CHAPTER #3: IND and IDE Submissions

3.1 Regulatory requirements for clinical studies involving a drug, biologic or dietary supplement

FDA’s Center for Drug Evaluation and Research (CDER) is responsible for regulating manufacturing, testing and importation of pharmaceutical drugs in the US. This includes new drug approvals, abbreviated new drug approvals (generics), over-the-counter drugs, animal drugs and biologics.

A drug is defined as:

a. article intended for use in diagnosis, cure, mitigation, treatment, or prevention of the disease;

b. articles (other than food) intended to affect the structure or any function of the body;

c. articles intended to be used as components of any of the above.

Below is a brief summary of regulatory requirements for clinical research involving drugs, biologics or dietary supplements. For additional information

3.1.1 Preclinical Regulatory Requirements

Preclinical testing begins after a potential drug has been identified in the lab. Preclinical testing involves lab and animal studies that evaluate the drug’s toxic and pharmacologic effects. Preclinical studies are also subject to the FDA regulations known as Good Laboratory Practices (GLP), 21 CFR 58. The GLP regulations specify minimum standards in such areas as personnel, facilities, equipment and operations.

Preclinical testing includes pharmacokinetics, the study of how the drug moves through living organisms. Researchers examine absorption, distribution, metabolism and excretion (also abbreviated as ADME) to ensure that the drug reaches its intended target and passes through the body properly. In addition to the biological tests, researchers conduct chemistry tests to establish the drug’s purity, stability and shelf life. Manufacturing tests are conducted to determine the feasibility of producing the drug on a large scale and to explore dosing, packaging and formulation (e.g., pill, inhaler, injection).

At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from two weeks to three months, depending on the proposed duration of use of the substance in the proposed clinical studies.

3.1.2 Determine if your Study is Exempt from IND Requirements

Many academic investigators will want to conduct a clinical study with an already approved drug. This is often done to establish efficacy in a new disease indication. FDA provides provisions for conducting studies of lawfully marketed drugs through the use of an IND exemption. A clinical investigation of a drug is exempt from the IND requirements if all of the criteria for an exemption in 21CFR312.2(b) are met:

1. The investigational drug is lawfully marketed in the United States;
2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product;
3. The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product;
4. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The investigation will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50;
6. The investigation will be conducted in compliance with FDA regulations 21 CFR 312.7: Promotion and charging for investigational drugs.

Thorough documentation is required to support this exemption criterion and may include prior publications or other public disclosures. If such evidence cannot be provided, a physician should submit a research IND (limited in scope) to the FDA. The physician is now considered sponsor-investigator.


3.1.3 Investigational New Drug (IND) Application (21 CFR Part 312)

After preclinical testing is completed, a sponsor or sponsor-investigator (see below) files an IND with FDA prior to beginning any human testing. An IND is a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any unapproved drug.

The application must show results of preclinical experiments; the chemical structure of the compound; how it is thought to work in the body; any side effects found in animal studies; and how the compound is manufactured (chemistry, manufacturing and controls section). The IND must also include a detailed clinical trial plan, including how, where and by whom the studies will be conducted.

Based on the information of the IND application, the FDA will determine if there is sufficient evidence to support initial human testing. The sponsor must wait 30 days after submitting the IND to the FDA for review. At the end of the 30 day review period, unless the FDA identifies a potential safety problem involving the use of the drug and asks for a delay, the sponsor may begin the proposed clinical testing.
The FDA requires that the IND submissions comply with Portable Document Specifications as outlined in the FDA's Guidance from September 2014.

### 3.1.4 Expanded Access to Investigational Drugs

The terms “expanded access,” “compassionate use,” “treatment use,” and “treatment IND” are used interchangeably to refer to use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition. *Investigational* drugs are new drugs that have not yet been approved by the FDA or approved drugs that have not yet been approved for a new use, and are in the process of being tested for safety and effectiveness.

The distinction between administering an investigational drug in the setting of a ‘traditional’ clinical trial versus expanded access lies in the intention. In a traditional clinical trial the intention is to understand the safety and effectiveness of the investigational drug; in expanded access the intention is treatment.

There are four general guidelines for a drug to be considered for expanded access use:

1. Patients with a serious or immediately life-threatening disease or condition, where there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
2. No comparable or satisfactory alternative therapy exists.
3. The potential patient benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated.
4. The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

There are two broad categories of expanded access: individual patient and groups of patients. Within each broad category there are unique types of expanded access programs available.

