Introduction

IDE Overview

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)'s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. 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 IDE 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 for investigational use only
- monitoring of the study and;
- required records and reports.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution. Sponsors need not submit a PMA or Premarket Notification 510(k), register their establishment, or list the device while the device is under investigation. Sponsors of IDE's are also exempt from the Quality System (QS) Regulation except for the requirements for design control.

Good Clinical Practices (GCP)

Good Clinical Practices (GCP) refers to the regulations and requirements that must be complied with while conducting a clinical study. These regulations that apply to the manufacturers, sponsors, clinical investigators, institutional review boards, and the medical device. 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.

Each of these regulations is discussed in detail throughout this section.

Definitions and Acronyms

Some of the pertinent definitions used in the IDE regulation are as follows.

Application Integrity Policy (AIP)

Application Integrity Policy (AIP) is FDA's policy for the integrity of data or information submitted in an application. If it is suspected that an applicant has submitted false or misleading information, the data are thoroughly investigated. Submitting false or misleading information may result in FDA refusal to review submissions until certain requirements are met.

Implant

Implant is a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

Institutional Review Board (IRB)

Institutional Review Board (IRB) is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB should be established, operated, and function in conformance with 21 CFR 56. The term has the same meaning as "institutional review committee" in section 520(g) of the FD&C Act.

Investigation

Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

Investigational device

Investigational device is a device, including a transitional device, that is the object of an investigation.

Investigational device exemptions (IDE)

IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor’s study application and all the requirements under 21 CFR 812 are met.

Investigator

Investigator is an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.

Monitor

When used as a noun, monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor, or a consultant to the sponsor, or an employee of or consultant to a contract research organization. When used as a verb "monitor" means to oversee an investigation.

Premarket Approval (PMA)

A premarket approval means any premarket approval application for a Class III medical device, including all information submitted with or incorporated by reference therein. (21 CFR 814.3)

Premarket Notification [PMN or 510(k)]

510(k) refers to the type of submission to FDA described under 21 CFR 807 Subpart E in which the applicant must establish that their device is substantially equivalent to a legally marketed device. This type of submission is used for most Class II devices and some Class I devices.

Significant risk device (SR device)

Significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.

Sponsor

Sponsor is a person or other entity that initiates but does not actually conduct the investigation. An entity other than an individual (e.g., a corporation or an agency) which uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor, not a sponsor-investigator, and the employees are considered to be investigators. The sponsor of an IDE must be located in the United States (see 21 CFR 812.18).

Sponsor-investigator

Sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

Subject

Subject is a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or who participates as a control. A subject may be in normal health or may have a medical condition or disease.

Transitional device

Transitional device is a device subject to section 520(l) of the FD&C Act and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

Unanticipated adverse device effect

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

References

21 CFR 812.1
21 CFR 812.3

Regulating In Vitro Diagnostic Device (IVD) Studies

http://www.fda.gov/cdrh/comp/ivdreg.html
http://www.fda.gov/cdrh/comp/ivdreg.pdf

Early Collaboration Meetings Under the FDA Modernization Act (FDAMA), guidance for Industry and CDRH Staff

http://www.fda.gov/cdrh/ode/guidance/310.pdf
http://www.fda.gov/cdrh/ode/guidance/310.html

Last updated date7/8/2003

Approval Process

Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending on 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.

Significant Risk Device

A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Guidance on distinguishing between significant risk and nonsignificant risks studies are outlined in the document http://www.fda.gov/oc/ohrt/irbs/devices.html

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).

In order to conduct a significant risk device study, a sponsor must:

- submit a complete IDE application (§812.20) to FDA for review and obtain FDA approval of the IDE;

submit the investigational plan and report of prior investigations (§812.25 and §812.27) to the IRB at each institution where the investigation is to be conducted for review and approval; and

- select qualified investigators, provide them with all necessary information on the investigational plan and report of prior investigations, and obtain signed investigator agreements from them.

Upon receipt of an IDE application, sponsors are notified in writing of the date that FDA received the original application and the IDE number assigned (Receipt of supplements and amendments are not acknowledged). An IDE application is considered approved 30 days after it has been received by FDA, unless FDA otherwise informs the sponsor prior to 30 calendar days from the date of receipt, that the IDE is approved, approved with conditions, or disapproved. In cases of disapproval, a sponsor has the opportunity to respond to the deficiencies and/or to request a regulatory hearing under 21 CFR Part 16.

Once an IDE application is approved, the following requirements must be met in order to conduct the investigation in compliance with the IDE regulation:

- Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

- Distribution - Investigational devices can only be distributed to qualified investigators §812.43(b).

- Informed Consent - Each subject must be provided with and sign an informed consent form before being enrolled in the study. 21 CFR 50, Protection of Human Subjects, contains the requirements for obtaining informed consent.

- Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols under §812.46 (see "Guideline for the Monitoring of Clinical Investigations").

- Prohibitions - Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited (§812.7).

- Records and Reports - Sponsors and investigators are required to maintain specified records and make reports to investigators, IRBs, and FDA (§812.140 and §812.150).

Nonsignificant Risk Device

Nonsignificant risk devices are devices that do not pose a significant risk to the human subjects. Examples include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters.

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 FDA for approval. Submissions for nonsignificant device investigations are made directly to the IRB of each participating institution. Sponsors should present an explanation to the IRB where the study will occur of 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 FDA within five working days [§812.150(b)(9)]. FDA considers an investigation of a nonsignificant risk device to have an approved IDE when IRB concurs with the nonsignificant risk determination and approves the study.

The sponsor also must comply with the abbreviated IDE requirements under §812.2 (b):

- Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.";

- IRB Approval – The sponsor must obtain and maintain Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study;

- Informed Consent – The sponsor must assure that investigators obtain and document informed consent from each subject according to 21 CFR 50, Protection of Human Subjects, unless documentation is waived by an IRB in accordance with §56.109(c);

- Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46). Guidance on monitoring investigations can be found in "Guideline for the Monitoring of Clinical Investigations";

- Records and Reports - Sponsors are required to maintain specific records and make certain reports as required by the IDE regulation.

- Investigator Records and Reports – The sponsor must assure that participating investigators maintain records and make reports as required (see Responsibilities of Investigators); and

- Prohibitions –Commercialization, promotion, test marketing, misrepresentation of an investigational device, and prolongation of the study are prohibited (§812.7).

IDE Exempt Investigations

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

    Additional guidance for an in vitro diagnostic device studies can be found in "Regulating In Vitro Diagnostic Device (IVD) Studies." http://www.fda.gov/cdrh/comp/ivdreg.html

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."

Depending upon the nature of the investigation, those studies which are exempt from the requirements of the IDE regulation may or may not be exempt from the requirements for IRB review and approval under Part 56 and the requirements for obtaining informed consent under Part 50. For guidance regarding the applicability of these regulations with respect to investigations being conducted under the provisions of §812.2(c), contact the reviewing IRB and/or the IDE Staff at (301) 594-1190.

Who Must Apply for an IDE

The sponsor of the clinical trial is responsible for submitting the IDE application to FDA (§812.40) and obtaining Institutional Review Board (IRB) approval before the study can begin. Foreign companies wanting to conduct a clinical study in the U.S. MUST have a U.S. sponsor (§812.18). Under certain circumstances, the clinical investigator may wish to submit an IDE and would, therefore, also act as the sponsor of the study.

When to Apply

Study approval must be obtained PRIOR to enrolling patients at the study site. Each site must have approval from the reviewing IRB for that site prior to beginning the study. For significant risk device studies, in addition to IRB approvals, the sponsor must also have an approved IDE from FDA prior to beginning the study at any site. The review of applications to FDA and to the IRBs are independent and, therefore, may be submitted simultaneously.

Pre-IDE Process

Sponsors are encouraged to contact FDA to obtain further guidance prior to the submission of an IDE application. This will be especially beneficial to new sponsors who have not previously had contact with the agency and for sponsors proposing to study new technologies or new uses for existing technologies. Early interaction with the agency should help to increase the sponsor's understanding of FDA requirements, regulations, and guidance documents, and will allow FDA personnel to familiarize themselves with the new technologies. Increased interaction between FDA and sponsors should help to speed the regulatory process and minimize delays in the development of useful devices intended for human use. The communication with FDA may take the form of a "Pre-IDE" meeting and/or a "Pre-IDE" submission.

Informal Guidance Meeting

Sponsors are encouraged to meet with the ODE reviewing division before the IDE application is submitted for review so that the reviewing division can provide any advice/guidance which can be used in the development of supporting pre-clinical data or the investigational plan for incorporation into the IDE application. These meetings may take the form of telephone conference calls, video conferences, or face-to-face discussions. The sponsor should contact the reviewing division directly or may contact the IDE staff for assistance.

Formal Guidance Meetings

Determination Meeting - A sponsor or applicant anticipating the submission of a PMA may submit a written request to discuss the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. This meeting is to focus on the broad outline of clinical trial design. The request and summary information for a meeting should be submitted as a pre-IDE submission and identified as a determination meeting request. FDA’s determination is provided to the applicant in writing within 30 days following the meeting.

Agreement Meeting - A sponsor or applicant may submit a written request for a meeting to reach an agreement with FDA regarding FDA's review of an investigational plan (including a clinical protocol). The request and summary information should be submitted as a pre-IDE submission and identified as an agreement meeting request. This meeting should take place no later than 30 days after receipt of the request. The written request should include a detailed description of the device, a detailed description of the proposed conditions of use of

the device, a proposed plan (including a clinical protocol) for determining whether there is a reasonable assurance of effectiveness, and, if available, information regarding the expected performance of the device. If an agreement is reached between FDA and the sponsor or applicant regarding the parameters of an investigational plan (including a clinical protocol), the terms of the agreement are put in writing and made part of the administrative record by FDA.

Additional guidance can be found in:

> "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA), Final Guidance for Industry and CDRH Staff"
> http://www.fda.gov/cdrh/ode/guidance/310.html
> http://www.fda.gov/cdrh/ode/guidance/310.pdf
>
> "Goals and Initiatives for the IDE Program," Blue Book Memorandum #D95-1
> http://www.fda.gov/cdrh/d951.html
>
> Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, March 1999
> http://www.fda.gov/cdrh/ode/d99-1.html
> http://www.fda.gov/cdrh/ode/d99-1.pdf

Pre-IDE Submissions

In addition to telephone contacts and informal or formal guidance meetings, sponsors may submit preliminary information as a "pre-IDE" submission. Sponsors are encouraged to submit pre-IDE submissions while the sponsor is preparing the formal IDE submission whenever the sponsor requires informal FDA guidance on troublesome parts of the IDE application, e.g., clinical protocol design, pre-clinical testing proposal, pre-clinical test results, protocols for foreign studies when the studies will be used to support future marketing applications to be submitted to FDA.

Upon completion of the review of the pre-IDE submission, the reviewing division will issue a response to the sponsor in a timely manner, usually within 60 days of receipt. The response may take the form of a letter or comments provided during a meeting or telephone conference call. If FDA's response is provided via comments during a meeting or a telephone conference call, a memo of the meeting or conference call will be prepared.

A pre-IDE submission must be clearly identified as such, submitted in duplicate, and addressed to:

Center for Devices and Radiological Health
Food and Drug Administration
IDE Document Mail Center (HFZ-401)
9200 Corporate Boulevard Rockville, MD 20850-3223

FDA Action on IDE Applications

Approval or Disapproval §812.30

FDA will notify the sponsor in writing of the date it receives an IDE application. FDA may approve, approve with

modification, or disapprove an IDE application. FDA may request additional information about an investigation. The sponsor may provide the requested information or the sponsor may treat such a request as a disapproval of the application and request a hearing in accordance with 21 CFR 16.

The clinical investigation may begin after FDA and the IRB approves an IDE for the investigation. An investigation may begin 30 days after FDA receives the IDE application for the investigation of a device if IRB approval has been obtained unless FDA notifies the sponsor that the investigation may not begin.

Grounds for disapproval or withdrawal

FDA may disapprove or withdraw approval of an IDE application if FDA finds that:

1. The sponsor has not complied with applicable requirements of the IDE Regulation, any other applicable regulations or statutes, or any condition of approval imposed by an IRB or FDA.

2. The application or a report contains untrue statements or omits required material or information.

3. The sponsor fails to respond to a request for additional information within the time prescribed by FDA.

4. There is reason to believe that the risks to the human subjects are not outweighed by the anticipated benefits to the subjects or the importance of the knowledge to be gained, that informed consent is inadequate, that the investigation is scientifically unsound, or that the device as used is ineffective.

5. It is unreasonable to begin or to continue the investigation due to the way in which the device is used or the inadequacy of:

   (i) the report of prior investigations or the investigational plan; (ii) the methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or (iii) the monitoring and review of the investigation.

Notice of Disapproval or Withdrawal

If FDA disapproves an IDE application or proposes to withdraw approval, FDA will notify the sponsor in writing. A disapproval order will contain a complete statement of the reasons for disapproval and will advise the sponsor of the right to request a regulatory hearing under 21 CFR 16. FDA will provide an opportunity for a hearing before withdrawal of approval unless FDA determines that there is an unreasonable risk to the public health if testing continues.

References:

21 CFR 812.2
21 CFR 812.3
21 CFR 812.30

Procedures for Handling Inquiries Regarding the Ned for an Investigational Device Exemptions Application for Research Involving Medical Devices, October 26, 2001 (#D01-01)

http://www.fda.gov/cdrh/ode/blue-ide-d01-1.html

Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998
Significant Risk And Nonsignificant Risk Medical Device Studies
http://www.fda.gov/oc/ohrt/irbs/devices.html

Regulating In Vitro Diagnostic Device (IVD) Studies
http://www.fda.gov/cdrh/comp/ivdreg.html
http://www.fda.gov/cdrh/comp/ivdreg.pdf

Guidance on IDE Policies and Procedures
http://www.fda.gov/cdrh/ode/idepolcy.html
http://www.fda.gov/cdrh/ode/idepolcy.pdf

"Goals and Initiatives for the IDE Program," Blue Book Memorandum #D95-1
http://www.fda.gov/cdrh/d951.html

Early Collaboration Meetings Under the FDA Modernization Act (FDAMA), Guidance for Industry and CDRH Staff
http://www.fda.gov/cdrh/ode/guidance/310.pdf

Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, March 1999
http://www.fda.gov/cdrh/ode/d99-1.html
http://www.fda.gov/cdrh/ode/d99-1.pdf

Review of IDEs for Feasibility Studies 5/17/89 (D89-1)
http://www.fda.gov/cdrh/d891.html

Guideline for the Monitoring of Clinical Investigations
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html

FDA Issues Guidance for Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products
http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01193.html

Guidance for Industry; Collection of Race and Ethnicity Data in Clinical Trials (Draft Guidance)
http://www.fda.gov/cder/guidance/5054dft.doc
http://www.fda.gov/cder/guidance/5054dft.pdf

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Responsibilities

Responsibilities of Sponsors for Significant Risk Device Studies

General responsibilities (§812.40)

Sponsors are responsible for selecting qualified investigators and providing them with the information that they need to conduct the investigation properly. They must also ensure proper monitoring of the investigation and IRB review and approval, submit an IDE application to FDA for significant risk device studies, and inform the IRB and FDA promptly of any significant new information about the investigation.

