when there is no immediate intent to change product labeling or advertising, investigators who are **planning rigorous, carefully controlled clinical investigations** of an off-label use of an approved drug/biologic should seek an IND. This is because the data from such studies conducted without an IND will not be considered by the FDA, even if positive and important for public health.

Example of when IND may not be needed: An investigator proposes a small pilot study of an approved drug for a novel use and states that an IND is not needed because the data will not be submitted to the FDA. The investigator explains that if the pilot data looks promising a larger trial will be submitted with an IND. The IRB is likely to approve the pilot study without an IND because a small pilot study is an appropriate first step in determining whether a change in labeling should be sought.

Example when IND is needed: An investigator proposes a multicenter randomized trial of an approved drug for a novel use and states that an IND is not needed because the data will not be submitted to the FDA. The IRB is **not** likely to approve the study without an IND because the data could be important and should be considered by the FDA.

- **Off-Label Prescriptions:** Neither an IND nor UCLA IRB review is required for off-label use of a marketed drug or biologic as **long as such use is strictly for clinical purposes, and the results are not collected for or presented as research**.

What is the Difference between a “Sponsor” and a “Sponsor- Investigator” IND?

The FDA makes the following distinction between a “sponsor” and a “sponsor-investigator” and a “commercial IND” and an “Investigator-Initiated IND.”

- **“Sponsor”** means 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.

A **“Commercial IND”** is submitted by a sponsor that intends to market the product upon FDA approval.

- **“Sponsor-Investigator”** means 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.

An **“Investigator-Initiated IND”** is submitted by a physician who both initiated and conducts a clinical investigation.

See [21 CFR 312.3](#) for other definitions and interpretation of terms related to the topic of investigational new drug applications.

NOTE: UCLA investigators submitting an Investigator-Initiated IND should name the physician investigator responsible for the clinical investigation, and not UCLA or University of California Regents.

How Should an Investigator Time the Request for an IND?

- **Pre-IND Advice:** Investigators considering submitting an IND application to the FDA should consult the FDA’s [Investigational New Drug Application Process](#) web page before submitting an IND application. To contact the appropriate division for the [Pre-IND Consultation Program](#), please refer to the [Pre-IND Consultation List](#).
- **The IND Submission:** The IND submission to the FDA and the IRB application should be initiated at the same time. The FDA has 30 days to review the IND application. Likewise, the IRB typically reviews an application within a 30-day window, but it may take longer to secure approval. Subjects may not be recruited or enrolled before FDA **and** IRB approval.

Situations and Methods that Allow for Expanded Access to Unapproved Drugs for Treatment

What are the situations in which expanded access to unapproved drugs may be allowed?

Physicians tend to use **“compassionate use”** to refer to the treatment of a seriously ill patient using an unapproved drug or biologic where no other available treatments are satisfactory. Instead, **it is preferable to use the names of the specific access programs** when discussing the use of investigational drugs or biologics outside of formal clinical trials.

FDA allows certain individuals ***not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics*** through the methods described below, under the following circumstances:

- Patient(s) have a ***serious or immediately life-threatening disease or condition***, and there is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition;
- Potential ***patient benefit justifies the potential risks of the treatment use*** and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
- Providing the investigational drug for the requested ***use will not interfere with clinical investigations that could support marketing approval*** of the expanded access use or otherwise compromise the potential development of the expanded access use.

IMPORTANT NOTES:

1. Use of investigational drugs or biologics through these methods requires prior review and approval by the IRB and the FDA.
2. The sponsor will likely hold the IND for these programs.
3. "Compassionate Use" is not the same as "Emergency Use" which is much more restrictive. Please see the [OHRPP Guidance on Emergency Use of a Test Article](#) for more information.

What are the Various Expanded Access Programs?

- ***Individual Patient and Intermediate-size Patient Population Use:*** The use of an investigational drug outside of a controlled clinical trial for an individual patient **or** a patient population smaller than what is typical of a treatment IND or treatment protocol.
- ***Treatment IND or Treatment Protocol:*** The use of an investigational drug outside of a controlled clinical trial for widespread treatment use.
- ***Open – Label Protocol:*** A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained.
- ***Parallel Track:*** A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that "parallel" the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics.
- ***Group C Treatment Investigational New Drug (IND):*** The "Group C" treatment IND was established by agreement between the FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside of a controlled clinical investigation.