**Helpful Resources:**


For detailed description of how a single-patient IND is executed at UC Davis, see UC Davis Policy and Procedure P&P 1.509.

3.1.5 New Drug Application (NDA)

After clinical trials have been completed demonstrating safety and effectiveness, the study sponsor (or drug manufacturer) will submit a New Drug Application (NDA) to the FDA for a license to market the drug for a specified indication in accordance with 21 CFR 314. NDAs contain all of the information about all of the studies, including preclinical testing, all clinical trials, dosing information, manufacturing details and proposed labeling for the new medicine. Most academic drug development efforts do not progress to this stage.

At NDA submission stage, FDA scientists review all the results from all the studies carried out over the years and determine if they show that the medicine is safe and effective enough to be approved. During this review, the FDA determines what the labeling should be and whether the sponsor can manufacture it properly and consistently. Once the drug is approved, it becomes available for physicians to prescribe for the indication approved by the FDA. The review process takes approximately 18 months.

3.1.6 Is an IND required for studies with dietary supplements?

Many clinical studies of academic investigators evaluate the effect of dietary supplements on the disease or physiological parameters. Some of these studies may require an IND submission. If the dietary supplements are investigated for diagnosis, cure, mitigation, treatment, or prevention of disease and are used to affect the structure or function of the body, then the dietary supplement will be considered a drug for the purposes of this study.

The study will be the subject to the same regulations as any other unapproved drug. Specifically, the FDA will be paying particular attention to the composition of the dietary supplement, its origin and manufacturing processes. When preparing the INDs for dietary supplements, make sure that the supplement manufacturer is willing to provide this information.

FDA Guidance: Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can be Conducted without an IND;

3.2 Regulatory requirements for clinical studies with devices

FDA’s Center for Devices and Radiological Health (CDRH) is responsible for regulating manufacturing and importation of medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

If a product is labeled, promoted or used in a manner that meets the definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act, it will be regulated as a medical device. A device is: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,

or

intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. In cases where it is not clear whether a product is a medical device the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) can assist in making a determination.

3.2.1 Device Classification

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes (Class I, Class II and Class III) based on the level of control necessary to assure the safety and effectiveness of the device. The device classification defines the regulatory requirements for an approval of a new device. Regulatory control increases from Class I to Class II to Class III.

Device classification depends on the intended use of the device and also upon indications for use. In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Examples:

**Class I devices:** elastic bandages, examination gloves, and hand-held surgical instruments.

**Class II devices:** powered wheelchairs, infusion pumps, and surgical drapes.

**Class III devices:** implantable pacemaker pulse generators and coronary stents.

To find the classification of your device, as well as whether any exemptions may exist, you need to find the regulation number that is the classification regulation for your device. One of the ways to accomplish this is to go directly to the classification database and search for a part of the device name (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf)
Once you have identified the correct classification regulation go to the device panel (medical specialty) to which the device belongs.

The search will provide you with the Device Classification and the appropriate CFR regulation. If the device is not classified, you can research similar devices on the FDA website (PMA and 510(k) databases) or use pre-IDE consultation for the FDA determination.


### 3.2.2 Significant Risk vs Non-significant Risk

Devices used on human subjects to conduct investigations of safety and effectiveness are considered “Investigational Devices” (Section 520(g) of FDCA).

**Significant Risk (SR) device** presents a potential for **serious risk of health, safety and welfare of a subject**, and:

- Intended to be used as an implant and;
- Purported to support or sustain human life;
- Is used for substantial importance in diagnosing, curing, mitigating or treating disease
Examples of SR devices include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Conversely, non-significant risk (NSR) device studies do not pose a significant risk to patients. Non-significant risk should not be confused with “minimal risk,” a term used by the FDA to classify studies. Examples of NSR devices include most day-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters.

SR devices must meet all regulatory requirements set in 21 CFR 812, including the requirement for approval by both IRB and the FDA before commencing the study. Significant risk devices require submission of an investigational device exemption (IDE) to CDRH (see below).

NSR device studies may commence without FDA approval, based solely on the IRB approval. However, the sponsor-investigator must follow abbreviated IDE requirements, which are, in essence, the same requirements as regular IDE only without FDA submission (21 CFR 812.2 (b)). The IRB acts as a surrogate overseer for the FDA.