FDA and IRB approval (§812.42)

A sponsor cannot begin an investigation or any part of an investigation until an IRB and FDA have both approved the application or supplemental application.

Selecting Investigators (§812.43)

A sponsor is responsible for selecting investigators qualified by training and experience to investigate the device.

Selecting Monitors (§812.43)

A sponsor must select monitors qualified by training and experience to monitor the investigational study in accordance with the IDE and other applicable FDA regulations.

Device Control (§812.43)

A sponsor can ship investigational devices only to qualified investigators participating in the investigation.

Investigator Agreements (§812.43)

A sponsor must obtain a signed agreement from each participating investigator that includes;

- the investigator's curriculum vitae,
- a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience, where applicable,
- an explanation of the circumstances that led to termination of a study if the investigator was involved in an investigation or other research that was terminated,
- a statement of the investigator's commitment to:
    - conduct the investigation in accordance with the agreement, the investigational plan, the IDE and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA,
    - supervise all testing of the device involving human subjects. and
    - ensure that the requirements for obtaining informed consent are met.

- sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. The sponsor shall also obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. (The financial certification or disclosure is submitted in the PMA or Premarket Notification 510(k) application. It should not be submitted in the IDE application.)

Informing investigators (§ 812.45)

A sponsor must supply all investigators participating in the investigation with copies of the investigational plan and a report of prior investigations of the device.

Monitoring (§ 812.46)

Securing Compliance

A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA must promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor must also require that the investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

Unanticipated Adverse Device Effects

The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

Resumption of Terminated Studies

For significant risk device investigations, a sponsor may not resume a terminated investigation without IRB and FDA approval. For a nonsignificant risk device investigation, a sponsor may not resume a terminated investigation without IRB approval. If the nonsignificant risk study was terminated for unanticipated adverse device effects, the sponsor must also obtain FDA approval.

Sponsor records (§ 812.140)

The sponsor must maintain accurate and complete records relating to the investigation. These records include;

- all correspondence including required reports,
- records of shipment of the device,
- records of disposition of the device
- signed investigator agreements including financial disclosure information,

- records concerning complaints and adverse device effects whether anticipated or not,
- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

See Records for additional information on recordkeeping requirements.

Sponsor Reports (§812.150)

The sponsor must provide the following reports in a timely manner to FDA, the IRB's, and/or the investigators.

- Unanticipated Adverse Device Effects
- Withdrawal of IRB Approval
- Withdrawal of FDA Approval
- Current List of Investigators
- Progress Reports
- Recalls and Device Disposition
- Final Report
- Informed consent
- Significant Risk Device Determination
- Other Reports

See Reports for more information regarding required reports.

Labeling (§812.5)

Under §812.5 an investigational device or its immediate package must bear a label with the following information:

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents, if appropriate; and
- the statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

The sponsor should provide detailed information on device labeling in the investigational protocol. This information may vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.

Promotion of Investigational Devices (§812.7)

Under §812.7, a sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot:

- Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
- Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the sponsor must promptly terminate the investigation.
- Represent that an investigational device is safe or effective.

However, the sponsor may advertise for research subjects to solicit their participation in a study. Appropriate advertising methods include but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects.

Advertisements should be reviewed and approved by the IRB to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process.

Additional guidance is available in the following guidance documents:

"Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998 - Recruiting for Study Subjects"
http://www.fda.gov/oc/ohrt/irbs/toc4.html

Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects
http://www.fda.gov/cdrh/comp/2229.html
http://www.fda.gov/cdrh/comp/2229.pdf

Responsibilities of Sponsors of Nonsignificant Risk Device Studies

Sponsors of nonsignificant risk studies must comply with the abbreviated IDE requirements set forth in (§812.2(b). The sponsor must:

1. Label the device in accordance with §812.5.

   Under §812.5 an investigational device or its immediate package must bear a label with the following information:

   - the name and place of business of the manufacturer, packer, or distributor;
   - the quantity of contents, if appropriate; and
   - the statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

The sponsor should provide detailed information on device labeling in the investigational protocol. This information may vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.

2. Obtain IRB approval of the investigation as a nonsignificant risk device study after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintain such approval.
3. Ensure that each investigator participating in an investigation of the device obtains informed consent under 21 CFR 50 for each subject under the investigator's care and documents the consent, unless documentation is waived by an IRB under §56.109(c).
4. Comply with the requirements of §812.46 with respect to monitoring investigations.

Securing Compliance

A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA must promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor must also require that the investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

Unanticipated Adverse Device Effects

The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

Resumption of Terminated Studies

For significant risk device investigations, a sponsor may not resume a terminated investigation without IRB and FDA approval. For a nonsignificant risk device investigation, a sponsor may not resume a terminated investigation without IRB approval. If the nonsignificant risk study was terminated for unanticipated adverse device effects, the sponsor must also obtain FDA approval.

5. Maintain certain records and submit required reports.

The following records must be maintained in one location and available for FDA inspection [§812.140(b)(4)]:

- the name and intended use of the device;
- the objectives of the investigation;
- a brief explanation of why the device is not a significant risk device;
- the name and address of each investigator;
- the name and address of each IRB;
- a statement of the extent to which the good manufacturing practices (21 CFR 820) will be followed in manufacturing the device.
- any other information required by FDA

The sponsor must maintain records concerning complaints and adverse device effects whether anticipated or not [§812.140(b)(5)].

The sponsor must provide the following reports in a timely manner to FDA, the IRB's, and/or the investigators [§812.150(b) (1) through (3) and (5) through (10)].

- Unanticipated Adverse Device Effects
- Withdrawal of IRB Approval
- Withdrawal of FDA Approval
- Progress Reports
- Recalls and Device Disposition
- Final Report
- Informed consent
- Significant Risk Device Determination
- Other Reports

See Reports for more information regarding the required reports.

6. Ensure that participating investigators maintain the records of each subject's case history and exposure to the device under §812.140(a)(3)(i) and ensure that participating investigators make the following required reports:

- Unanticipated Adverse Device Effects [§812.150(a)(1)]
- Withdrawal of IRB Approval [§812.150(a)(2)]
- Informed consent [§812.150(a)(5)]
- Other reports requested by a reviewing IRB or FDA [§812.150(a)(7)]

See Reports for more information about required reports.

7. Comply with the prohibitions in §812.7 against promotion and other practices

Under § 812.7, a sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot:

- Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
- Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the sponsor must promptly terminate the investigation.
- Represent that an investigational device is safe or effective.

However, the sponsor may advertise for research subjects to solicit their participation in a study. Appropriate advertising methods include but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects.

Advertisements should be reviewed and approved by the IRB to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process.

Additional guidance is available in the following guidance documents:

"Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998 - Recruiting for Study Subjects"
http://www.fda.gov/oc/ohrt/irbs/toc4.html

Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects
http://www.fda.gov/cdrh/comp/2229.html
http://www.fda.gov/cdrh/comp/2229.pdf

Responsibilities of Investigators for Significant Risk Device Studies

The investigator is responsible for protecting the rights, safety, and welfare of subjects. An investigator must conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, the IDE regulation and other applicable FDA regulations, and any conditions of approval imposed by an IRB and FDA. (§812.100)

While waiting approval of an IDE application, an investigator may determine whether or not potential subjects would be interested in participating in an investigation, but cannot request written informed consent or allow any subjects to participate before obtaining IRB and FDA approval. (§812.110)

Informed Consent

An investigator is responsible for obtaining informed consent under 21 CFR Part 50.

Supervision of device use (§812.110)

An investigator can permit use of the investigational device only with subjects under his/her supervision and cannot not supply an investigational device to any person not authorized under the IDE regulation to receive it.

Financial Disclosure (§812.110)

The clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the IDE applicant (or sponsor) to submit certification or disclosure of financial interests under 21 CFR 54. The investigator must update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

Device Disposal (§812.110)

Upon completion or termination of a clinical investigation or the investigator's part of the investigation or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or dispose of the device as the sponsor directs.

Records (812.140)

The investigator must maintain accurate and complete records relating to the investigation. These records include;

- all correspondence including required reports,
- records of receipt, use, or disposition of the investigational device,
- records of each subject's case history and exposure to the device,
- the protocol and documentation (date and reason) for each deviation from the protocol,
- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

See Records for additional information on recordkeeping requirements.

Investigator Reports (812.150)

The investigator must provide the following reports in a timely manner to the sponsor and/or the IRB.

- Unanticipated Adverse Device Effects
- Withdrawal of IRB Approval
- Progress Reports
- Deviations from the Investigational Plan
- Informed Consent
- Final Report
- Other Reports

See Reports for more information regarding required reports.

Responsibilities of Investigators for Nonsignificant Risk Device Studies

Informed Consent

An investigator is responsible for obtaining informed consent under 21 CFR Part 50.

Records

Clinical investigators must maintain the records of each subject's case history and exposure to the device under §812.140(a)(3)(i). Case histories include case report forms and supporting data, including signed and dated consent forms and medical records, including progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Records must include documents demonstrating informed consent and, for any use of a device the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history of each individual must document that informed consent was obtained prior to participation in the study.

Reports

Clinical investigators must make the following required reports:

- Unanticipated Adverse Device Effects [§812.150(a)(1)]
- Withdrawal of IRB Approval [§812.150(a)(2)]
- Informed consent [§812.150(a)(5)]
- Other reports requested by a reviewing IRB or FDA [§812.150(a)(7)]

See Reports for additional information regarding specific reports.

Financial Disclosure

If the data in a nonsignificant risk device study is submitted in a marketing application, then 21 CFR 54, Financial Disclosure, applies. The clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the IDE applicant (or sponsor) to submit certification or disclosure of financial interests. The investigator must update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study. (§ 812.110)

Responsibilities of Monitors

The sponsor is responsible for selecting monitors qualified by training and experience to monitor the investigational study. Monitors may be employees of the sponsor or an organization contracted by the sponsor to perform the duties of the study monitor.

The monitor is responsible for securing compliance with the requirements of the IDE regulation (§ 812.46). The monitor must assure that the investigators are complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the

reviewing IRB or FDA.

The IDE regulation requires that the sponsor identify the name and address of the monitor and provide written monitoring procedures [§812.25(e)]. While the IDE regulation does not specify the content of the written monitoring procedures, FDA has published a guideline, "Guideline for The Monitoring of Clinical Investigations, January 1988" on acceptable approaches to monitoring clinical investigations involving FDA-regulated products.

References:

21 CFR 812 Subpart C
21 CFR 812 Subpart E
21 CFR 812.140
21 CFR 812.150

Sponsor's Responsibilities For Significant Risk Device Investigations (Nov. 1995)
http://www.fda.gov/cdrh/manual/sponsor.html

Investigators' Responsibilities For Significant Risk Device Investigations (Nov. 1995)
http://www.fda.gov/cdrh/manual/invest.html

Guideline for The Monitoring of Clinical Investigations
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html

Guidance for Clinical Trial Sponsors on the Establishmentand Operation of Clinical Trial Data Monitoring Committees (Draft)
http://www.fda.gov/cber/gdlns/clindatmon.htm
http://www.fda.gov/cber/gdlns/clindatmon.pdf

Guidance on IDE Policies and Procedures
http://www.fda.gov/cdrh/ode/idepolcy.pdf
http://www.fda.gov/cdrh/ode/idepolcy.html

"Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998 - Recruiting for Study Subjects"
http://www.fda.gov/oc/ohrt/irbs/toc4.html

Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects
http://www.fda.gov/cdrh/comp/2229.html
http://www.fda.gov/cdrh/comp/2229.pdf

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Application

A sponsor of a *significant risk* device study must submit a complete IDE application to FDA. There are no preprinted forms for an IDE application; however, an IDE application must include certain required information. The sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained, that the investigation is scientifically sound, and that there is reason to believe that the device as proposed for use will be effective.

Required Elements

The following information must be included in an IDE application for a significant risk device investigation. A sponsor cannot begin a significant risk device investigation until FDA and IRB approval are granted. Three copies of a signed IDE application are required and the application must include the following in the order provided (§ 812.20):

1. Name and address of sponsor;

2. Report of prior investigations (§ 812.27);

   A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation.

   Specific contents of the report must include:

   - a bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device;
   - copies of all published and unpublished adverse information;
   - copies of other significant publications if requested by an IRB or FDA;
   - a summary of all other unpublished information (whether adverse or supportive) that is relevant to an evaluation of the safety and effectiveness of the device; and
   - if nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the Good Laboratory Practice (GLP) regulation in 21 CFR Part 58. If the study was not conducted in compliance with the GLP regulation, include a brief statement of the reason for noncompliance.

3. Investigational plan (§812.25)

   The investigational plan shall include the following items in the following order:

   - purpose (the name and intended use of the device and the objectives and duration of the investigation);
   - protocol (a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness);

- risk analysis (a description and analysis of all increased risks to the research subjects and how these risks will be minimized; a justification for the investigation; and a description of the patient population including the number, age, sex, and condition);
- description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation);
- monitoring procedures (the sponsor's written procedures for monitoring the investigation and the name and address of each monitor; see "Guideline for the Monitoring of Clinical Investigations" for a more detailed discussion); and
- additional records and reports (a description of any records or reports of the investigation other than those required in Subpart G of the IDE regulation).

4. A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device;

5. An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. Information that must be included in the written agreement are found in § 812.43;

6. Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study.

7. A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available);

8. The name and address of any institution (other than those above) where a part of the investigation may be conducted;

9. The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization;

10. Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required. [§25.34(g)];

11. Copies of all labeling for the device;

12. Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR 50, Protection of Human Subjects; and

13. Any other relevant information that FDA requests for review of the IDE application.
Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference.

Suggested Content For Original IDE Application Cover Letter

It is recommended that the cover letter include the following information *in the order provided* to assist in the administrative processing of the application.

1. Statement that the information provided is an original IDE submission.

2. Device Information:

    - Device Name
    - Intended Use

3. Sponsor contact information:

    - Name
    - Address
    - Contact Person
    - Telephone Number
    - Fax

    Please note that the sponsor MUST be located in United States [21 CFR 812.18(a)].

4. Manufacturer Information:

    - Name
    - Address
    - Contact Person
    - Telephone Number
    - Fax

5. Applicant Information:

    If the organization submitting the application is not the sponsor, such as a consultant or a lawyer, include contact information for the applicant organization or individual.

6. Provide the following information, if applicable:

    Pre-IDE/Pre-IDE meetings.

    Describe any discussions with the FDA reviewing division regarding this device. If a Pre-IDE was submitted, state the Pre-IDE number and the name of FDA reviewer, if known. If a Pre-IDE meeting occurred, provide the name of the FDA contact person and a copy of the meeting minutes.

