

Guidance on IDE Policies and Procedures

This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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Center for Devices and Radiological Health

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Comments and suggestions may be submitted at any time for Agency consideration to the IDE Staff, HFZ-403, Office of Device Evaluation, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact the IDE Staff at (301) 594-1190. This guidance replaces the guidance entitled, "Clarifications of IDE Policies and Procedures" (September 13, 1991).

Additional Copies: World Wide Web/CDRH home page :<http://www.fda.gov/cdrh> or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 882 when prompted for the document shelf number.

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IDE POLICIES AND PROCEDURES

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Chapter I *General IDE Policies*

This document is intended to provide guidance¹ to Office of Device Evaluation (ODE) reviewers on issues frequently encountered during the review of Investigational Device Exemptions (IDE) applications. In the first chapter of this document, general issues pertinent to the review of IDE applications are presented. This is followed by a discussion in Chapter II of several new regulations which affect the IDE Program. Finally in Chapter III, the four main mechanisms by which unapproved devices may be made available to patients faced with life-threatening or serious conditions are discussed.

In some cases, rather than repeating information that has been previously provided in ODE Blue Book Memoranda or other guidances, only summary information is presented. Whenever possible, however, specific procedures to be followed are identified, including references to appropriate ODE Blue Book Memoranda and IDE boilerplate letters.

Pre-IDE Process

In order to facilitate the initiation of clinical trials under the IDE regulation, the Food and Drug Administration (FDA) encourages sponsors to begin communicating with the ODE reviewing division prior to the submission of the original IDE application. This communication may take the form of a “Pre-IDE” meeting and/or a “Pre-IDE” submission.

Pre-IDE Meetings

Two types of pre-IDE meetings are possible: meetings in which FDA provides “informal guidance” and meetings where FDA provides “formal guidance” as provided for in Section 201 of the FDA Modernization Act of 1997.

“Informal Guidance” Meetings

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. Regardless of the form of the pre-IDE meeting, all meetings should be recorded by the ODE reviewing division and reported on a quarterly basis to ODE senior management. Minutes of the meeting should include the date of the meeting, the attendees, whether material was submitted prior to the meeting for

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discussion/review by ODE staff, a summary of the discussion, and any recommendations or guidance provided by FDA.

“Formal Guidance” Meetings

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). As required by the statute, 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 should be put in writing and made part of the administrative record by FDA.

Detailed procedures for implementing this new requirement will be issued in the near future.

Pre-IDE Submissions

Sponsors are encouraged to submit pre-IDE submissions to the ODE reviewing division while the sponsor is preparing a 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, or other information.

Pre-IDE submissions are logged into the pre-IDE tracking system by the Document Mail Center (DMC). After logging-in the document, the DMC will jacket the submission in a white folder, attach a tracking sheet, print an acknowledgment letter to the pre-IDE sponsor, and forward the submission and letter to the appropriate review division. The division should verify that the submission belongs in their division and, after signing the acknowledgment letter and placing a copy of it in the pre-IDE, mail the letter to the sponsor.

Upon completion of the review of the pre-IDE submission, the division is responsible for issuing 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 should be prepared. The division is responsible for ensuring that all memos, reviews, letters, etc. are included in the jacketed file copy for documentation. Upon completion of the review, the document should be returned to the DMC for filing.

See Blue Book Memorandum#D95-1, entitled, “Goals and Initiatives for the IDE Program” for additional guidance.

Interactive IDE Review

By communicating frequently with the regulated industry during the IDE review process, rather than only at the completion of the review, deficient information can be addressed within fewer review cycles. This is of significant benefit to both industry and ODE staff. Therefore, ODE reviewers, with the concurrence of their supervisors, should feel free to use the telephone or telefacsimile to aid in the interactive review process. Documentation of this communication should be included in the IDE record, and hardcopies of information transmitted by telefacsimile should be logged into the IDE database.

See Blue Book Memorandum #D95-1 for additional guidance on the interactive review process and the IDE Telefacsimile Policy.

Informed Consent Documents

As part of the IDE process, ODE staff reviews and approves sample informed consent documents (ICDs). The sample ICD should comply with 21 CFR 50 and be consistent with the approved protocol. When reviewing an ICD, reviewers should ensure that the eight basic elements identified in section 50.25(a) are adequately addressed, but should recognize that each reviewing IRB routinely modifies the language and format of the ICD to be consistent with their institution’s policies and requirements. Once FDA approves a sample ICD, the sponsor is responsible for ensuring that the ICD used at each participating institution includes the required informed consent elements. If the IRB requires significant changes in any of the required elements, the IDE sponsor should submit the modified ICD to FDA for review and approval before using the document at the institution. It is the sponsor’s responsibility to determine whether the changes warrant FDA review.

