FDA BASICS

INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs)

1. RESEARCH STUDIES THAT REQUIRE AN IND

In general, the IND regulations in part 312 require that human research studies be conducted under an IND if all of the following conditions exist:

• The research involves a drug as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1)).

• The research is a clinical investigation as defined in the IND regulations (21 CFR 312.3).

• The clinical investigation is not otherwise exempt from the IND requirements in part 312 (see section IV of this guidance).

https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf
[pp2-3]

2. IS AN IND NEEDED FOR RESEARCH USING MARKETED DRUGS?

Whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

• The drug product is lawfully marketed in the United States.

• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

• In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

• The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

• The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product)

https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf [pp 4-5]

For FDA guidance, here is FDA contact info:

For products regulated by CDER, an inquiry concerning the application of the IND regulations should be directed to the Chief, Project Management Staff, in the appropriate CDER review division. For products regulated by CBER, the inquiry should be directed to the applications division of the appropriate review Office.

• Organizational charts listing the CDER review divisions and their telephone numbers are available on the Internet at http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm.

• Organizational charts listing the CBER review divisions and their telephone numbers are available on the Internet at http://www.fda.gov/AboutFDA/CentersOffices/ OrganizationCharts/ucm135943.htm.

• If the relevant review division is not known, we recommend the sponsor contact CDER's Division of Drug Information (druginfo@fda.hhs.gov) or CBER's Division of Manufacturer's Assistance and Training (matt@cber.fda.gov), Office of Communication, Outreach and Development.

Office of Communications, Division of Drug Information, Food and Drug Administration Phone: 301-796-3400; Fax: 301-847-8714 druginfo@fda.hhs.gov

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and/or

Office of Communication, Outreach and Development, HFM-40 Center for Biologics Evaluation and Research Food and Drug Administration Phone: 800-835-4709 or 301-827-1800 http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Outreach and Information Center Center for Food Safety and Applied Nutrition Food and Drug Administration Phone: 888-723-3366 http://www.fda.gov/Food/GuidanceRegulation/default.htm

INVESTIGATIONAL DEVICE EXEMPTIONS (IDEs)

1. RESEARCH USING A MEDICAL DEVICE

All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

- an investigational plan 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;
- labeling stating that the device is for investigational use only;
- monitoring of the study and;
- required records and reports.

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

2. WHAT ARE THE APPLICABLE REGULATIONS?

The primary regulations that govern the conduct of clinical studies are included in the Code of Federal Regulations, Title 21 (21 CFR):

- 21 CFR 812, *Investigational Device Exemptions*, covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.
- 21 CFR 50, *Protection of Human Subjects*, provides the requirements and general elements of informed consent;
- 21 CFR 56, *Institutional Review Boards*, covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols;
- 21 CFR 54, *Financial Disclosure by Clinical Investigators*, covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.
- 21 CFR 820 Subpart C, *Design Controls of the Quality System Regulation*, provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.

3. SIGNIFICANT RISK vs. NONSIGNIFICANT RISK DEVICES

Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending upon the level of risk. The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations.

Studies of devices that pose a **significant risk** require both FDA and an Institutional Review Board (IRB) approval prior to initiation of a clinical study. FDA approval is obtained by submitting an IDE application to FDA (§812.20).

A **nonsignificant risk** device study requires only IRB approval prior to initiation of a clinical study. Sponsors of studies involving nonsignificant risk devices are not required to submit an IDE application to the FDA for approval. Submissions for nonsignificant device investigations are made directly to the IRB of each participating institution. Sponsors should present to the reviewing IRB an

explanation why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days [§812.150(b)(9)]. The FDA considers an investigation of a nonsignificant risk device to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study.

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm

4. EXEMPT IDE INVESTIGATIONS

All clinical investigations of devices must have an approved IDE or be exempt from the IDE regulations. Investigations that are exempted from 21 CFR 812 are described in §812.2(c) of the IDE regulations. Studies exempt from the IDE regulations include:

1. a legally marketed device when used in accordance with its labeling
2. a diagnostic device if it complies with the labeling requirements in §809.10(c) and if the testing:
    a. is noninvasive;
    b. does not require an invasive sampling procedure that presents significant risk;
    c. does not by design or intention introduce energy into a subject; and
    d. is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;
3. consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved PMA, cleared Premarket Notification 510(k), or are exempt from 510(k)] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
4. a device intended solely for veterinary use;
5. a device shipped solely for research with laboratory animals and contains the labeling "CAUTION – Device for investigational use in laboratory animals or other tests that do not involve human subjects."

Additional guidance for **an in vitro diagnostic device** studies can be found in "Regulating In Vitro Diagnostic Device (IVD) Studies

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm

5. EARLY FEASIBILITY STUDIES OF DEVICES

An early feasibility study (EFS) is a limited clinical investigation of a device early in development. It typically:

- enrolls a small number of subjects;
- is used to evaluate the device design concept with respect to initial clinical safety and device functionality; and
- may guide device modifications.

CDRH's EFS Program facilitates the conduct of early feasibility studies in the United States to increase access for patients to potentially beneficial technologies and to support device innovation. EFS concepts are described in the FDA guidance document, "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical studies, Including Certain First in Human (FIH) Studies".

For Pre-submission guidance from the FDA on Devices:

Please refer to the final guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff."

DATA AND SAFETY MONITORING

WHAT ARE THE FDA AND NIH REQUIREMENTS FOR DATA AND SAFETY MONITORING?

FDA: Sponsors of studies evaluating new drugs, biologics, and devices are required to monitor these studies (see 21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 21 CFR 812.46 for devices).

Government agencies that sponsor clinical research, such as the NIH and the VA, have required the use of Data Safety Monitoring Committees ("DMCs") in certain trials. Current FDA regulations, however, impose no requirements for the use of DMCs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted.

All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors, and investigators. DMCs have generally been established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome Contains Nonbinding Recommendations 4 such as a cardiovascular event or recurrence of cancer. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but a DMC is not required or recommended for most clinical studies. DMCs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes.

https://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf

FDA Guidance on Establishment and Operation of Clinical Trial Data Monitoring Committees

https://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

NATIONAL INSTITUTES OF HEALTH

NIH Policy

For all interventional trials, the NIH requires documentation of an IRB-approved data and safety monitoring plan (DSM Plan). NIH further requires, as part of the DSMP, the appointment of a Data and Safety Monitoring Board (DSMB) for all clinical trials that involve:

- investigation of a research question having direct implications for clinical care and/or public health (including all Phase III trials), and/or
- a high-risk intervention, and/or
- a highly vulnerable patient population.

https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-data-and-safety-monitoring-extramural-clinical-studies

The National Institutes of Health (NIH) strongly recommends data and safety monitoring in the form of a DSMB for all Phase III clinical trials. For Phase I and Phase II clinical trials, a DSMB may be established if the principal investigator, their institution, or the clinical trial sponsor deems it necessary. For example, a Phase I or II clinical trial that has multiple clinical sites, is blinded (masked), is studying a particularly high-risk intervention(s), is involving a vulnerable population(s), or has a high probability of early termination for safety or efficacy, should consider establishing a DSMB.

NIH Policies and Guidance for Data Safety Monitoring can be found at:

https://humansubjects.nih.gov/data_safety

NIH Guidance for Data Safety Monitoring:

https://grants.nih.gov/grants/guide/notice-files/not98-084.html

NIH GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS:

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIH Guidelines for establishing and Operating Data and Safety Monitoring

https://www.niaaa.nih.gov/research/guidelines-and-resources/guidelines-establishing-and-operating-data-and-safety-monitoring