7. Waiver Requests.

    Identify any requests for waivers and include a justification for the waiver.

8. Referenced Files.

    Identify any files that are referenced in the IDE application, such as Premarket Approval, Premarket Notification 510(k), IDE, or device master files. If files were not submitted by the sponsor, include a letter from the owner of the files that grants FDA permission to reference the files in its review of the current application.

Suggested Format For IDE Submissions

In order to facilitate FDA's handling of IDE applications, the following recommendations are offered:

- Use paper with nominal dimensions of 8 1/2" by 11".
- Use at least a 1 1/2" wide left margin to allow for binding into jackets.
- Use 3-hole punched paper to allow for binding into jackets.
- If the submission exceeds 2" in thickness, separate into volumes and identify volume number.
- Clearly and prominently identify submission as original IDE application or, for additional submissions to an IDE application, clearly identify the FDA assigned document number (e.g., G960000) and the reason for the submission (e.g., amendment or supplement) and the type of submission (e.g., Response to FDA letter; Addition of New Institution, etc.).
- All copies of each submission must be identical.
- Do not combine IDEs, PMAs and 510(k)s together; they must be separate submissions.
- Unless the IDE sponsor has provided authorization in writing for another person to submit information on the sponsor's behalf, only the IDE sponsor may amend, supplement, or submit reports to the IDE.
- Sequentially number the pages, providing a detailed table of contents, and use tabs to identify each section. This will help to facilitate the review of your submission.

Common Problems With Original IDE Applications

The sponsor should assure that the device, all preclinical testing, and the investigational plan are described and provide adequate justification for the initiation of the clinical trial. Submitters should avoid submitting the IDE application prematurely. There are three common areas that are frequently deficient in IDE applications.

- Inadequate report of prior investigations
- Inadequate investigational plan
- Inadequate/incomplete design and manufacture

<u>Common deficiencies with report of prior investigations</u>

A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation.

1. Laboratory Studies
    - inadequate description of methods
    - inadequate or no summary or conclusion
    - conclusions not supported by data
2. Reports of Animal Studies
    - no rationale for animal selection
    - no statistical justification for the number of animals selected
    - inappropriate duration or follow-up
    - failure to address compliance with Good Laboratory Practices for Nonclinical Studies, 21 CFR 58

3. Reports of Prior Publications

    - incomplete searches
    - copies of relevant publications not included
    - omission of adverse information
    - failure to identify relevant parts or information and to summarize

Common deficiencies with investigational plan

- questionable scientific soundness
- failure to clearly develop or define study objectives
- inadequate description of the protocol
- failure to identify all risks
- failure to develop proper monitoring procedures

Common deficiencies with design and manufacture

Design

Inadequate characterization or description of the device and its operation due to inadequate or omitted:

- Design/engineering drawing of device
- Rationale for device design
- Device and performance specifications
- Description of materials (including biocompatibility information)
- Description of function - how does device and/or components/subsystems work together to achieve desired function
- Validation testing for subsystems and main system

Manufacture

Inadequate or missing description of the controls used to ensure that the devices are produced consistently and as designed.

Suggested Original IDE Application Administrative Checklist

Following is a suggested checklist that submitters may use to ensure that their original IDE application is administratively complete. The first section is a screening to determine whether an IDE application is required to be submitted to FDA. The next section is the information suggested to be included in the cover letter or cover page of the IDE application. Inclusion of this information should help speed FDA's administrative processing of the application. The last section is a checklist to ensure that all the information required by regulation is addressed in the application.

Screening Information - Is an IDE application to FDA necessary?

Is the investigation within the categories exempt from the IDE regulation under §812.2(c)? (If yes, stop. IDE application is not required. IRB clearance and informed consent is recommended; please check institution's policies.)	Yes/No
Is this a nonsignificant risk device investigation? (If yes, stop. Submission to and approval from FDA is not required for nonsignificant risk devices. Follow abbreviated requirements (§812.2(b)) including IRB approval and informed consent.)	Yes/No
If the answer to both of these questions is no, an IDE application must be submitted to FDA and approval must be obtained from both FDA and the IRB before the study may begin	

Checklist for Cover Letter

Element	**Included**
Statement that submission is an original IDE application.	Yes/No
Device Information: • Device Name • Intended Use	Yes/No
Sponsor – (must be located in United States) [§812.18(a)]: • Name • Address • Contact Person • Telephone Number • Fax	Yes/No
Manufacturer Information • Name • Address • Contact Person • Telephone Number • Fax	Yes/No

Applicant Information (Note: IDE application will not be approved without a U.S. sponsor) [§812.18(a)] • Name • Address • Contact Person • Telephone Number • Fax	Yes/No
If applicable, provide the following information: • Pre-IDE submission/Pre-IDE meetings • Waiver Requests/Justification • Referenced Files	Yes/No

Checklist for an IDE Application

Elements [§812.20(b)]	**Included**
Format for submission: Table of contents (recommended) Paginated pages (recommended)	Yes/No
Report of Prior Investigations (§ 812.27): Are the following items provided and are they comprehensive and adequate to justify the proposed investigation?	
• Report of all prior clinical, animal and laboratory testing	Yes/No
• Bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device	Yes/No
• Copies of all published and unpublished adverse information	Yes/No

• Summary of all other unpublished information, whether adverse or supportive, that is relevant to an evaluation of safety and effectiveness of the device	Yes/No
• Statement whether nonclinical tests comply with the good laboratory practice (GLP) regulation in Part 58 If any studies were not conducted in compliance with the GLP regulation, a brief statement of the reason for the noncompliance must be provided. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.	Yes/No
If any item is not provided, a justification for its omission must be provided.	
Investigational Plan (§ 812.25): Are the following items included, preferably in the following order:	
Purpose: Are the following clearly defined? • name and intended use of the device • objectives of the investigation • duration of the investigation (specify in months and years)	Yes/No
Protocol: Are the following items provided and adequate? • a written protocol describing the methodology to be used including: • objectives, hypothesis to be tested, or question to be answered • description of the type of trial (i.e., controlled/open, double-blind/single-blind, etc.) • detailed description of the conduct of the trial • description of statistical methods • case report forms • an analysis of the protocol demonstrating its scientific soundness	Yes/No
Risk Analysis: Are the following items provided and adequate to determine that the benefit and knowledge to be gained from the investigation outweigh the risks to the subjects? • a description and analysis of all increased risks to the research subjects • the manner in which risks will be minimized • a justification for the investigation • a description of patient population, including number, age, sex and condition	Yes/No

Description of the Device**:** Are the following items provided and adequate? • a description of each important component, ingredient and property • the principle of operation of the device • a description of any anticipated changes in the device during the investigation	Yes/No
Monitoring Procedures**:** Are the following items present? • the written procedure for monitoring the investigation • the name and address of the individual(s) who will monitor the study	Yes/No
Manufacturing Information: [812.20(b)(3)] Is adequate manufacturing information provided to allow a judgement about the quality control of the device (e.g., that the device will meet the intended specifications) based on the description of methods, facilities and controls used for: a. manufacturing b. processing c. packing d. storage e. installation	Yes/No
Investigator Information: [812.20(b)(4)] Are the following items included?	
Example of investigator agreement [see § 812.43(c)] which should include: 1. the investigator's curriculum vitae; 2. where applicable, a statement of the investigator's relevant experience (including the dates, location, extent and type of experience); 3. if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination; and 4. a statement of the investigator's commitment to: • conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA; • supervise all testing of the device involving human subjects; and • ensure that the requirements for obtaining informed consent are met	Yes/No

5. Investigator's commitment to provide sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study.	
Certification that all participating investigators have signed the agreement and that no investigator will be added until the agreement is signed. [812.29(b)(5)]	Yes/No
Name and address of investigators who have signed the agreement.	Yes/No
IRB Information: Are the following items included?	
Name, address, and chairperson of each IRB	Yes/No
Certification of the action taken by each IRB, (i.e., approval letter) • How many IRBs have approved the investigation? • How many IRBs are currently reviewing the investigation or will review it in the future?	Yes/No
Names and addresses of any institutions (other than those identified above) where a part of the investigation may be conducted	Yes/No
Sales Information: [812.7(b)] Is the following information provided?	
Is the device to be sold	Yes/No
If yes, is the amount to be charged provided	Yes/No
Explanation of why sale does not constitute commercialization	Yes/No
§ 812.7(b) prohibits the commercialization of an investigational device by charging subjects or investigators for a device a price larger than necessary to recover costs of manufacture, research, development, and handling.	
Environmental Impact Assessment: [§812.20(b)(9)] An environmental impact assessment or a claim for categorial exclusion is no longer required. [§25.34(g)]	

Labeling: [§812.5] Are copies of all labeling for the device provided and include the following?	
Does the labeling contain the statement "CAUTION-Investigational Device. Limited by Federal (or United States) Law to Investigational Use." [§ 812.5(a))]	Yes/No
Does the labeling contain adequate information for the purposes of the investigation, in accordance with § 812.5(a), including the name and place of business of the manufacturer, packer, or distributor, the quantity of contents, and a description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions? If any item is not addressed, a justification for its omission must be provided.	Yes/No
Note: The device may not be promoted as safe and effective for the use for which it is being investigated. [§812.7(d)]	
Informed Consent Materials: [21 CFR 50, 812.25(g)]	
Are all forms and informational materials to be presented to the subject included?	Yes/No
Does the informed consent form seek consent from the subject or a legally authorized representative, when appropriate (e.g., when the subject is a minor)?	Yes/No
Does the informed consent form contain the basic required elements? (see 21 CFR Part 50.25(a)) Required Elements: • a statement that the study involves research • an explanation of the purposes of the research • the expected duration of the subject's participation • a description of the procedures to be followed • identification of any procedures which are experimental • a description of any reasonably foreseeable risks or discomforts to the subject • a description of any benefits to the subject or others • a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject • a statement describing the extent to which confidentiality of the subject's records will be maintained and that FDA may inspect the records • an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of or sources of further information • an explanation of whom to contact for answers to questions about the study and the subject's rights and whom to contact in the event of a research-related injury • a statement that participation is voluntary and that subjects may refuse to participate or discontinue participation at any time without penalty or loss of benefits	Yes/No

Additional Elements Required When Justified: • A statement that the procedure or treatment may involve unforeseeable risks to subject, or to the embryo or fetus if the subject were to become pregnant • Anticipated circumstances under which the investigator may terminate the subject's participation without regard to the subject's consent • Any additional costs to subject as a result of participation • Consequences of a subject's decision to withdraw and procedures for withdrawal • A statement that significant new findings which may relate to the subject's willingness to participate will be provided to the subjects • The approximate number of subjects involved in the study • Does the consent process involve a "short form" written consent [21 CFR Part 50.27(b)(2))]. If yes, a copy of the "short form" and a written summary of what is to be said to the subject or representative should be provided.	Yes/No/NA
The informed consent form may not contain exculpatory language [21 CFR Part 50.20]	
Other Information: Provide additional information supportive of the investigation and any information FDA has identified (through previous contact with the agency or through guidance documents) as required. If any item is not provided, a justification for its omission must be provided.	

Address for IDE Applications

Sponsors of a significant risk device investigation must submit three copies of a signed "Application for Investigational Device Exemption." That is, the cover page of your application should identify the submission as an application for investigational device exemption and the page should be signed by the sponsor. There are no IDE application forms. Mail the cover page and accompanying materials to the following address:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850-3223

All correspondence relating to an IDE should also be sent to this address. The IDE correspondence should be submitted in triplicate and reference the IDE number. The outside wrapper of each submission should identify the contents, for example, "IDE Application," "Supplemental IDE," "Waiver," etc.

IDE Modifications

Changes in investigational plan that require prior approval (§ 812.35)

A sponsor must obtain approval of a supplemental application and IRB approval (when appropriate under conditions described in §56.110 and §56.111 prior to implementing a change to an investigational plan except in situations described below. If a sponsor intends to conduct an investigation that involves an exception to informed consent under §50.24 (see Informed Consent), the sponsor must submit a *separate* investigational device exemption (IDE) application [§812.20(a)].

FDA believes that the following types of protocol changes would require an approved IDE supplement because they are likely to have a significant effect on the scientific soundness of the trial design and/ or validity of the data resulting from the trial:

- change in indication,
- change in type or nature of study control,
- change in primary endpoint,
- change in method of statistical evaluation, and
- early termination of the study (except for reasons related to patient safety).

In addition, FDA believes that expanding the study by increasing either the number of investigational sites or the number of study subjects participating in a clinical investigation affects the rights, safety, and welfare of the subjects. Therefore, the study may not be expanded without submission and approval of an IDE supplement.

The IDE supplement should be identified with the IDE number on the cover sheet and submitted in triplicate. The outside wrapper of the submission should identify the contents as "Supplemental IDE."

Changes that do not require prior FDA approval.

The sponsor of an IDE may modify the device and/or clinical protocol without approval of a new application or supplemental applications if the modifications meet certain criteria. The notice must be provided to FDA within 5 working days of making the change.

1. Emergency Use.

   FDA approval of a supplement does not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. However, such deviation must be reported to FDA within 5-working days after the sponsor learns of it [§812.150(a)(4)]. Additional information can be found in "Guidance on IDE Policies and Procedures"

   http://www.fda.gov/cdrh/ode/idepolcy.html
   http://www.fda.gov/cdrh/ode/idepolcy.pdf

2. Certain Developmental Changes.

   Criteria

   An FDA approved supplement is not required for developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

This determination is made by the sponsor and must be based on credible information. Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of §820.30 (See Design Controls), preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing. The sponsor must provide notice to FDA within 5-working days of making these changes.

Generic types of device and manufacturing changes include changes to the control mechanism, principle of operation, energy type, environmental specifications, performance specifications, ergonomics of patient-user interface, dimensional specifications, software or firmware, packaging or expiration dating, sterilization, and the manufacturing process (including the manufacturing site). Sponsors may refer to ``Deciding When to Submit a 510(k) for a Change to an Existing Device'' for assistance in identifying the types of changes which *may* qualify for implementation under this provision. Any specific change within a particular type may or may not be appropriate under the 5-day notice provision because changes in each of these categories could range from minor to significant depending upon the particular device, the type of modification, and the extent of the modification. The impact of the change would still need to be determined by information generated by design controls or other appropriate means to assess the significance of the change to the device design or manufacturing process and the appropriateness of a 5-day notice submission.

Please note that all developmental changes need to be reported to the IRB in the sponsor's annual report. In addition, the changes may be subject to IRB review procedures under 21 CFR 56.110.

All changes to the basic principles of operation of a device are considered to be significant changes that should be submitted in an IDE supplement.

5-day Notice

The sponsor must submit a notice of the change to the IDE no later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). These notices must be identified as a ``notice of IDE change.''

For a developmental or manufacturing change to the device, the notice must include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice must include a summary of the information which served as the credible information supporting the change. FDA will only notify the sponsor if questions arise or additional information is needed.