3.2.3 Investigational Device Exemption (IDE) (21 CFR Part 812)

An investigational device exemption (IDE) is a regulatory submission to the CDRH. If approved, it allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.

IDE requirements:

- Study approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- informed consent from all patients obtained and documented;
- the device is labeled “CAUTION: Investigational Device. Limited to investigational use only;”
- Sponsor-investigator complies with monitoring requirements;
- Records and reports are maintained;
- Investigator cannot promote or commercialize (charge for) the device.


You can also follow the FDA Guidance: Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf
Two important elements of the guidance are:

- FDA is approval of an early feasibility study, including some first-in-human studies, may be based on less nonclinical data than would be expected for other types of studies (e.g., traditional feasibility or pivotal).

- The introduction of new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study, while still maintaining compliance with FDA human subject protection requirements, including obtaining informed consent and Institutional Review Board (IRB) (or ethics committee) oversight.

An IDE paper copy of the signed cover letter and the complete paper submission should be accompanied by the electronic eCopy of the submission. An electronic copy (eCopy) is defined as an exact duplicate of the paper submission, created and submitted on a compact disc (CD), digital video disc (DVD), or a flash drive.

Compassionate use IDE submissions and Emergency use IDE submissions are exempt for eCopy requirements.

For more details, see the FDA Guidance: eCopy Program for Medical Device Submissions.

### 3.2.4 Abbreviated IDE

Studies of non-significant risk devices are subject to abbreviated IDE requirements. An IDE submission to the FDA is not required under the abbreviated requirements, but the requirements for labeling, informed consent, monitoring, records and reports, and promotional practices contained in FDA regulations still apply (21 CFR 812.2(b)). In addition, the concept of “non-significant risk” to determine whether abbreviated IDE procedures are appropriate should not be confused with “minimal risk” to determine whether expedited IRB review is appropriate. For a device study to be eligible for expedited IRB review, it must be a non-significant risk device AND present no more than minimal risk to the subject (ref. 21 CFR 56.110).

**Requirements under abbreviated IDE (see Appendix 2 for more details):**

- The device is not a banned device;
- The sponsor will label the device in accordance with 21 CFR 812.5;
- The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
- The sponsor will ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care consent under 21 CFR 50 and documents it, unless documentation is waived;
- The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
3.2.5 IDE Exemptions

Some studies may be exempt from the IDE regulations. The exemption criteria is explained in 21 CFR 812.2[c], and briefly summarized below:

1. a legally marketed device when used in accordance with its labeling,
2. a diagnostic device if it is:
   - noninvasive;
   - does not require an invasive sampling procedure that presents significant risk;
   - does not by design or intention introduce energy into a subject;
   - and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;
3. consumer preference testing...of legally marketed device(s)
4. a device intended solely for veterinary use;
5. a device shipped solely for research with laboratory animals

A local IRB provides the determination of the Exemptions upon reviewing the study and applying the criteria listed above.

3.2.6 Emergency Use of an Unapproved Device

If this situation is encountered, act in accordance with UCDMC P&P 1509. “Emergency Treatment of an Investigational Drug, Device or Biologic (FDA Regulated Products) in a Life Threatening Situation.”

An unapproved medical device is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval (510(k)) or an approved IDE. Emergency use is permitted if the treating physician determines that:

- The patient has life-threatening condition that needs immediate treatment
- No generally acceptable alternative treatments exist
- Because of an immediate need there is no time to use existing procedures for CDRH approval

Next, the treating physician needs to undertake the following protective measures:
• An independent assessment by an uninvolved physician
• Informed consent from the patient or legal representative
• Approval of the IRB Chair
• Approval from the IDE sponsor, if any
• Prior FDA approval for shipment or emergency use of the investigational device is not required, but the use should be reported to the FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use

Note that if a physician, who is faced with an emergency situation contacts the FDA to discuss his/her patient's condition, the FDA will only act in an advisory role, rather than in an approving role. The responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician.