On occasion, after FDA has approved a sample ICD, the agency will receive a modified version of the document, along with certification of IRB approval. FDA should review the ICD to ensure that the document still conforms with Part 50. If the document no longer complies with the regulation, a letter should be issued acknowledging IRB approval and describing how the ICD deviates from the sample ICD already approved by FDA. The letter should also remind the sponsor of his/her obligation to ensure that each ICD conforms to the sample ICD already approved by FDA.

Extensions for Submitting Additional Information to an IDE

Under certain circumstances, FDA may require an IDE sponsor to submit additional information within an established time period. For example, an IDE sponsor is required to provide FDA with certain additional information within 45-days of the date of a conditional approval letter. An IDE

sponsor is also required to respond to FDA within 45-days of receiving notice of a deficient progress report.

If a sponsor is not able to provide the requested information within the established time period, a sponsor may request an extension of time. Such a request should be submitted to FDA in writing as an IDE supplement. FDA's approval of an extension request may be oral or in writing, depending on the length of time requested. FDA's approval of a request for up to 60 additional days may be oral, i.e., handled in a telephone conversation. If FDA's approval is oral, a memo of the conversation approving the request should be included in the IDE file. FDA's approval of a request for an extension of time beyond 60 days, however, should be in writing. Extensions of more than 60 days are normally granted for extenuating circumstances such as pre-clinical testing that cannot be completed within the established time frame, or when a United States (U.S.) sponsor cannot obtain the requested information from a foreign entity within the established time frame.

Monitoring of Clinical Investigations

The IDE regulation requires that the sponsor identify the name and address of the monitor and provide written monitoring procedures. While the IDE regulation does not specify the content of the written monitoring procedures, the agency has published a guideline (53 FR 4723, February 17, 1988) on acceptable approaches to monitoring clinical investigations involving FDA-regulated products. The Center for Devices and Radiological Health (CDRH) has identified the following procedures that sponsors should follow with respect to monitoring clinical investigations:

1. Submission of written monitoring procedures are not required for studies sponsored by a sponsor-investigator where only one investigator is involved in the study. It is assumed that the sole investigator will serve as the study monitor, unless otherwise specified. For these types of studies, adherence to the regulatory responsibilities for a sponsor and investigator are adequate to assure compliance with the IDE regulation, protection of subject's rights and safety, and data integrity.
2. Written monitoring procedures are required for all studies involving more than one investigator. If the sponsor does not identify the monitor's name and address, this should be identified as a deficiency in the IDE response letter. If an IDE application does not contain written monitoring procedures, or is in variance with the guideline, the following paragraph should be included as an advisory paragraph in the FDA response letter:

“Your application [does not include/includes only minimally acceptable] monitoring procedures. We have enclosed the FDA guideline (53 FR 4723, February 17, 1988) which presents acceptable approaches to monitoring clinical investigations. Your procedures may vary, but should be sufficient to assure the

protection of the rights and safety of the subjects involved in the clinical investigation and the quality and integrity of the resulting data.”

When FDA receives an IDE supplement requesting expansion of a study from a sole investigator at a single site to multiple investigators at either a single site or multiple sites, the reviewer should assure the adequacy of the monitoring procedures. In either situation, the reviewer should issue a deficiency letter if written monitoring procedures were not included or were not adequate in the IDE supplement.

Counting Investigational Sites in an IDE

ODE’s policy on counting investigational sites is as follows:

- Each institutional review board (IRB) counts as one site. For the majority of IDE studies, each participating institution has its own IRB. In these studies, each IRB is counted as one site.

For some IDE studies, however, participating institutions may not have their own IRBs. Instead, one IRB may have oversight responsibility for more than one participating institution. If the same investigator is conducting the study at each institution and the institutions are located in close proximity to the IRB, these institutions may be counted as one site. If, however, additional physicians are conducting the investigation and their use of the device is not under the immediate direction of the investigator, these physicians are considered investigators and these institutions are counted as additional sites even though the sites are under the same IRB.

NOTE: If one IRB assumes responsibility for more than one institution and the institutions are geographically separated, then each institution counts as one site. For example, if a California IRB has oversight of a study being conducted at both a California and New Jersey institution, this would count as two investigational sites.

- FDA does not have jurisdiction over institutions located outside of the U.S.; therefore, such sites are not counted in the site limit designated in the IDE approval letter.
- If an investigational site is terminated during the course of the clinical trial and no subjects were enrolled in the trial at that site, the site does not count towards the overall site limit. If, however, subjects were enrolled before termination, the site is counted towards the study site limit.

Clinical Study Sites Located Outside the United States

As stated above, FDA does not have jurisdiction over clinical study sites located outside the U.S. As a result, sponsors may proceed at those sites at their own discretion. FDA, however, encourages sponsors to follow a uniform protocol at the domestic and foreign investigational sites.