3. Certain changes to the clinical protocol.

Criteria

An FDA approved supplement is not required for changes to clinical protocols that do not affect:

- The validity of the data or information in the approved protocol, or the patient risk to benefit relationship relied upon to approve the protocol;
- The scientific soundness of the investigational plan; or
- The rights, safety, or welfare of the human subjects involved in the investigation.

This determination is made by the sponsor and must be based on credible information. Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation must include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing. The sponsor must provide notice to FDA within 5-working days of making these changes.

Examples of these types of changes may include the following changes:

- Modification of inclusion/exclusion criteria to better define the target patient population
- Increasing the frequency at which data or information is gathered
- Inclusion of additional patient observations or measurements
- Modifying the secondary endpoints (Secondary endpoints usually support a secondary labeling claim that the sponsor wants to make for the device and are not used to determine the safety or effectiveness of the device.)

5-day Notice

The sponsor must submit a notice of the change to the IDE no later than 5-working days after making the change. Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. These notices must be identified as a ``notice of IDE change.''

For a protocol change, the notice must include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as the credible information supporting the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects. FDA will only notify the sponsor if questions arise or additional information is needed.

<u>Changes to be submitted in the annual report.</u>

Minor changes in the following areas:

- the purpose of the study,
- risk analysis,
- monitoring procedures,

- labeling,
- informed consent materials, and
- IRB information

may be reported in the annual progress report for the IDE if the changes do not affect: (i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; (ii) The scientific soundness of the investigational plan; or (iii) The rights, safety, or welfare of the human subjects involved in the investigation [812.150(b)(5)]. If the changes do affect the above criteria, then prior approval must be obtained.

IDE supplements for new facilities

FDA will review initial IDE applications that do not contain a certification of IRB approval for each site. FDA may approve the investigational sites without IRB approval. The sponsor is required to submit the certification in an IDE supplement when he obtains IRB approval. If the site is already approved and the supplement is just the certification of IRB approval, FDA usually does not provide a written response to the certification since the site has previously been approved by FDA.

If the sponsor has determined the number of investigational sites for the study but not yet identified all the sites at the time the IDE is submitted, FDA may grant a waiver to the sponsor. The waiver would allow the sponsor to enroll the sites, obtain IRB approvals, and then submit all the certifications of IRB approval to FDA at one time (or at 6 month intervals if it takes that long to enroll the sites) instead of requesting each site as it is identified.

Once the IDE is approved, the sponsor may submit an IDE supplement to request approval of additional clinical study sites. FDA will respond in writing to the supplement approving or denying the request. The sponsor is required to submit;

- Identification of the investigational site,
- certification of IRB approval,
- information updating the initial IDE application (if the investigation is changed), and
- a description of any modifications required by the IRB as conditions of approval.

Certification of IRB approval for a new sites does not need to be included in the request but the sponsor will need to submit it to us once he has IRB approval.

The sponsor may not begin any part of the investigation at an institution until:

- IRB approval is obtained;
- FDA receives certification of IRB approval; and
- FDA approves the supplemental application.

Additional information can be found in the following guidance document.

> Changes or Modifications During the Conduct of a Clinical Investigation
> http://www.fda.gov/cdrh/ode/guidance/1337.html
> http://www.fda.gov/cdrh/ode/guidance/1337.pdf

References:

21 CFR 812.20
21 CFR 812.25
21 CFR 812.27
21 CFR 812.35

IDE Refuse to Accept Procedures 5/20/94 (D94-1)
http://www.fda.gov/cdrh/d941.html

Waiver For Additional Investigational Sites (Excerpt from the IDE Form Letter to a Sponsor)
http://www.fda.gov/cdrh/manual/waiver.html

Changes or Modifications During the Conduct of a Clinical Investigation
http://www.fda.gov/cdrh/ode/guidance/1337.html
http://www.fda.gov/cdrh/ode/guidance/1337.pdf

Guideline for the Monitoring of Clinical Investigations
http://www.fda.gov/cdrh/manual/monitor.html
http://www.fda.gov/cdrh/ode/428.pdf

Last modified dateJuly 21, 2003

Reports

Sponsor Reports

The following reports are required by the sponsor under §812.150. All reports to FDA should be identified as IDE Supplements and submitted in triplicate.

Unanticipated Adverse Device Effects

The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

Withdrawal of IRB Approval

The sponsor must notify FDA and all reviewing IRBs and participating investigators of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval.

Withdrawal of FDA Approval

The sponsor must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval within 5 working days after receipt of the notice.

Current List of Investigators

Every six months the sponsor must submit to FDA a current list of the names and addresses of all investigators participating in a significant risk device investigation.

Progress Reports (or Annual Reports)

At regular intervals and at least yearly, the sponsor must provide progress reports to all reviewing IRBs. For a significant risk device, the sponsor must also submit the progress report to FDA. A suggested format is provided below.

Recalls and Device Disposition

The sponsor must notify FDA and all reviewing IRB's of any request that an investigator return, repair, or dispose of any unit of an investigational device. The notice must be made within 30 working days after the request is made and must state why the request was made.

Final Report

For a significant risk device, the sponsor must notify FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor must also submit a final report to FDA and all

reviewing IRBs and participating investigators within 6 months after the completion or termination of the investigation. A suggested format is provided below. For a nonsignificant risk device, the sponsor must submit a final report to all reviewing IRBs within 6 months after completion or termination.

Informed consent

Sponsors must submit a copy of any report by an investigator of the use of a device without first obtaining informed consent. The report must be made to FDA within 5 working days after receipt of the notice of such use.

Significant Risk Device Determination

If an IRB determines that the device is a significant risk device and not a nonsignificant risk device as the sponsor had proposed to the IRB, a report must be submitted to FDA within 5 working days after the sponsor learns of the IRB's determination.

Other Reports

The sponsor must provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA.

Suggested Format For IDE Progress Report

1. Basic Elements

    - IDE Number
    - Device name and indication(s) for use
    - Sponsor's name, address, phone number, and fax
    - Contact person

2. Study Progress
   (Data from beginning of the study should be reported, unless otherwise indicated.)

    - Brief summary of the study progress in relation to the investigational plan
    - Number of investigators/investigational sites (attach list of investigators)
    - Number of subjects enrolled (by indication or model)
    - Number of devices shipped
    - Brief summary of results
    - Summary of anticipated and unanticipated adverse effects
    - Description of any deviations from the investigational plan by investigators (since last progress report)

3. Risk Analysis

- Summary of any new adverse information (since the last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
- Reprints of any articles published from data collected from this study
- New risk analysis, if necessary, based on new information and on study progress

4. Other Changes

    - Summary of any changes in manufacturing practices and quality control (including changes not reported in a supplemental application)
    - Summary of all changes in the investigational plan not required to be submitted in a supplemental application

5. Future Plans

    - Progress toward product approval, with projected date of PMA or 510(k) submission
    - Any plans to change the investigation, e.g., to expand the study size or indications, to discontinue portions of the investigation or to change manufacturing practices (NOTE: Actual proposals for these changes should be made in a separate supplemental application).

Suggested Format for IDE Final Report

1. Basic Elements

    - IDE Number
    - Device name and indication for use
    - Sponsor's name, address, phone number, and fax number
    - Contact person

2. Study Progress
   (Data from beginning of the study should be reported, unless otherwise indicated.)

    - Brief summary of study progress in relation to investigational plan
    - Number of investigators/investigational sites (attach list of investigators)
    - Number of subjects enrolled (by indication or model)
    - Number of devices shipped
    - Disposition of all devices shipped
    - Brief summary of results
    - Summary of anticipated and unanticipated adverse effects
    - Description of any deviations from the investigational plan by investigators (since last progress report)

3. Risk Analysis

    - Summary of any new adverse information (since last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
    - Reprints of any articles published from data collected from this study

4. Other Changes

    - Summary of any changes in manufacturing practices and quality control (including changes not reported in a supplemental application)

- Summary of all changes in investigational plan not required to be submitted in a supplemental application

5. Marketing Application or Future Plans

    - Progress toward product approval, with date (or projected date) of PMA or 510(k) submission; or indication that marketing of device is not planned.
    - Any plans to submit another IDE application for this device or a modification of this device.

Investigator Reports

The investigator must provide the following reports in a timely manner under §812.150.

Unanticipated Adverse Device Effects

The investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible but no later than 10 working days after the investigator first learns of the effect.

Withdrawal of IRB Approval

The investigator must report to the sponsor a withdrawal of approval of the reviewing IRB within 5 working days.

Progress Reports

The investigator must submit progress reports to the sponsor, the monitor, and the reviewing IRB at regular intervals but no less than on a yearly basis.

Deviations from the Investigational Plan

The investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. The notice must be provided as soon as possible but no later than 5 working days after the emergency occurred. If it is not an emergency, prior approval from the sponsor is required for changes in or deviations from the investigational plan. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the sponsor is required to obtain prior IRB approval and also to obtain FDA approval for a significant risk device investigation by submitting a supplemental application.

Informed Consent

If an investigator uses a device without obtaining informed consent, the investigator must report the used to the sponsor and to the reviewing IRB within 5 working days after the use occurs.

Final Report

The investigator must submit a final report to the sponsor and to the reviewing IRB within 3 months after termination or completion of the investigation.

Other Reports

The investigator must provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA.

Investigator Annual Progress Reports and Final Reports

The IDE regulations do not specify the content of the annual progress or final reports. Therefore, the contents of these reports may largely be dictated by the sponsor. With respect to reports to the IRB, the IRB itself may specify what information it wishes to be included in these reports. Because FDA does require the information listed below, it is suggested that, at a minimum, the annual progress and final reports to the sponsor and the IRB include the following items:

1. IDE number
2. Device name
3. Indications for use
4. Brief summary of study progress in relation to investigational plan
5. Number of subjects enrolled
6. Number of devices received, used, and, in the final report, the final disposition of unused devices
7. Brief summary of results and, in the final report, conclusions
8. Summary of anticipated and unanticipated adverse device effects
9. Description of any deviations from investigational plan
10. Reprints of any articles published by the investigator in relation to the study

References:

21 CFR 812.150

Overdue IDE Annual Progress Report Procedures, Blue Book Memo, 7/23/93 (D93-1)
http://www.fda.gov/cdrh/d931.html

Last modified date12/31/2001

Records

Sponsor Records for Significant Risk Device Studies

The sponsor must maintain accurate and complete records relating to the investigation under §812.140. These records include:

- all correspondence including required reports,
- records of shipment of the device,
    - name and address of the consignee
    - type and quantity of the device, date of shipment, and batch number or code
- records of disposition of the device
    - batch number or code of any devices returned to the sponsor, repaired, or disposed of in other ways
    - reasons for and the method of disposal
- signed investigator agreements including financial disclosure information,
- records concerning complaints and adverse device effects whether anticipated or not,
- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

Sponsor Records for Nonsignificant Risk Device Studies

The following records must be maintained in one location and available for FDA inspection under §812.2(b):

- the name and intended use of the device;
- the objectives of the investigation;
- a brief explanation of why the device is not a significant risk device;
- the name and address of each investigator;
- the name and address of each IRB;

- a statement of the extent to which the good manufacturing practices (21 CFR 820) will be followed in manufacturing the device.

The sponsor must also maintain records concerning complaints and adverse device effects whether anticipated or not [§812.140(b)(5)].

Investigator Records for Significant Risk Device Studies

The investigator must maintain accurate and complete records relating to the investigation under §812.140. These records include:

- all correspondence including required reports,
- records of receipt, use, or disposition of the investigational device,
    - type and quantity of device
    - date of receipt
    - batch number or code
    - name of person that received, used, or disposed of each device
    - why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- records of each subject's case history and exposure to the device which must include,
    - signed and dated consent forms
    - condition of each subject upon entering the study
    - relevant previous medical history
    - record of the exposure to the investigational device, including the date and time of each use and any other therapy
    - observations of adverse device effects
    - medical records (physician and nurse progress notes, hospital charts, etc.)
    - results of all diagnostic tests
    - case report forms

    - any other supporting data

- the protocol and documentation (date and reason) for each deviation from the protocol.

- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

Investigator Records for Nonsignificant Risk Device Studies

Clinical investigators must maintain the records of each subject's case history and exposure to the device under §812.140(a)(3)(i). Case histories include case report forms and supporting data, including signed and dated consent forms and medical records, including progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Records must include documents demonstrating informed consent and, for any use of a device the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history of each individual must document that informed consent was obtained prior to participation in the study.

Maintenance of Records

Sponsors and investigators must maintain the required records for a period of two years after the date the investigation is completed or terminated or the records are no longer required to support a PMA or PDP, whichever date is later.

An investigator or sponsor may withdraw from the responsibility to maintain records for the time required by transferring custody to another person who will accept responsibility for them. If an investigator or sponsor transfers custody of the records to another person, FDA must be notified within 10 working days after the transfer occurs.

Sponsors, IRBs, and investigators are required to permit authorized FDA employees reasonable access at reasonable times to inspect and copy all records of an investigation. Upon notice, FDA may inspect and copy records that identify subjects.

FDA has authority to inspect facilities at which investigational devices are being held including any establishments where devices are manufactured, packed, installed, used, or implanted.

For more information on FDA's inspection program, see Enforcement of Good Clinical Regulations.

References:

§812.140
§812.145

Computerized Systems Used in Clinical Trials
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.pdf

Last modified date: July 21, 2003

Institutional Review Boards (IRB)

Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights, safety and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights, safety and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents). The IRB must monitor and review an investigation throughout the clinical study.

If an IRB determines that an investigation involves a significant risk device, it must notify the investigator and, if appropriate, the sponsor. The sponsor may not begin the investigation until approved by FDA.

Currently, FDA does not require IRB registration. The institutions where the study is to be conducted should be contacted to determine if they have their own IRB. If the study is conducted at a site that does not have its own IRB, the investigators should be queried to see if they are affiliated with an institution with an IRB that would be willing to act as the IRB for that site in the study. There are also independent/contract IRBs that can be contracted with to act as the IRB for a site. A list of IRBs associated with the Consortium of Independent Review Boards is available from the IDE Staff at 301-594-1190. (Please note: FDA does not approve or endorse any IRBs.) Additionally, an IRB can be established in accordance with 21 CFR 56.

An IRB must comply with all applicable requirements of the IRB regulation (Part 56) and the IDE regulation (Part 812) in reviewing and approving device investigations involving human testing. FDA does periodic inspections of the IRB's records and procedures to determine compliance with the regulations.