3.2.7 Compassionate Use of Investigational Devices

This is NOT an emergency use. Compassionate use request to utilize an investigational device in the mitigation, diagnosis and treatment of a serious disease requires an IDE Supplement. The sponsor or investigator has to submit the protocol for use of the device in a single patient or a group of patients. In order to permit this use, CDRH will review the following information:

• No comparable alternative treatment exists
• Sufficient evidence of safety
• Clinical use will not interfere with ongoing clinical investigations

3.2.8 Treatment Use

This is NOT an emergency use. A request for Treatment Use of an investigational device in the mitigation, diagnosis and treatment of a serious disease requires a Treatment IDE Submission. If approved, Treatment IDE enables a wider group of patients to receive the investigational device for the same indication as it is being studied under the sponsor IDE. Treatment IDE will remain open even after the sponsor trial has been completed. The following provision have to be met:

• Device is investigated in a controlled clinical trial under IDE for the same use
• Sponsor is actively pursuing market approval
• No comparable alternative treatment exists
• Clinical use will not interfere with ongoing clinical investigations
• Sufficient evidence of safety and effectiveness

3.2.9 Humanitarian Use

HUD (Humanitarian Use Device) designation requests are the first step in seeking marketing approval of a HUD. The second step is a submission of a Humanitarian Device Exemption (HDE) application to the Center for Devices and Radiological Health (CDRH) or to the Center for Biologics Evaluation and Research (CBER).

HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a
disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.” [21 CFR 814.39(n)]. The request for HUD designation is described in the FDA Guidance “Designating Humanitarian Use Devices” [http://www.fda.gov/ForIndustry/ DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/ LegislationRelatingtoHUDsHDEs/ucm283517.htm].

If the request is granted, the investigator proceeds with the submission of HDE. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

3.2.10. PMA vs 510(k)

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, FDA needs to see sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). The content of PMA is similar to the NDA for new drugs, and contains manufacturing sections, pre-clinical laboratory studies and clinical investigations.

Some devices (from Class I or Class II) may be able to be approved under a different pathway colloquially called 510(k). The name refers to requirements outlined in section 510(k) of Food, Drug and Cosmetics Act. If the device is considered substantially equivalent to one or more similarly marketed devices (known as “predicate” devices), a claim of substantial equivalence can be made. A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design and other parameters.

3.3 Investigators, Sponsors, and Sponsor-Investigators

Investigator means 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. “Sub-investigator” includes any other individual member of that team [21 CFR 321.3].

Sponsor means a person who takes responsibility for and initiates a clinical investigation [21 CFR 312.3]. 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.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed [21 CFR 312.3]. The term does not include any person other than an individual. If an academic investigator submits an IND or IDE and is the principal investigator, the investigator is the Sponsor-Investigator and he/she is responsible for regulatory compliance.
Academic investigators sometimes equate the term “Sponsor” with the source of the study funding. In fact, there are two types of sponsors: regulatory sponsor and financial sponsor. The regulatory sponsor is the person/entity who initiates and takes responsibility for a clinical investigation. The regulatory sponsor submits the IND or IDE and is responsible for communications with the FDA. The regulatory sponsor may be a pharmaceutical company, a private or academic organization, or an individual.

A financial sponsor may be a company, a department, a non-profit or a government agency. If a pharmaceutical (or device) company is supplying a drug (or device) for an academic study, but will not be submitting the IND or IDE, the company is not the regulatory sponsor. For commercial INDs, the financial and regulatory sponsors are usually the same (i.e. the pharmaceutical or device company).

Helpful delineation of the ownership of the study processes (adapted from the UCOP Office of General Counsel)

<table>
<thead>
<tr>
<th>Issue</th>
<th>Sponsor-initiated study</th>
<th>Investigator-initiated study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Author</td>
<td>Sponsor</td>
<td>Investigator</td>
</tr>
<tr>
<td>Holds IND/IDE</td>
<td>Sponsor</td>
<td>Investigator (or University)</td>
</tr>
<tr>
<td>Injuries and indemnifications</td>
<td>Sponsor pays (except when caused by the institution or PI non-compliance, negligence or misconduct)</td>
<td>Institution pays (except for product defects)</td>
</tr>
<tr>
<td>Data</td>
<td>Sponsor owns CRFs and reports provided by sponsor; UC owns medical records and other data</td>
<td>UC owns protocol, documents, research results, data</td>
</tr>
<tr>
<td>IP</td>
<td>Sponsor owns patentable inventions conceived and reduced to practice; UC owns everything else</td>
<td>UC owns all inventions and IP</td>
</tr>
<tr>
<td>Funding</td>
<td>Sponsor</td>
<td>Grants, Institution, Department</td>
</tr>
</tbody>
</table>