IRB Requirements

What is required for IRB review of the study application?

- ***Full Committee Review:*** Because studies involving unapproved drugs for clinical investigations and for treatment involve by their nature more than minimal risk and do not meet any of the federally-defined expedited review categories, the initial review of such studies is always conducted by a convened meeting of the full board.

- **IND Number:** When a clinical investigation requires an IND number, the IRB will not issue final approval until the IND number is reported to and verified by the IRB. Verification can be accomplished by providing a copy of the sponsor's protocol with the IND number listed, or by submitting correspondence from the sponsor or FDA indicating the IND number for the study. However, the IRB will review the research before the IND application is submitted to or approved by to the FDA. The FDA does not require local IRB approval before issuing an IND number.
- **Investigator's Brochure:** For any study involving an investigational drug or biologic, one copy of the Investigator's Brochure must be submitted with the IRB application.
- **Protocol:** If there is a sponsor or multicenter protocol, a copy of that protocol must accompany the IRB application.
- **FDA Form 1572:** This form is required for FDA purposes and does not need to be submitted to the IRB.

What information must be included in the consent documents?

First and foremost, the requirements for UCLA IRB approval of all consent documents are outlined in federal and state regulations as well as UCLA guidance. Specific information is required for the use of drugs in clinical research and for the use of unapproved drugs for treatment as described below:

- **Purpose and Background Section:**
 - Must include a clear statement that the drug or biologic is investigational and has not been approved or, if studying an approved drug or biologic, that it is approved but not for the use being studied.
 - Should include a brief lay description of what the drug or biologic is and how it is thought to act.
 - Must not state or imply that the issuance of an IND is an approval or endorsement by the FDA.
- **Confidentiality Section:**
Must state that the FDA and the study sponsor may review subject medical records and research records which identify the subjects.
- **Alternatives Section:**
If studying an approved drug or biologic, must explain that subjects can receive drug or biologic without participating in the study. An exception to this may be granted if the off-label prescription of the drug or biologic is unrealistic or unsafe outside of a carefully controlled clinical study.
- **Costs Section:**
Must state how the costs of the study drug or biologic will be covered, including the costs of the administration of the drug if applicable.
- **Agreement to Participate Section:**
Must include information that subject will be given a copy of the "Research Participants Bill of Rights."

For additional guidance on preparing a consent form for review and approval by the UCLA IRB please refer to OHRPP Guidance on [Obtaining and Documenting Informed Consent](#) and copies of the [templates for the UCLA consent forms](#).

Control of Investigational Drugs and Biologics

What are the local dispensing policies and regulations?

Hospitals or other clinical settings have their own policies regarding the use of investigational drugs and biologics in order to assure patient safety and comply with JCAHO standards, California law, and California Department of Health Services regulations. Investigators conducting research in clinical settings other than those listed below should consult those local policies and the personnel charged with compliance with those policies. Consultation should take place before preparing the budget for the clinical study.

What are the UCLA dispensing policies and regulations?

- Please contact the UCLA Drug Information Center:

UCLA Drug Information Center
Investigational Drug Section
Ronald Reagan UCLA Medical Center
Department of Pharmaceutical Services
757 Westwood Plaza Room B524
Los Angeles, CA 90095
310-267-8522
Fax 310-267-3652

- The [UCLA Investigational Study Drug Application](#) must be completed to request Ronald Reagan UCLA Pharmaceutical Services participation in the Clinical Research Protocol

What are the investigator responsibilities for the control of investigational drugs or biologics?

Investigators conducting studies in which an investigational drug or biologic will be used must ensure adequate control of the drug or biologic. Adequate control and handling of investigational drug/biologic include all of the following. The investigator must:

- Ensure that the investigational drug or biologic is ***used only in accordance with the IRB-approved protocol.***
- Administer the investigational drug or biologic ***only to participants under the investigator's direct personal supervision*** or under the supervision of a sub-investigator directly responsible to the investigator.
- ***Not supply*** the investigational drug or biologic ***to any person not authorized to receive it.***
- ***Maintain adequate records*** of the disposition of the investigational drug or biologic, including dates of dispensing, quantity currently maintained for dispensing, and amount of the investigational product dispensed to participants.
- ***Return any unused supplies*** of the investigational drug or biologic to the study sponsor, or otherwise provide for disposition of the unused supplies as directed by the sponsor. If the investigation is terminated, suspended, discontinued, or completed.
- ***Take adequate precautions, to prevent theft*** or diversion of the substance into illegal channels of distribution if the investigational drug is subject to the Controlled Substances Act. These precautions include: storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure to which access is limited.