References:

21 CFR 56
§ 812.30

Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998
http://www.fda.gov/oc/ohrt/irbs/default.htm

Cooperative Research
http://www.fda.gov/oc/ohrt/IRBs/research.html

Frequently Asked Questions on IRB Organization, Membership, Procedures, and Records
http://www.fda.gov/oc/ohrt/IRBs/faqs.html

Non-local IRB Review
http://www.fda.gov/oc/ohrt/IRBs/nonlocalreview.html

Continuing Review After Study Approval

http://www.fda.gov/oc/ohrt/irbs/review.html

Sponsor - Investigator - IRB Interrelationship
http://www.fda.gov/oc/ohrt/irbs/toc4.html

A Self-evaluation Checklist for IRBs
http://www.fda.gov/oc/ohrt/irbs/irbchecklist.html

FDA Institutional Review Board Inspections
http://www.fda.gov/oc/ohrt/IRBS/operations.html#board

Significant Differences in FDA and HHS Regulations for Protection of Human Subjects
http://www.fda.gov/oc/ohrt/irbs/aooendixe.html

Compliance Program 7348.809 – Institutional Review Board Program
http://www.fda.gov/ora/compliance_ref/bimo/7348_809/irb-cp7348-809.pdf

Links:

Information for Health Professionals - Clinical Trials and Institutional Review Boards
http://www.fda.gov/oc/oha/default.htm#clinical

Institutional Review Board Guidebook, 1993, National Institutes of Health, Office of Extramural Research, Office for Protection from Research Risks
http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm

Last modified date: July 21, 2003

Informed Consent - Protection of Human Subjects

Introduction

No clinical investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent from the subject. Informed Consent is a written notification to human subjects involved in clinical investigations that provides them with sufficient opportunity to consider whether or not to participate in the study. The informed consent document must include all the basic elements of informed consent (outlined below) or it may be a short form written consent document stating that the elements of informed consent have been presented orally (§50.27). If the short form method is used, there must be a witness to the oral presentation.

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

The written consent form must be approved by the Institutional Review Board (IRB) and contain the following basic elements (§50.25):

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2. A description of any reasonably foreseeable risks or discomforts to the subject.

3. A description of any benefits to the subject or to others which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7. An explanation of whom to contact for answers to pertinent questions about the research and research

subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9. Additional elements of informed consent. When appropriate, one or more of the following elements of information must be provided to each subject:

    a. A statement that a particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
    b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
    c. Any additional costs to the subject that may result from participation in the research.
    d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
    e. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
    f. The approximate number of subject's involved in the study.

The consent form must be signed by the subject or the subject's legally authorized representative. Each signed consent must be maintained by the clinical investigator and a copy of the informed consent must be provided to the human subject.

A combination of oral and written consent may be used. The short form method of informed consent includes a written summary and a "short form." A written summary is a document of what is to be said to the subject or representative and must be approved by the IRB. The summary must include all the basic elements of informed consent (discussed above). A short form is a document stating that the elements of informed consent (§50.25) have been presented orally to the subject or the subject's legally authorized representative.

After oral presentation is provided, the summary must be signed by the witness and the presenter (investigator or investigator's representative). The short form must be signed by the subject (or the representative) and the witness. A copy of the summary must be provided to the subject (or the representative) in addition to a copy of the short form. The signed documents must be maintained by the clinical investigator.

Exception from Informed Consent Requirements for Emergency Research

Criteria for exception from informed consent

There are special cases under emergency care research in which the human subject is in a life-threatening situation and it is not feasible to obtain informed consent. In order to allow such research to proceed, there are special provisions for exception from informed consent requirements (§50.24).

The IRB responsible for the review, approval, and continuing review of the clinical investigation may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:

    a. the subjects will not be able to give their informed consent as a result of their medical condition;
    b. the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
    c. there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. Participation in the research holds out the prospect of direct benefit to the subjects because:

    a. subjects are facing a life-threatening situation that necessitates intervention;
    b. appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
    c. risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with the elements of informed consent (§50.25). These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation as discussed in (7)(e) below.

7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:

    a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

b. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
c. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

IRB Responsibilities

The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

The IRB must also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation.

Records of IRB determinations must be retained by the IRB for at least 3 years after completion of the clinical investigation. These records must include the IRB determinations of exemption from informed consent and also the documentation of IRB denial, including documentation of findings and disclosure of the findings to the clinical investigator and the sponsor. The records must be accessible for inspection and copying by FDA [§56.115(b)].

Sponsor Responsibilities

The sponsor must monitor the progress of all investigations involving an exception from informed consent. When the sponsor receives information concerning the public disclosures under (7)(b) and (7)(c) above from the IRB, the sponsor must promptly submit copies of the information that was disclosed to the IDE file and to

Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, identified by the IDE number.

The sponsor also must monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the exception criteria or because of other relevant ethical concerns. The sponsor must promptly provide this information in writing to FDA, investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that have been asked to review this or a substantially equivalent investigation.

IDE Application

Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IDE is required even if an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments to an approved IDE [§812.35].

References:

21 CFR 50

Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, 1998
http://www.fda.gov/oc/ohrt/irbs/default.htm

A Guide to Informed Consent
http://www.fda.gov/oc/ohrt/IRBS/informedconsent.html

Frequently Asked Questions on Informed Consent Process and Informed Consent Document Content
http://www.fda.gov/oc/ohrt/IRBS/faqs.html

Declaration of Helsinki
http://www.fda.gov/oc/health/helsinki89.html
(World Medical Association’s recommendations to every physician in biomedical research involving human subjects)

The Belmont Report, April 18, 1979
http://www.fda.gov/oc/ohrt/irbs/belmont.html

Significant Differences in FDA and HHS Regulations for Protection of Human Subjects
http://www.fda.gov/oc/ohrt/irbs/appendixe.html

Guidance on IDE Policies and Procedures
Text-http://www.fda.gov/cdrh/ode/idepolcy.html
PDF-http://www.fda.gov/cdrh/ode/idepolcy.pdf

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent - Requirements for Emergency Research
http://www.fda.gov/OHRMS/DOCKETS/98fr/000805GL.pdf

Recommended Links

Information for Health Professionals - Clinical Trials and Institutional Review Boards
http://www.fda.gov/oc/oha/default.htm#clinical

Institutional Review Board Guidebook, 1993, National Institutes of Health, Office of Extramural Research, Office for Protection from Research Risks
http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm

Last modified date01/02/2002

Financial Disclosure

Introduction

FDA reviews data generated in clinical studies to determine whether medical device applications are approvable. Financial interest of a clinical investigator is one potential source of bias in the outcome of a clinical study. To ensure the reliability of the data, the financial interests and arrangements of clinical investigators must be disclosed to FDA.

This requirement applies to any clinical study submitted in a marketing application that the applicant or FDA relies on to establish that the product is effective or is used to show equivalence to an effective product, and any study in which a single investigator makes a significant contribution to the demonstration of safety. The requirement does not apply to studies conducted under the emergency use, compassionate use, or treatment use provisions. Financial compensation or interests information is used, in conjunction with information about the design and purpose of the study, as well as information obtained through on-site inspections, in the agency's assessment of the reliability of the data.

Certification

Anyone who submits a Premarket Approval or Premarket Notification 510(k) after February 2, 1999 that contains a covered clinical study must submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting covered clinical studies in the application. Applicants must certify to the absence of certain financial interests of clinical investigators on Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigations FDA Form 3454 http://forms.psc.gov/forms/FDA/fda3454.pdf or to disclose those financial interests on Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455 http://forms.psc.gov/forms/FDA/fda3455.pdf.

Information to be Disclosed

The financial arrangements that must be disclosed include the following:

- Compensation made to the investigator in which the value of the compensation could be affected by the study outcome.

- Significant payments to the investigator or institution with a monetary value of $25,000 or more (e.g. grants, equipment, retainers for ongoing consultation, or honoraria) over the cost of conducting the trial. Any such payments to the investigator or institution during the time the investigator is conducting the study and for one year following study completion, must be reported.

- Proprietary interest in the device, such as a patent, trademark, copyright, or licensing agreement.
- Significant equity interest in the sponsor such as ownership, interest, or stock options. All such interests whose value cannot be readily determined through reference to public prices must be reported. If the sponsor is a publicly traded company, any equity interest whose value is greater than $50,000 must be reported. Any such interests held by the investigator while the investigator was conducting the study and for one year following study completion must be reported.

This requirement applies to investigators and subinvestigators including their spouses and dependent children, but does not apply to full or part-time employees of the sponsor or to hospital or office staff.

Please note that if the study was completed prior to February 2, 1999, the requirements are reduced. That is, the sponsor does not need to report equity interest in a publicly held company or significant payments of other sorts. Other reporting still applies.

Sponsors are responsible for collecting financial information from investigators and clinical investigators are responsible for providing financial disclosure information to the sponsor.The investigator's agreement with the sponsor should require the investigator to provide to the sponsor accurate financial disclosure information. (See Responsibilities). Certification or disclosure information should not be included in the IDE application.

FDA Actions

If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:

- Initiating agency audits of the data derived from the clinical investigator in question;
- Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome;
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and
- Refusing to use the data from the covered clinical study as the primary basis for an agency action, such as PMA approval or 510(k) clearance.

Please note that FDA does NOT prohibit financial compensation to clinical investigators nor does FDA require or recommend divesture. FDA believes that divestiture could adversely affect development of new products.

References:

21 CFR 54
21 CFR 812.110(d)
21 CFR 812.43(c)(5)

Guidance for Industry: Financial Disclosure by Clinical Investigators
http://www.fda.gov/oc/guidance/financialdis.html

Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigations FDA Form 3454
http://forms.psc.gov/forms/fda3454.pdf

Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455
http://forms.psc.gov/forms/fda3455.pdf

Last modified date: July 21, 2003

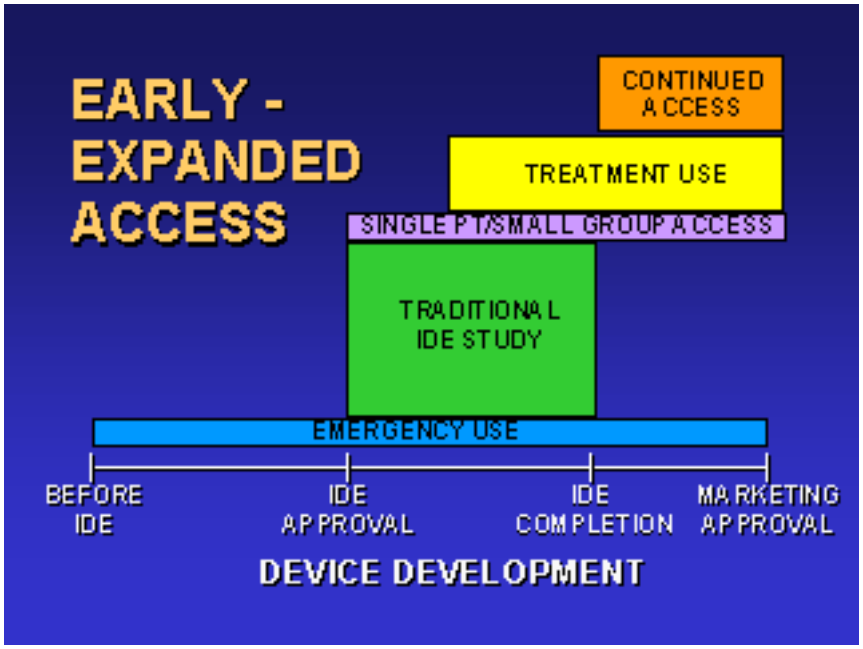
Early/Expanded Access

Introduction

An unapproved medical device may normally only be used on human subjects through an approved clinical study in which the subjects meet certain criteria and the device is only used in accordance with the approved protocol by a clinical investigator participating in the clinical trial. However, there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which there no other alternative therapy exists. Patients/physicians faced with these circumstances may have access to investigational devices under one of four main mechanisms by which FDA may make an unapproved device available:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

These mechanisms can be utilized during a certain time-frame in the IDE process if the criteria are met. FDA approval is required except in the case of emergency use. The mechanisms are summarized below followed by an in depth discussion of criteria and requirements.



Emergency Use

Emergency situations may arise in which there will be a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Emergency use of an unapproved device may occur before an IDE is approved.

Criteria:

- Life-threatening or serious disease or condition
- No alternative
- No time to obtain FDA approval

Time-frame: Before or after initiation of the clinical trial

There are special cases under emergency research in which the human subject is in a life-threatening situation and it is not feasible to obtain informed consent. In order to allow such research to proceed, special provisions for exception from informed consent requirements must be met. In addition, the IRB and a physician not participating in the investigation must review and approve the investigation. The sponsor must also submit a separate IDE application to FDA.

Detailed information on conditions for exception from informed consent can be found under Informed Consents, Exception from Informed Consent Requirements for Emergency Research.

Compassionate Use (or Single Patient/Small Group Access)

The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group.

Criteria:

- Serious disease or condition
- No alternative

Time-frame: During clinical trial

FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening, disease or condition. In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur.

Prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section §812.35(a) in order to treat the patient. The IDE supplement should include:

1. A description of the patient's condition and the circumstances necessitating treatment;
2. A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed. (Informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor)

The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from a serious disease or condition for which no alternative therapy adequately meets their medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

Treatment Use

An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.

Criteria:

- Life-threatening or serious disease
- No alternative
- Controlled clinical trial
- Sponsor pursuing marketing approval

Time-frame: During clinical trial

A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the treatment investigational device exemptions (IDE) regulation. (§812.36)

The treatment use provision of the IDE facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device

ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials.

An ``immediately life-threatening'' disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. ``Treatment use'' of a device includes the use of a device for diagnostic purposes.

FDA would consider the use of an investigational device under a treatment IDE if:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

Applications for treatment use

A treatment IDE application must include, in the following order:

1. The name, address, and telephone number of the sponsor of the treatment IDE;
2. The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
3. An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
4. A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
5. Written procedures for monitoring the treatment use and the name and address of the monitor;
6. Instructions for use for the device and all other labeling as required under section §812.5(a) and (b);
7. Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;
8. A statement of the sponsor's commitment to meet all applicable responsibilities under the IDE regulations (21 CFR 812) and Institutional Review Boards regulations (21 CFR 56) and to ensure compliance of all participating investigators with the informed consent requirements of 21 CFR 50;
9. An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
10. If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56.

Applications should be identified on the outside envelope as a treatment IDE application and reference the IDE number. The original and two copies should be mailed to the following address:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Room, HFZ-401
9200 Corporate Blvd.
Rockville, MD 20850-3223

FDA action on treatment IDE applications

Approval of treatment IDE's

Treatment use may begin 30 days after FDA receives the treatment IDE submission. FDA may notify the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

Disapproval or withdrawal of approval of treatment IDE's

FDA may disapprove or withdraw approval of a treatment IDE if:

1. The required criteria [§812.36(b)] are not met or the treatment IDE application does not contain the required information [§812.36(c)];
2. FDA determines that any of the grounds for disapproval or withdrawal of approval apply [§812.30(b)(1) through (b)(5)]. See Approval Process, FDA Actions, for additional information;
3. The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;
4. The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:
    a. may be effective for its intended use in its intended population; or
    b. would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;
5. There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;
6. The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;
7. The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;
8. Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or
9. The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

Notice of disapproval or withdrawal

If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set

forth in the IDE regulations [§812.30(c)] For more information, see Approval Process, FDA Actions.