3.4 Sponsor-Investigator Responsibilities

Sponsor-Investigator responsibilities under an IND or IDE are covered in 21 CFR Part 312 (for drugs) and 21 CFR Part 812 (for devices). Also see FDA Guidance “Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects” (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf), and ICH E6 (GCP)–Section 4 (http://ichgcp.net/4-investigator).
Below is a brief summary of the responsibilities and available resources for Sponsor-Investigators under an IND:

**21CFR part 50 details sponsor obligations.** Sponsors are responsible for:

- Selecting qualified investigators,
- Providing them with the information they need to conduct an investigation properly,
- Ensuring proper monitoring of the investigation(s),
- Ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND,
- Maintaining an effective IND with respect to the investigations,
- And ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects of risks with respect to the drug.

Additional specific responsibilities of sponsors are described elsewhere in this part

§312.53 Selecting investigators and monitors
§312.54 Emergency Research under 50.24 of this chapter
§312.55 Informing Investigators
§312.56 Review of ongoing investigations
§312.57 Recordkeeping and record retention
§312.58 Inspection of sponsor’s records and reports
§312.59 Disposition of unused supply of investigational drug

**21CFR part 64 details investigator obligations.** Investigators are responsible for:

- Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations,
- For protecting the rights, safety, and welfare of subjects under the investigator’s care;
- And for the control of drugs under investigation.
- An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter.

Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

§312.61 Control of the investigational drug
§312.62 Investigator recordkeeping and record retention
§312.64 Investigator reports
§312.66 Assurance of IRB review
§312.68 Inspection of investigator’s records and reports
§312.69 Handling of controlled substances
§312.70 Disqualification of a clinical investigator.

A helpful checklist of the FDA regulations along with corresponding onsite documents can be found in 11.4 Maintain Study Documentation of this Guidebook.
3.5 Create a Monitoring Plan

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirement(s).

Typically, academic sites are familiar with monitors assigned by a sponsor or a contract research organization (CRO). However, GCP requires that investigator-initiated trials enrolling human subjects also provide a monitoring plan to assure that the data collected throughout the study are accurate. In addition, the Code of Federal Regulations requires monitoring under 21CFR 312 subpart D (for INDs) and 21CFR 812 subpart C (for IDEs). Sponsors (including Sponsor-Investigators) of clinical investigations conducted under an IND or IDE are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to FDA. This oversight is maintained through the regular review of the source data, case report forms, informed consents, regulatory documents, and any other essential documents by a monitor.

During a monitoring visit, a monitor reviews individual subject records and source documents, regulatory binder(s), and other essential documents and compares the information with data recorded on the case report forms (CRF) or entered in the electronic case report form (eCRF). The monitor is obligated to ensure the following:

- Subjects meet eligibility requirements
- The rights and safety of human subjects are protected
- Informed consent has been obtained and documented appropriately
- Conduct of trial is in compliance with protocol, good clinical practice (GCP), and applicable regulatory requirements.
- Subject was followed and treated according to the protocol
- Reported trial data are accurate, complete, and 100% verifiable from source documents. All pertinent information in the subject records must be accurately recorded on the CRF.
- The CRF is complete, legible, and consistent throughout visits.

For further information on what is involved in monitoring, see Clinical Trials Website: http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html

3.6 Create a DSMB/C if Required

This section discusses the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) (also known as Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs)) that may carry out important aspects of clinical trial monitoring.

A clinical trial Data Monitoring Committee is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the investigator regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

DMCs have the practical position of seeing data and safety information in more frequent intervals and with typically more statistical expertise to make enhanced assessments about a study’s progress and determine the study’s future.
What do they do?

DMC/Bs perform the following general functions:

- Objectively appraise a study’s progress
- Assess data quality via a formal and planned process
- Provide analytical expertise and rigor
- Determine the statistical significance of efficacy and/or risk-benefit ratio
- Serve as “Another set of eyes.”