See [Sample Investigational Agent Accountability Record](#).

Reporting Requirements

What are the post-approval reporting requirements?

The UCLA IRB and the FDA require adverse events (AE) associated with the use of drugs under an IND be reported in a timely manner. When an IND is issued, there are additional and separate federal requirements for reporting adverse events to the FDA. The UCLA IRB also requires that the reporting of unanticipated problems, protocol violations and incidents and updated safety information.

- **When the study sponsor holds the IND,**
 - Investigators need to report *all* adverse events to the sponsor and the sponsor will submit appropriate reports to the FDA.
 - Investigators need to understand and comply with the similar but separate reporting requirements for the UCLA investigator as described in the [UCLA Summary Sheet of Post-Approval Reporting Requirements for Investigators](#).
 - Investigators need to determine if their department or unit has any additional reporting requirements, for example, Investigators in the JCCC have slightly different reporting requirements.
- **When the investigator holds the IND** for a specific study protocol (as in the case of investigator-initiated/investigator-sponsor INDs),
 - The investigator has responsibilities for reporting adverse events to the FDA.
 - Investigators need to understand and comply with the similar but separate reporting requirements for the UCLA investigator as described in the [UCLA Summary Sheet of Post-Approval Reporting Requirements for Investigators](#).
 - Investigators need to determine if their department or unit has any additional reporting requirements, for example, Investigators in the JCCC have slightly different reporting requirements.

Investigators should also review the OHRPP Guidance [Post-Approval Reporting Requirements for Investigators: Reporting of Unanticipated Problems, Including Adverse Events, Protocol Violations, Deviations and Incidents and the Reporting of Updated Study Safety Information](#) for a detailed description of the UCLA reporting requirements.

What are the obligations of the Investigator for reporting to the Sponsor?

Clinical investigators have reporting obligations to the study sponsor as described in the FDA regulations [21 CFR 312](#). Investigators need to report the following to the Sponsor:

- Drug disposition
- Case histories
- Progress reports
- Safety reports
- Final reports
- Financial disclosure report
- Specific record keeping and record retention

What are the obligations for the Sponsor and the Investigator-Sponsor for reporting to the FDA?

When an Investigator files an IND, the Investigator is considered the Sponsor and as such carries all of the FDA regulatory responsibilities and reporting obligations of both the Investigator and Sponsor as outlined below and described in the FDA regulations [21 CFR 312](#). Please refer to the regulations for complete information. Sponsor and Investigator-Sponsor reporting obligations to the FDA under an IND include:

- Protocol amendments
- Information amendments
- IND Safety Reports
- Annual Reports
- Withdrawal of an IND
- Specific record keeping and retention

References and Regulations

- [FDA Center for Drug Evaluation and Research](#)
 - [Information For Sponsor-Investigators Submitting INDs](#)
 - [Pre-IND Consultation Program](#)
 - [Physician Request for an IND Under Expanded Access Program](#)
 - [Forms](#)
- [FDA Guidance for Institutional Review Boards and Clinical Investigators: Drugs and Biologics](#)
- Applicable Regulations
 - [21 CFR 11: Electronic Records; Electronic Signatures](#)
 - [21 CFR 54: Financial Disclosure by Clinical Investigators](#)
 - [21 CFR 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General](#)
 - [21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals](#)
 - [21 CFR 312: Investigational New Drug Application](#)
 - [21 CFR 314: Applications for FDA Approval to Market a New Drug](#)
 - [21 CFR 320: Bioavailability and Bioequivalence Requirements](#)
 - [21 CFR 330: Over-The-Counter Human Drugs Which Are Generally Recognized As Safe And Effective And Not Misbranded](#)
 - [21 CFR 601: Biologics Licensing](#)

Change history:

6/9/2016: Clarified that investigators rather than the University are sponsors of Investigator-initiated INDs.