Safeguards

Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (21 CFR 50) and institutional review boards (21 CFR 56).

Reporting requirements

The sponsor of a treatment IDE must submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. The date of these reports are based on the period of time since initial approval of the treatment IDE. *After* filing of a marketing application, progress reports must be submitted annually in accordance with the IDE regulation.

See "Suggested Format For IDE Progress Report" under Reports for guidance on the content of a progress report. The progress report must also include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/ clearance of the device.

The sponsor of a treatment IDE is responsible for submitting all other reports required under §812.150 (Reports), such as unanticipated adverse device effects and final reports. The reports are submitted as supplements to the original IDE application. See Reports for additional guidance.

Continued Access

FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA.

Criteria:

- Public health need or
- Preliminary evidence that the devcie will be effective and there are no significant safety concerns

Time-frame: After completion of the clinical trial

The sponsor of a clinical investigation is permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the Agency if there is:

- A public health need for the device; or
- Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

The continued enrollment of subjects in an investigation while a marketing application is being prepared by the

sponsor and/or reviewed by ODE is known as an "extended investigation." Extended investigations permit patients and/or physicians continued access to the devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. The Continued Access Policy may be applied to any clinical investigation that meets the criteria identified above; however, it is intended to be applied late in the device development process, i.e., after the controlled clinical trial has been completed.

A sponsor's request for an extended investigation should be submitted as an IDE supplement and include the following information:

1. A justification for the extension;
2. A summary of the preliminary safety and effectiveness data generated under the IDE;
3. A brief discussion of the risks posed by the device;
4. The proposed rate of continued enrollment (the number of sites and subjects);
5. The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
6. A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device.

There is significant overlap between the treatment IDE regulation and the Continued Access Policy. Both the Continued Access Policy and the treatment IDE regulation are intended to provide additional access to an unapproved device, once preliminary evidence regarding safety and effectiveness is available to FDA. However, because a treatment IDE can be submitted earlier in the IDE process, i.e., once promising evidence of safety and effectiveness has been collected under the IDE but while the clinical study is ongoing, it could provide access to a wider group of patients at an earlier stage in the IDE process. The treatment IDE regulation also has a more narrow application than the Continued Access Policy in that treatment use is intended to address only those patients who have an immediately life-threatening or serious disease or condition whereas the Continued Access Policy, which is applied after completion of the clinical trial, may be considered for any clinical investigation.

References:

§812.36, §812.47, §50.24

Guidance on IDE Policies and Procedures
http://www.fda.gov/cdrh/ode/idepolcy.html
http://www.fda.gov/cdrh/ode/idepolcy.pdf

"Continued Access to Investigational Devices During PMA Preparation and Review," Blue Book Memorandum, D96-1
http://www.fda.gov/cdrh/d961.html

IRB Information Sheets: Emergency Use of Unapproved Medical Devices
http://www.fda.gov/oc/ohrt/irbs/devices.html#emergency

Last modified date: July 21, 2003

Enforcement of Good Clinical Practices (GCP) Regulations

Inspection Program

Sponsors, IRBs, and investigators, or any person acting on their behalf, are required to permit authorized FDA employees reasonable access at reasonable times to inspect and copy all records relating to an investigation. Any establishment where devices are held, including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept, are subject to inspection. Furthermore, if FDA has reason to suspect that adequate informed consent was not obtained or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading, FDA may inspect and copy records that identify subjects.

To assure compliance with the IDE and related regulations, FDA inspects sponsors, clinical investigators, and institutional review boards. Nonclinical laboratories that perform animal studies in which the data are used to support research or marketing permits are included in the inspection program. The inspection program is referred to as bioresearch monitoring (BIMO) and is overseen the CDRH's Office of Compliance, Division of Bioresearch Monitoring.

The regulations enforced by the bioresearch monitoring program for medical devices are found in four sections of the CFR:

- 21 CFR 812 - Investigational Device Exemptions
- 21 CFR 50 - Protection of Human Subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies

The objectives of the bioresearch monitoring program are to ensure the quality and integrity of data and information submitted in support of research and marketing permits that include IDE, PMA, and 510(k) submissions and to ensure that human subjects taking part in investigations are protected from undue hazard or risk. This is achieved through audits of clinical data contained in PMA's prior to approval, data audits of IDE and 510(k) submissions, inspections of Institutional Review Boards and nonclinical laboratories, and enforcement of the prohibition against promotion, marketing, or commercialization of investigational devices.

In addition, the Division is also charged with the implementation of the FDA's Application Integrity Policy (AIP) for medical devices and radiological health products. If it is suspected that an applicant has submitted false or misleading information, the data are thoroughly investigated. Submitting false or misleading information may result in FDA refusal to review submissons until certain requirements are met, as well as the initiation of legal actions.

References:

§ 812.145

Bioresearch Monitoring Agreement for PMAs and PDPs
http://www.fda.gov/cdrh/ode/p98-1.html

Compliance Programs

7348.808 - Good Laboratory Practices for Nonclinical Studies
http://www.fda.gov/ora/compliance_ref/bimo/7348_808/default.htm
http://www.fda.gov/ora/compliance_ref/bimo/7348_808/48-808.pdf (3.22 mb PDF version)

7348.809 – Institutional Review Board
http://www.fda.gov/ora/compliance_ref/bimo/7348_809/irb-cp7348-809.pdf

7348.810 - Sponsors, Contract Research Organizations and Monitors
http://www.fda.gov/ora/compliance_ref/bimo/7348_810/default.htm
http://www.fda.gov/ora/compliance_ref/bimo/7348_810/48-810.pdf (1.84 mb PDF version)

7348.811 - Clinical Investigators
http://www.fda.gov/ora/compliance_ref/bimo/7348_811/default.htm
http://www.fda.gov/ora/ftparea/compliance/48_811.pdf (3.24 MB PDF version)

Integrity of Data and Information Submitted to ODE May 29, 1991 (I91-2)
http://www.fda.gov/cdrh/i91-2.html

Application Intregrity Policy
http://www.fda.gov/ora/compliance_ref/rpm_new2/rpm10aip.html

Recommended Links:

Office of Compliance - Bioresearch Monitoring Program
http://www.fda.gov/cdrh/comp/bimogen.html

Bioresearch Monitoring (BIMO) Reengineering
http://www.fda.gov/cdrh/comp/bimoteam.html

Office of Regulatory Affairs - Compliance References: Bioresearch Monitoring (BIMO)
http://www.fda.gov/ora/compliance_ref/bimo/default.htm

FDA/Office of Regulatory Affairs
Application Integrity Policy Information
http://www.fda.gov/ora/compliance_ref/aip_page.html

Disqualification of Clinical Investigators

Disqualification Proceedings

If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the IDE, Informed Consent, or IRB requirements under 21 CFR 812, 21 CFR 50, or 21 CFR 56, or has repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report, FDA will provide the investigator written notice of the matter under complaint and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered from the investigator and accepted, the disqualification process will be terminated. If an explanation is offered but not accepted, the investigator will be given an opportunity for a regulatory hearing under 21 CFR 16 on the question of whether the investigator is entitled to receive investigational devices.

After evaluating all available information, including any explanation presented by the investigator, if FDA determines that the investigator has repeatedly or deliberately failed to comply with the requirements, or has deliberately or repeatedly submitted false information either to the sponsor of the investigation or in any required report, the FDA will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing IRB that the investigator is not entitled to receive investigational devices. The notification will provide a statement of the basis for such determination.

An investigator who has been determined to be ineligible to receive investigational devices may be reinstated as eligible when FDA determines that the investigator has presented adequate assurances that the investigator will employ investigational devices solely in compliance with the IDE and related regulations.

Review of IDE and Marketing Applications

Each investigational device exemption (IDE) and each cleared 510(k) or approved PMA application submitted that contains data reported by an investigator who has been determined to be ineligible to receive investigational devices will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval or clearance of any marketing application.

FDA will eliminate the unreliable data submitted by the investigator from consideration and review the remaining data. If FDA determines that the remaining data are inadequate to support a conclusion that it is reasonably safe to continue the investigation under IDE, FDA will notify the sponsor who will have an opportunity for a regulatory hearing. If a danger to the public health exists, however, FDA will terminate the IDE immediately and notify the sponsor and the reviewing IRB of the determination. In such a case, the sponsor will have an opportunity for a regulatory hearing before FDA on the question of whether the IDE should be reinstated. If FDA determines from the remaining data that the continued 510(k) clearance or PMA approval of the marketing application for which the data were submitted cannot be justified, FDA will proceed to withdraw approval or rescind clearance of the medical device.

References:

§ 812.119

FDA Debarment List
http://www.fda.gov/ora/compliance_ref/debar/default.htm

Disqualified/Restricted/Assurances List For Clinical Investigators
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Public Health Service Administrative Actions Listing (Note: This is not an FDA document.)
http://silk.nih.gov/public/cbz1bje.@www.orilist.html

Last modified date: July 21, 2003

Import and Export of Investigational Devices

Import

A person who imports or offers to import an investigational device shall be considered an agent for the foreign exporter and shall either act as the sponsor of the clinical investigation or ensure that another person acts as the agent and the sponsor of the investigation. That is, the sponsor of an IDE MUST be located in the United States. See "Responsiblities for Sponsors" for further information. Any investigational device imported into the U.S. must be labeled and used in accordance with FDA regulations.

Export

FDA has jurisdiction over the export of unapproved devices exported for use in foreign studies. Please note that FDA does not have jurisdiction over the manner in which the investigational study is conducted outside the U.S. and an IDE is not necessary for a study conducted entirely at foreign sites. However, FDA has authority to accept or deny data that has been collected during a study at a foreign site that is submitted to support a research or marketing application. (See Frequently Asked Questions for more information on FDA acceptance of foreign data.)

Export of an investigational device is subject to the provisions set forth in sections 801(e) and 802 of the FD&C Act. The export of investigational medical devices follows a two tiered system depending on the country to which the device is exported. Products may be exported under 802 of the Act to tier one countries or under 801(e) of the Act to non-tier one countries. Under 801(e), it may be necessary to obtain FDA approval prior to export.

Tier one countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa or member countries the European Union or of the European Economic Area (EEA) (Export under 802 of the FD&C Act)

An unapproved device intended for investigational use may be exported to ***Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa or member countries the European Union or of the European Economic Area (EEA)*** without FDA authorization if the unapproved device is exported in accordance with the laws of that country. Devices being exported to these countries are not required to meet the requirements of the IDE regulation. No notification to FDA is required; however, under section 802 of the FD&C Act these devices;

- must meet the requirements of section 801(e)(1), that is, the device,
  - must be in compliance with the specifications of the foreign purchaser,
  - must not be in conflict with the laws of the country to which it is intended for export,
  - must be labeled on the outside of the shipping package that it is intended for export,
  - must not be sold or offered for sale in U.S. commerce,
- must be manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practice requirements or meet international standards as certified by an international standards organization,
- cannot be adulterated other than by lack of marketing approval,

- cannot present an imminent hazard to the public health, and
- must be labeled and promoted in accordance with the requirements and conditions for use in the country in which the device is intended for export.

Certificate of Exportability

Even though the FDA does not require a firm to obtain written permission prior to export, a firm may find itself in a situation where a foreign purchaser requests proof of compliance with U.S. law prior to export. The FDA will provide a Certificate of Exportability (COE) under section 802 to facilitate export of a medical device under section 802.

Non-tier one countries – Export under 801(e)(2) of the FD&C Act

Medical devices for investigational use to countries other than those identified above requires that the device meet the requirements of 801(e) of the act. That is, the device must meet the requirements of 801(e)(1) of the act (noted above) and the exportation must be authorized by the FDA. The exporter must submit information to FDA that would enable the agency to determine that exportation is not contrary to the public health or safety and that the foreign country approves of the exportation.

In order for FDA to make the determination that export is not contrary to the public health and safety, manufacturers are required to submit with their export requests basic data regarding the safety of the device.

There are two circumstances in which FDA does not recommend the submission of safety data with an export request:

- the device has an FDA-approved investigational device exemption (IDE) and will be marketed or used for clinical trials in the importing country for the same intended use; or

- the manufacturer has been informed by an Institutional Review Board (IRB) in the U.S. that the device is a non-significant risk device and the device will be marketed or used for clinical trials in the importing country for the same intended use.

To determine whether exportation of the device has approval of the country to which it is intended for export, a letter from the foreign country approving importation is required. Official foreign government liaisons are contained in the CDRH Foreign Liaison Listing. If the manufacturer is exporting to a country within the European Economic Area (EEA) a device that has been awarded the "CE mark," FDA will accept documentation of the "CE mark" in lieu of a letter from the foreign government approving importation.

To obtain FDA's approval to export investigational devices to these countries, a

request that includes the following information must be submitted to FDA:

- A complete description of the device intended for export;
- The status of the device in the U.S. e.g., whether it is investigational, banned, etc.; and
- A letter from the appropriate foreign liaison (person with authority to sign a letter of acceptance for the foreign government identified in the CDRH Foreign Liaison Listing), which must be either in English or accompanied by a certified English translation, stating:
    - the device is not in conflict with the laws of the country to which it is intended for export;
    - the foreign government has full knowledge of the status of the device in the U.S.; and
    - import is permitted or there is no objection to the import of the product.

The requester should flag the request "Export Request" and send it, along with any questions concerning the export of medical devices to:

Food and Drug Administration
Center for Devices and Radiological health
Office of Compliance
Information Processing and Office Automation Branch (HFZ-307)
2094 Gaither Road
Rockville, Maryland 20850
Telephone Number (301) 827-4555

Please note that in addition to medical devices exported for use in investigational studies, any unapproved Class III device which is not authorized for distribution in a tier one country may not be exported to a non tier-one country under any circumstances without first obtaining permission from FDA through a request for export under 802(e)(2).

Recordkeeping Requirements for All Exported Investigational Devices

The exporter must maintain records of all devices exported and the countries to which they were exported. FDA has proposed in a *Federal Register* notice dated April 2, 1999, "Exports: Notification and Recordkeeping Requirements," that these records include the product's name, type of device, consignee name and address, date and quantity exported. In addition, the exporter must maintain documentation that the device meets the requirements of section

801(e)(1). FDA has proposed that these records be maintained at least 5 years after date of exportation.

References

§ 812.18

The FDA Export Reform and Enhancement Act of 1996/Export Certification Package including "Instructions for Requests for Certificate to Foreign Governments", Facts-On-Demand #865. Instructions for obtaining documents through the F-O-D automatic fax back service are available at
http://www.fda.gov/cdrh/dsma/fod.html.

Device Advice "Exporting Medical Devices"
http://www.fda.gov/cdrh/devadvice/39.html.