In accordance with its analytic and ethical responsibilities, a DMC is tasked to determine whether a study can proceed with enrollment, as designed. It has the authority to halt a study, suspending enrollment, pending crucial changes to the protocol’s design, recruitment strategy, risk minimization, or other modification. It can also terminate a study due to statistically significant efficacy or increased risk of harm to participants.

When are they needed?

A fundamental reason to establish a DMC/B is to enhance the safety of trial participants in situations, in which safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. All clinical trials require safety monitoring, but not all trials require monitoring by a formal DSMC/B.

DMC/Bs are established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DMC/Bs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity.

Formal data and safety monitoring is also necessary to assure confidence in a study’s interim and final outcomes:

- To verify or validate efficacy and/or safety information significant to a novel therapy;
- To gauge data quality to confirm the research question/hypothesis in developing treatments;
- To assess efficacy and safety when “lives and wellbeing depend on valid results.”

The FDA recommends that sponsors consider using a DMC/B when:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-center.
In studies with one or more of these characteristics, the additional oversight provided by a DMC/B can further protect study participants. In other studies, such as short-term studies for relief of symptoms as noted above, such committees are generally not warranted.

[FDA Guidance: The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors - Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm]

**DMC/B Charters**

DMC/Bs typically operate under a written charter that includes well-defined standard operating procedures. Such charters are important for the same reason that study protocols and analytical plans are important—they document that procedures were pre-specified and thereby reduce concerns that operations inappropriately influenced by interim data could bias the trial results and interpretation. The sponsor may draft this charter and present it to the DMC/B for agreement, or the DMC/B may draft the charter with subsequent concurrence by the sponsor. Topics to be addressed would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC/B meetings, procedures for assessing conflict of interest of potential DMC/B members, the method and timing of providing interim reports to the DMC/B, and other issues relevant to committee operations. FDA may request that the sponsor submit the charter to FDA well in advance of the performance of any interim analyses, ideally before the initiation of the trial (see 21 CFR 312.23(a)(6)(iii)(g); 21 CFR 312.41(a); 21 CFR 812.150(b)(10)). In such cases, FDA would usually consider the charter when FDA reviews the study protocol.

**3.7 Assistance for IND/IDE Preparation**


**3.8 Post Information on clinicaltrials.gov**

Clinicaltrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Title VIII of FDAAA, Public Law 110-85, amended the PHS Act by adding new section 402(j), 42 U.S.C. § 282(j). The new provisions require that additional information be submitted to clinicaltrials.gov established by the National Institutes of Health (NIH)/National Library of Medicine (NLM). This includes expanded information on clinical trials and information regarding the results of clinical trials.

At UC Davis clinicaltrials.gov registration requirement applies to:

- Any study initiated by a UC Davis investigator under IND/IDE would have to be registered and results uploaded in the timely manner. The Sponsor-Investigator submits a certification (FDA Form 3674) attesting that the data will be submitted as available. Single patient, emergency use INDs do not fall under the referenced section, and therefore are not required to submit certification.
- Any study not conducted under IND/IDE but involving drug or device
• Studies that intend to publish in scientific peer-reviewed journals need to be registered and results entered into ct.gov. Investigators intending to publish clinical studies results in an ICMJE journal (International Committee of Medical Journal Editors) must register before enrollment of first patient. The ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. In June 2007 the ICMJE adopted the WHO’s definition of clinical trial: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

Non-compliance with clinicaltrials.gov registration may result in fines up to $10,000/day.

In 2013, the Centers for Medicare and Medicaid Services (CMS) issued a Transmittal requiring new mandatory reporting of the clinicaltrials.gov clinical trial number (also known as NCT#) on all hospital and professional claims for related items/services. Effective January 1, 2015, it will be mandatory to report the clinical trial number on claims for items/services provided in all clinical trials that are qualified for coverage. In order for the NCT# to correctly appear on the claims, the study teams need to type the number in the corresponding field of the BRIDGE.

As of August 2013, Clinicaltrials.gov (NCT#) must be added in the BRIDGE for all studies.

For UC Davis-specific instructions on how to register a trial on clinicaltrials.gov, please reference http://www.ucdmc.ucdavis.edu/clinicaltrials/ClinicalTrialsGov/clinicaltrialsgov.html

Other Relevant Links

NIH Guidance on ClinicalTrials.gov Registration Requirements
ClinicalTrials.gov Protocol Registration System
http://prsinfo.clinicaltrials.gov/