Last modified date 01/02/2002

Frequently Asked Questions

Adverse Events

If my device has been approved and marketed in a foreign country and I am conducting clinical trials in the U.S., should I report an adverse event from the U.S. trial under the IDE program or the Medical Device Reporting (MDR) program?

If your device is not marketed in the U.S., you should report an adverse event under the IDE program (812.150). The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

If the adverse event occurs in a foreign country in which it is legally marketed and not under the control of a clinical study, the adverse event should be discussed in the IDE progress report since the adverse information may affect risk analysis.

The adverse event should not be reported under the MDR program because the MDR program only applies to medical devices that are legally marketed in the U.S.

My device is marketed in the U.S. I am conducting a clinical trial in the U.S. for the same device, but for a different indication for use, should I report an adverse event under the IDE program or the MDR program?

Adverse events that occur in subjects enrolled in the clinical trial should be reported under the IDE program (812.150). The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of

the adverse effect.

Adverse events that occur in the U.S. but outside of the clinical trial would be reported through MDR; however, the adverse event should be discussed in the IDE progress report since the adverse information may affect risk analysis.

Clinical Investigator

Can a clinical investigator submit an IDE?

Yes, a clinical investigator can sponsor his/her own study in which case they are considered a sponsor-investigator and must comply with all the responsibilities of both the sponsor and investigator.

Does the clinical investigator need to sign form FDA-1572?

No, this is a form used for drug studies. For device studies, the sponsor should develop an investigators agreement which includes the elements of 21 CFR 812.43(c). The sponsor should have all investigators sign the agreement prior to participating in the study.

Confidentiality

Are IDE records released to the public?

FDA will not disclose the existence of an IDE unless:

- FDA determines that the information had been previously disclosed to the public;
- FDA approves a PMA for a device subject to an IDE; or
- a notice of completion of a Product Development Protocol (PDP) is in effect.

If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except for information on banned devices and a report of an adverse effect to an individual on whom an investigational device has been used. [(§812.38)]

Data or information contained in the file is not available for public disclosure before approval of an application for PMA or the effective date of a notice of completion of a PDP. Upon approval FDA will release a summary of the safety and effectiveness data on which the decision was based. Other disclosable information available after the device has been approved includes any protocol for a test or study, adverse reaction reports, and correspondence after confidential information has been deleted. Information available for public disclosure is outlined in 21 CFR 814 Premarket Approval of Medical Devices section §814.9.

Early Collaboration

Can I receive advice from FDA on pre-clinical testing and/or on my clinical protocol?

Yes. There are numerous guidance documents available from FDA that provide recommendations on the pre-clinical and clinical testing of devices. Additionally, FDA accepts pre-IDE submissions where you can submit

information to FDA and receive advice. This may include a pre-clinical testing plan and/or a draft clinical protocol. Additional information on pre-IDE submissions may be found in the documents "Goals and Initiatives for the IDE Program" http://www.fda.gov/cdrh/d951.html and "Pre-IDE Program: Issues and Answers" http://www.fda.gov/cdrh/ode/d99-1.html.

Additionally, there are two types of early collaboration meetings available that are discussed in "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)
http://www.fda.gov/cdrh/ode/guidance/310.html
http://www.fda.gov/cdrh/ode/guidance/310.pdf

FDA Contacts

I have questions about the IDE regulations. Who should I contact at FDA?

For general questions about the requirements of the IDE regulation, contact:

Division of Small Manufacturers, International and Consumer Assistance (HFZ-220)
Center for Devices and Radiological Health
1350 Piccard Dr.
Rockville, MD 20850-4314
Phone: 301-443-6597 or 800-638-2041
Fax: 301-443-8818
Email: dsma@cdrh.fda.gov

For specific questions regarding IDE policies or procedures for the review of IDE applications, contact:

IDE Staff
Investigational Device Exemptions Program (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850-3223
Telephone 301-594-1190

Foreign companies/studies

Can a foreign company submit an IDE/Is a U.S. Sponsor required?

A foreign company cannot sponsor an IDE; they must have a U.S. agent who acts as the sponsor (see 21 CFR 812.18(a)). The U.S. agent must fulfill all the responsibilities of a sponsor identified in the IDE regulation.

Do clinical studies have to be conducted in the U.S. / Will foreign studies be accepted?

Marketing applications may be based on data from studies conducted in other countries. All device studies conducted outside of the U.S. but approved under an Investigational Device Exemption (IDE) are governed by the FDAs IDE, Informed Consent, and IRB requirements. [21 CFR 812, 21 CFR 50, 21 CFR 56]

FDA will accept a foreign clinical study involving a medical device not conducted under an IDE only if the study conforms to whichever of the following provides greater protection of the human subjects:

- the ethical principles contained in the 1983 version of the Declaration of Helsinki http://www.fda.gov/oc/ohrt/irbs/helsinki83.html, or
- the laws and regulations of the country in which the research was conducted.

When foreign clinical data is used to support a marketing application, the applicant should ensure that the foreign data are applicable to the U.S. population and U.S. medical practice, that the clinical investigators have recognized competence, and that FDA can validate the data through an on-site inspection or other appropriate means, if necessary.

Additional information can be found in the following guidance documents:

Acceptance of Foreign Clinical Studies; Guidance for Industry
http://www.fda.gov/cder/guidance/fstud.htm
http://www.fda.gov/cder/guidance/fstud.pdf

IRB Information Sheets: Acceptance of Foreign Clinical Studies
http://www.fda.gov/oc/ohrt/irbs/toc4.html#foreign

Humanitarian Device Exemption

My device treats a disease in which only a small number of people are affected. Are there any provisions for these types of devices?

Yes. The Safe Medical Devices Act (SMDA) of 1990 provided for a humanitarian device exemption to encourage the discovery and use of devices that benefit fewer than 4,000 individuals in the U.S. This provision allows FDA to grant an exemption from the effectiveness requirements of sections 514 (Special Controls) and 515 (Premarket Approval) of the FD&C Act after finding that:

- the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals per year in the U.S.;
- the device is not available otherwise, and there is no comparable device available to treat or diagnose the disease or condition; and
- the device will not expose patients to unreasonable or significant risk, and the benefits to health from the use outweigh the risks.

Devices granted an exemption may only be used at facilities that have an established institutional review committee, and the humanitarian use must be approved by the committee before use begin.

Additional information on Humanitarian Use Devices can be found at http://www.fda.gov/cdrh/ode/hdeinfo.html.

In Vitro Diagnostic devices

Do the IDE regulations apply to in vitro diagnostic devices?

Many *in vitro* diagnostic (IVD) devices are exempt from the IDE regulations. Under section §812.2(c) of the IDE regulation, studies exempt from the IDE regulation include diagnostic devices if the testing:

1. is noninvasive;
2. does not require an invasive sampling procedure that presents significant risk;
3. does not by design or intention introduce energy into a subject; and
4. is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;

IVD devices that are under study, including IVD devices that are exempt from the IDE regulation, must comply with labeling requirements under 21 CFR 809.10(c)(2). One of two statements is required, as applicable for each case: "For Research Use Only. Not for use in diagnostic procedures", or "For Investigational Use Only. The performance characteristics of this product have not been established."

Studies which are exempt from the requirements of the IDE regulation are not exempt from the requirements for IRB review and approval under Part 56 and the requirements for obtaining informed consent under Part 50. In addition, IDE exempt studies are not exempt from §812.119, Disqualification of a clinical investigator.

For guidance regarding the applicability of these regulations with respect to investigations being conducted under the provisions of §812.2(c), contact the reviewing IRB and/or the IDE Staff at (301) 594-1190.

Additional guidance for *in vitro* diagnostic device studies can be found in "Regulating In Vitro Diagnostic Device (IVD) Studies." http://www.fda.gov/cdrh/comp/ivdreg.html

Institutional Review Board (IRB)

Where can I find an IRB?

The institutions where the study is to be conducted should be contacted to determine if they have their own IRB. If the study is conducted at a site that does not have its own IRB, the investigators should be queried to see if they are affiliated with an institution with an IRB that would be willing to act as the IRB for that site in the study. There are also independent/contract IRBs that can be contracted with to act as the IRB for a site. A list of IRBs is available from the IDE staff at 301-594-1190. (Please note: FDA does not approve or endorse any IRBs.) Additionally, an IRB can be established in accordance with 21 CFR 56. Additional information on IRBs is available in the FDA Information Sheets located at http://www.fda.gov/oc/ohrt/irbs/default.htm

Labeling

Are there special labeling requirements for investigational devices?

Yes. Under § 812.5 an investigational device or its immediate package must bear a label with the following information:

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents, if appropriate; and
- the statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

If the investigational device is used solely for research on laboratory animals, the label must contain the following statement: "CAUTION -- Device for investigational use in laboratory animals or other tests that do not involve human subjects."

The sponsor should provide detailed information on device labeling in the investigational plan. This information may vary depending on the device and the nature of the study. Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.

New Indication for Marketed Device

Do IDE regulations apply if the device has already been approved for a different indication for use?

Yes, the clinical study of a new indication for an already marketed device falls under the IDE regulation.

Promotion of Investigational Devices

Can I advertise my investigational device? What other restrictions apply?

Under § 812.7, a sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot:

- Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
- Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the sponsor must promptly terminate the investigation.
- Represent that an investigational device is safe or effective.

However, the sponsor may advertise for research subjects to solicit their participation in a study. Appropriate advertising methods include but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects

Advertisements should be reviewed and approved by the IRB to assure that it is not unduly coercive and does

not promise a certainty of cure beyond what is outlined in the consent and the protocol. No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection processes.

Additional guidance is available in the following guidance documents:

> "IRB Information Sheets - Recruiting for Study Subjects"
> http://www.fda.gov/oc/ohrt/irbs/toc4.html
>
> Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects
> http://www.fda.gov/cdrh/comp/2229.html
> http://www.fda.gov/cdrh/comp/2229.pdf

Reimbursement Policy

Will insurance cover my treatment with an investigational device?

In the past Medicare coverage was denied for devices which were under an IDE and had not yet received premarket notification clearance and/or premarket approval because the treatments were considered experimental. However, there are devices which are refinements of existing technologies or replications of existing technologies made by other manufacturers. Many of these devices are under an FDA-approved IDE as a means of gathering the scientific information needed for FDA to establish the safety and effectiveness of that particular device, even though there is evidence that the device type can be safe and effective.

On September 8, 1995, FDA entered into an agreement with the administrator of the Medicare program, the Health Care Finance Administration (HCFA), to provide information about devices under an IDE to aid in its reimbursement decisions. [Please note that HCFA is now know as the Centers for Medicare & Medicaid Services (CMS).] Under this agreement certain devices could be viewed as "reasonable and necessary" by Medicare and treatments could be covered if all other applicable Medicare coverage requirements are met. Specifically, FDA will place all IDEs it approves in one of two categories:

Category A - Experimental

The IDE involves innovative devices in which "absolute risk" has not been established (i.e., initial questions of safety and effectiveness have not been resolved and thus FDA is unsure whether the device type can be safe and effective)

Category B - Investigational; Non-experimental

The clinical investigations involves device types believed to be in classes I or II or device types believed to be in class III where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved). This category includes device types that can be safe and

effective because, for example, other manufacturers have obtained FDA approval for that device type. Nonsignificant risk studies may also be included in this category.

FDA provides the category determination on the IDE approval letter to the sponsor and also forwards this information to HCFA.

It is hoped that this agreement will provide Medicare beneficiaries with greater access to advances in medical technology and encourage clinical researchers to conduct high quality studies of newer technologies.

Please note that this agreement covers Medicare coverage only. FDA has no authority over commerical health insurance carriers. Many commercial health insurance carriers do not cover any investigational devices. It is advised that you check with your insurance company before you receive treatment with an investigational device.

For additional guidance, see "Implementation of the FDA/HCFA Interagency Agreement Regarding Reimbursement Categorization of Investigational Devices 9/15/95 (D95-2)" http://www.fda.gov/cdrh/d952.html

Significant/Nonsignificant Risk

Is my study significant risk or nonsignificant risk?

FDA has a guidance document to help explain how to determine whether a device study is significant or nonsignificant risk. It is located at http://www.fda.gov/oc/ohrt/irbs/devices.html#risk If the sponsor believes a device study is nonsignificant risk, the sponsor can provide information to the IRBs reviewing the study explaining why the device study does not pose a significant risk. If the IRBs agree and approve the study, the research may be conducted and FDA does not need to be notified. However, if an IRB determines the study is significant risk, the sponsor must notify FDA in writing (21 CFR 812.150(b)(9)). The study may not begin until FDA approves the study or provides a determination that the investigation is nonsignificant risk.

Statistical Guidance

How many subjects and sites do I have to include in the study?

The number of subjects and sites to include in a study depends on the study objectives and the study design needed to result in a statistically valid conclusion.

It is recommended that more than one site be included in order to provide assurance that study results are reproducible.

FDA has developed guidance documents to assist manufacturers in developing a statistically valid study.

- Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices http://www.fda.gov/cdrh/ode/ot476.html
- Perspectives on Clinical Studies for Medical Device Submissions (Statistical)-PDF http://www.fda.gov/cdrh/ode/78.pdf

Study sites

I am a patient. Where can I find a clinical study that will help me?

There is no centralized repository for information on device clinical trials. Your health care provider may be able to provide information. Hospitals associated with medical schools are often involved in research and institutions that are participating in clinical trials will sometimes place advertisements in newspapers or magazines to recruit subjects.

At this time, FDA does not maintain a clinical trials database for medical devices and our regulations do not permit us to release information regarding investigational devices. However, the National Institutes of Health maintains a clinical trials database for trials that they support. It may be accessed through the Internet: http://clinicaltrials.gov

Please remember that participating in a clinical trial may not help you. The safety and effectiveness of an investigational device is not known.

Waivers

Can the sponsor get a waiver from certain IDE requirements?

Under § 812.10, a sponsor may request FDA to waive any requirement of the IDE regulation. A waiver request with supporting documentation may be submitted as part of an application or separately. FDA may, by letter, grant a waiver of any requirement that is not required by the FD&C Act and that is unnecessary to protect the human subject by providing a letter to the sponsor outlining the waiver.

Example of an FDA letter granting a waiver for additional investigational sites: http://www.fda.gov/cdrh/manual/waiver.html

Last modified date: July 21, 2003

Related Topics

Pre-Clinical Studies and Good Laboratory Practices (GLP)

Overview

Good Laboratory Practices (GLP) under 21 CFR 58 applies to nonclinical laboratory studies (safety studies) that are intended to support applications for research and marketing permits including Investigational Device Exemption and Premarket Approval applications. Compliance with this part is intended to ensure the quality and integrity of safety data obtained from animal studies submitted to FDA.

If information on nonclinical laboratory studies is provided in the IDE application as part of the report of prior investigations, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58 must be provided. If any study was not conducted in compliance with the GLP regulations, a brief statement of the reason for the noncompliance must be provided. [§812.27]

Regulations

21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=58

References

7348.808 Good Laboratory Practice (Bioresearch Monitoring Office of Compliance Non-Clinical Laboratories)
http://www.fda.gov/ora/compliance_ref/bimo/7348_808/default.htm
http://www.fda.gov/ora/compliance_ref/bimo/7348_808/48-808.pdf (3.22 mb PDF version)

Quality System Design Controls

Devices approved under an investigational device exemption (IDE) are exempt from the Quality System (QS) regulation, except for the design control requirements under §820.30. However, the sponsor may state an intention to comply with other parts of the QS regulation. The extent to which the Quality System regulation will be followed in manufacturing the device must be documented in the sponsor's IDE records [§812.140(b)(4)(v)].

All manufacturers (or specification developers) of Class II and III devices, and Class I devices automated by computer software are required to follow design controls [§820.30] during the development of their device. A few Class I devices that are not automated by computer software are also subject to design controls. These devices are identified at 21 CFR § 820.30(a)(2)(ii).

The design control requirements are basic controls needed to ensure that the device being designed will perform as intended when produced for commercial distribution. Clinical evaluation is an important aspect of the design verification and validation process during the design and development of the device. Since most of the device design occurs prior to and during the IDE stage, it is necessary that manufacturers who intend to

commercially produce the device follow design control procedures. If a manufacturer were to wait until the IDE studies were complete, it would be too late to take advantage of the design control process, and the manufacturer would not be able to fulfill design control requirements of the quality system regulation for that device.

The manufacturer or specification developer must establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met. Design controls include establishing and maintaining plans that describe the design and development activities and also define responsibility for implementation. The plans must identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process.

Early in the design development process, design inputs or design requirements are identified. The design input should address topics such as user and patient needs, the intended use, performance characteristics, chemical and physical characteristics, safety, toxicity and biocompatibility, electromagnetic compatibility (EMC), reliability, regulatory requirements, historical data such as consumer complaints and MDRs, human factors, labeling and packaging, reliability, compatibility with accessories and auxiliary devices, compatibility with the environment of the intended use, risk analysis, voluntary standards, sterility, manufacturing processes, etc.

Although risk analysis is mentioned only in §820.30(g) Design validation, conducting risk analysis early in the design process enables designers to identify unreasonable risks and work to reduce or eliminate them during the early phases of design development. Conducting another risk analysis of the design toward the end of the design development process helps to identify any unreasonable risks that remain in the device or were introduced during design development.

Design reviews should be conducted periodically at major decision points during the design development process. Examples of major decision points are approval of the design input, completion of verification activities, and completion of validation activities. Design reviews are conducted to evaluate the adequacy of the design to meet requirements and also to identify problems with the design itself or the design process.

During the design process, the device design is verified and validated to assure that the design meets the users’ requirements. Design verification can be conducted at all stages and levels of design. Verification involves reviewing, inspecting, testing, checking, auditing or otherwise establishing whether or not components, subsystems, systems, the final device, processes, services, and documents conform to requirements or design inputs. Typical verification tests may include biocompatibility testing, risk analysis, package integrity testing, testing for conformance to standards, reliability testing, evaluating how well the product withstands sterilization, etc. Design validation ensures that the device meets the defined user needs and intended uses and includes testing of production units under simulated and/or actual use conditions. Clinical trials may be a part of the design validation process. Other methods of design validation include 510(k) historical database searches; literature searches; and review of labels, labeling, packaging, and other historical product information.

The IDE application is not required to include information regarding adherence to the design controls, and FDA does not inspect design controls during bioresearch monitoring inspections. However, procedures must be in place and documentation must be maintained in the design history file to demonstrate that the manufacturer is in compliance with the design control requirements of §820.30 and has carried out the activities identified in the design plan. The design history file must be made available for FDA inspection. FDA will evaluate the adequacy of manufacturers' compliance with design control requirements in pre-approval inspections for Class III devices and also during routine quality systems inspections for all classes of devices subject to design control.

References:

§ 820.1
§ 820.30
§812.20(b)(3)
§812.140(b)(4)(v)

Medical Device Quality Systems Manual: A Small Entity Compliance Guide; Chapter 3 Design Controls
http://www.fda.gov/cdrh/qsr/03desgn.html

Design Control Guidance for Medical Device Manufacturers
http://www.fda.gov/cdrh/comp/designgd.html
http://www.fda.gov/cdrh/comp/designgd.pdf

Do It By Design - An Introduction to Human Factors in Medical Devices
http://www.fda.gov/cdrh/humfac/doit.html
http://www.fda.gov/cdrh/humfac/doitpdf.pdf

Human Factors Points to Consider for IDE Devices
http://www.fda.gov/cdrh/humfac/ide_hf.html
http://www.fda.gov/cdrh/humfac/ide_hf.pdf

Device Use Safety: Incorporating Human Factors in Risk Management
http://www.fda.gov/cdrh/humfac/1497.html
http://www.fda.gov/cdrh/humfac/1497.pdf

Human Factors Principles for Medical Device Labeling
http://www.fda.gov/cdrh/dsma/227.html

Human Factors

Medical devices are used in many environments and often under adverse operating conditions. These issues affect the nature and complexity of the user interface. The interaction of the user's capabilities, the operating environment, and device user interface will determine the extent to which a device is used safely and effectively.

The QS regulation requires manufacturers to address the user interface of the equipment during device design and development. The user interface includes all aspects of a device (including its labeling) that users see, feel and hear when operating the device.

The user interface needs of health professionals and lay or untrained users of medical devices are addressed in design input and are confirmed through design validation during the IDE stage of development.

"Human factors" is the study of the interaction of people and machines to ensure the safety and effectiveness of that interaction. The discipline encompasses various methods used to improve human/equipment compatibility, including the user interface, user instructions, and training programs to avoid user error. Human factors consideration is critical to ensuring proper design and is best done by systematic consideration of human factors in the development of the device user interface.

References:

Human Factors Points to Consider for IDE Devices
http://www.fda.gov/cdrh/humfac/ide_hf.html
http://www.fda.gov/cdrh/humfac/ide_hf.pdf

Device Use Safety: Incorporating Human Factors in Risk Management
http://www.fda.gov/cdrh/humfac/1497.html
http://www.fda.gov/cdrh/humfac/1497.pdf

Human Factors Principles for Medical Device Labeling
http://www.fda.gov/cdrh/dsma/227.html

Recommended Link

Human Factors Program
http://www.fda.gov/cdrh/humanfactors.html

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Regulations

21 CFR 812 - Investigational Device Exemptions
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=812

21 CFR 50 - Protection of Human Subjects
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=50

21 CFR 56 - Institutional Review Boards
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=56

21 CFR 54 - Financial Disclosure by Clinical Investigators
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=54

21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=58

21 CFR 820 - Quality System Regulation
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=820

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Clinical Trials and IDE Guidance Documents

A Device Clinical Trials Data Bank - Public Health Need and Impact on Industry; A Report to Congress (11/01/1999)
http://www.fda.gov/cdrh/modact/113b.html
http://www.fda.gov/cdrh/modact/113(b)final.pdf

Acceptance of Foreign Clinical Studies; Guidance for Industry (03/13/2001)
http://www.fda.gov/cder/guidance/fstud.htm
http://www.fda.gov/cder/guidance/fstud.pdf

Accountability Analysis for Clinical Studies for Ophthalmic Devices; Draft (08/04/1999)
http://www.fda.gov/cdrh/ode/1350.html
http://www.fda.gov/cdrh/ode/1350.pdf

Bioresearch Monitoring Agreement for PMAs and PDPs (02/23/1998)
http://www.fda.gov/cdrh/ode/p98-1.html

Center for Devices and Radiological Health's Investigational Device Exemption (IDE) Refuse to Accept Policy (06/30/1993)
http://www.fda.gov/cdrh/ode/4859.pdf

Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff (05/29/2001)
http://www.fda.gov/cdrh/ode/guidance/1337.html
http://www.fda.gov/cdrh/ode/guidance/1337.pdf

Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers [excimer] (10/10/1996)
http://www.fda.gov/cdrh/ode/2093.html
http://www.fda.gov/cdrh/ode/2093.pdf

Computerized Systems Used in Clinical Trials (04/01/1999)
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.pdf

Continued Access to Investigational Devices During PMA Preparation and Review (Blue Book Memo) (D96-1) (07/15/1996)
http://www.fda.gov/cdrh/d961.html

Discussion Points for Expansion of the 'Checklist of Information Usually Submitted in an Investigational Device Exemption (IDE) Application for Refractive Surgery Lasers' Draft Document (09/05/1997)
http://www.fda.gov/cdrh/ode/rslaschk.html
http://www.fda.gov/cdrh/ode/rslaschk.pdf

Disqualified/Restricted/Assurances List For Clinical Investigators
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Draft Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees (11/16/2001)
http://www.fda.gov/cber/gdlns/clindatmon.htm
http://www.fda.gov/cber/gdlns/clindatmon.pdf

Draft Intravascular Brachytherapy - Guidance for Data to be Submitted to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications (05/24/1996)
http://www.fda.gov/cdrh/ode/955.pdf

Draft Version Cardiac Ablation Preliminary Guidance (Data to be Submitted to the FDA in Support Investigation Device Exemption Application (03/01/1995)
http://www.fda.gov/cdrh/ode/619.pdf

Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff (02/28/2001)
http://www.fda.gov/cdrh/ode/guidance/310.html
http://www.fda.gov/cdrh/ode/guidance/310.pdf

FDA Guidelines for Multifocal Intraocular Lens IDE Studies and PMAs (05/29/1997)
http://www.fda.gov/cdrh/ode/iolmulti.pdf

Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigations FDA Form 3454
http://forms.psc.gov/forms/FDA/fda3454.pdf

Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455
http://forms.psc.gov/forms/FDA/fda3455.pdf

Format for IDE Progress Reports (06/01/1996)
http://www.fda.gov/cdrh//manual/idemanul.html

Goals and Initiatives for the IDE Program #D95-1 (blue book memo) (07/12/1995)
http://www.fda.gov/cdrh/d951.html

Guidance Document for the Preparation of IDEs for Spinal Systems (01/13/2000)
http://www.fda.gov/cdrh/ode/87.html
http://www.fda.gov/cdrh/ode/87.pdf

Guidance for Industry: Financial Disclosure by Clinical Investigators (03/20/2001)
http://www.fda.gov/oc/guidance/financialdis.html

Guidance for Industry; Collection of Race and Ethnicity Data in Clinical Trials (Draft Guidance) (01/23/2003)
http://www.fda.gov/cder/guidance/5054dft.pdf

Guidance for Investigational Device Exemptions for Solutions for Hypothermic Flushing, Transport, and Storage of Organs for Transplantation; Final Guidance for Industry and FDA Reviewers (01/16/2001)
http://www.fda.gov/cdrh/ode/guidance/1164.html
http://www.fda.gov/cdrh/ode/guidance/1164.pdf

Guidance on IDE Policies and Procedures; Final (01/20/1998)
http://www.fda.gov/cdrh/ode/idepolcy.html
http://www.fda.gov/cdrh/ode/idepolcy.pdf

Guideline for the Monitoring of Clinical Investigations (01/01/1988)
http://www.fda.gov/cdrh/manual/monitor.html
http://www.fda.gov/cdrh/ode/428.pdf

Human Factors Points to Consider for IDE Devices (01/17/1997)
http://www.fda.gov/cdrh/humfac/ide_hf.html
http://www.fda.gov/cdrh/humfac/ide_hf.pdf

IDE Refuse to Accept Procedures #D94-1 (blue book memo) (05/20/1994)
http://www.fda.gov/cdrh/d941.html

Implementation of the FDA/HCFA Interagency Agreement Regarding Reimbursement Categorization of Investigational Devices, Att. A Interagency Agreement, Att. B Criteria for Catergorization of Investigational Devices, & Att. C -List #D95-2 (blue book memo) (09/15/1995)
http://www.fda.gov/cdrh/d952.html

Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators (04/06/1998)
http://www.fda.gov/oc/ohrt/irbs/default.htm

Integrity of Data and Information Submitted to ODE #I91-2 (blue book memo) (05/29/1991)
http://www.fda.gov/cdrh/i91-2.html

Investigational Device Exemption (IDE) Study Enrollment for Cardiac Ablation of Typical Atrial Flutter; Final Guidance for Industry and FDA Reviewers (11/08/2000)
http://www.fda.gov/cdrh/ode/guidance/1199.html
http://www.fda.gov/cdrh/ode/guidance/1199.pdf

Investigational Device Exemptions [IDE] Manual (FDA 96-4159)\DSMICA (06/01/1996)
http://www.fda.gov/cdrh/manual/idemanul.html
http://www.fda.gov/cdrh/manual/idemanul.pdf

Investigators' Responsibilities For Significant Risk Device Investigations (11/01/1995)

http://www.fda.gov/cdrh/manual/invest.html

New IDE / PMA Development and Review Model and Pilots
http://www.fda.gov/cdrh/pmat/pmathome.html

Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1
http://www.fda.gov/cdrh/ode/d99-1.html
http://www.fda.gov/cdrh/ode/d99-1.pdf

Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (03/19/1999)
http://www.fda.gov/cdrh/comp/2229.html
http://www.fda.gov/cdrh/comp/2229.pdf

Refractive Implants: Guidance for Investigational Device Exemptions (IDE) and Premarket Approval (PMA) Applications; Draft (08/01/2000)
http://www.fda.gov/cdrh/ode/guidance/1145.html
Http://www.fda.gov/cdrh/ode/guidance/1145.pdf

Regulating In Vitro Diagnostic Device (IVD) Studies (12/17/1999)
http://www.fda.gov/cdrh/comp/ivdreg.html
http://www.fda.gov/cdrh/comp/ivdreg.pdf

Review of IDEs for Feasibility Studies #D89-1 (blue book memo) (05/17/1989)
http://www.fda.gov/cdrh/d891.html

Significant Risk and Non-Significant Risk Medical Device Studies - D86-1 (10/01/1995)
http://www.fda.gov/cdrh/d861.html

Sponsor's Responsibilities For Significant Risk Device Investigations (11/01/1995)
http://www.fda.gov/cdrh/manual/sponsor.html

Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices (01/01/1996)
http://www.fda.gov/cdrh/ode/ot476.html

Suggested Content for Original IDE Application Cover Letter (02/27/1996)
http://www.fda.gov/cdrh/manual/idemanul.html

Waiver For Additional Investigational Sites (Excerpt from the IDE Form Letter to a Sponsor) (11/01/1995)
http://www.fda.gov/cdrh/manual/waiver.html

Links

CDRH Office of Compliance - Bioresearch Monitoring Program
http://www.fda.gov/cdrh/comp/bimogen.html

Office of Regulatory Affairs - Compliance References: Bioresearch Monitoring (BIMO)
http://www.fda.gov/ora/compliance_ref/bimo/default.htm

FDA Office of Good Clinical Practices
http://www.fda.gov/oc/gcp/

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