Although FDA does not have jurisdiction over clinical study sites located outside the U.S., FDA may accept, in support of a premarket approval application (PMA), the data generated from such sites. If the foreign clinical study was not conducted pursuant to the IDE regulation, the PMA regulation requires that the PMA applicant verify in the marketing application that the data generated from the foreign study site(s) are valid and that the investigators at the foreign site(s) conducted the study(ies) in accordance with the “Declaration of Helsinki” or the laws and regulations of the foreign country(ies), whichever afforded greater protection to the human subjects. If the country’s standards are used, the PMA applicant should state in detail any differences between the country’s standards and the “Declaration of Helsinki” and explain why the country’s standards afforded greater protection to the human subjects. (See 21 CFR 814.15)

Transfer of IDE Sponsorship

In order for FDA to acknowledge a transfer in sponsorship of an IDE, the following minimal information should be submitted by the former sponsor as an IDE supplement:

1. Identification of the new sponsor, including the new sponsor’s name and address, contact person, and telephone number;
2. Effective date of the transfer;
3. Certification that all relevant IDE records will be transferred to the new sponsor by the date the transfer takes effect; and
4. Information described below which is required to be submitted by the new sponsor.

The new sponsor should provide the former sponsor with the following minimal information for inclusion in the IDE supplement:

1. An agreement that the new sponsor will assume all sponsor responsibilities for the study; and
2. An agreement that the new sponsor will comply with any terms or outstanding conditions of approval of the investigation.

If a new sponsor is correctly identified and the required information is provided, FDA will acknowledge the change in sponsorship by issuing IDE boilerplate G-41. If the above referenced

minimal information has not been submitted, FDA will issue IDE boilerplate G-42 indicating that FDA is unable to acknowledge change of sponsorship.

In order to obtain complete documentation of the transfer of sponsorship, the following information is required to be submitted by the new sponsor. This information may be submitted in the original transfer of sponsorship request or it may be submitted after FDA acknowledges the transfer:

1. A statement that either there are no changes to the investigation caused by the transfer, or that the sponsor requests approval for specific changes to the investigational plan that may affect the scientific soundness of the investigation or the rights, safety, and welfare of the subjects (e.g., in areas of manufacturing, protocols, monitoring, informed consent, or labeling);
2. Acknowledgment that all investigators and participating IRBs have been, or will be, informed of the transfer by the effective date; and
3. Certification that the sponsor will not permit investigators to participate in the investigation until they have signed the investigator agreement.

It should be noted that the IDE regulation does not permit foreign entities to sponsor clinical studies in the U.S. (21 CFR 812.18(a)). Therefore, if a non-U.S. sponsor is identified as the new sponsor of the study, the supplement should be disapproved. Boilerplate letter G-42A should be used when disapproving a supplement under these circumstances.

United States Agents for Foreign Sponsors

As stated above, pursuant to 21 CFR 812.18(a), clinical studies conducted in the U.S. cannot be sponsored by foreign entities. Therefore, an IDE application cannot be approved in the absence of a U.S. sponsor. If an original IDE application is submitted from an entity outside the U.S., the application will be considered incomplete until a U.S. sponsor is identified. Similarly, if an IDE supplement is submitted for a proposed change in sponsorship to a foreign entity, the supplement will be disapproved. See boilerplate Letter G-42A.

Closing an IDE

The procedures for closing an IDE vary depending upon at what point in the process the decision to close the IDE occurs. If FDA has not yet approved the IDE, the sponsor may simply request to withdraw their IDE from FDA review. If the sponsor submits such a request, FDA will acknowledge the request by issuing boilerplate G-39 and the IDE will then be considered closed. After this point, if the sponsor decides to pursue an investigation of the device, a new IDE would need to be submitted; however, the closed IDE may be referenced in the new application.

If FDA has approved the IDE but no subjects have been enrolled, the sponsor may still request withdrawal of their IDE. In this case, however, the sponsor should state that no subjects had been enrolled and account for all devices (i.e., state that no devices were shipped or that all shipped devices have been returned, destroyed or otherwise disabled).

Once subjects have been enrolled in the study, the sponsor should not terminate the IDE until all enrolled subjects have completed follow-up in accordance with the approved investigational plan. The sponsor may cease enrollment in the study, but complete follow-up should be obtained for all subjects already entered into the study. Boilerplate G-35 may be used to acknowledge termination of subject enrollment. This letter reminds the sponsor of the need to follow all subjects in accordance with the investigational plan.

When follow-up is complete for all enrolled subjects, the sponsor should submit a final report to FDA and all reviewing IRBs within six months. The ODE Guidance entitled “Suggested Format for IDE Final Report” outlines the information that should be included in a final report. Boilerplate G-33 acknowledges termination of the study and submission of the final report and closes the IDE. Boilerplate G-34 is used when the final report is inadequate and additional information is requested. The IDE is not officially closed until the final report is complete. It should be noted that the sponsor may reference a PMA or 510(k) application to fulfill the IDE requirement for submitting a final report. If the PMA or 510(k) application contains a summary of the progress of the device investigation, the sponsor may submit a letter to FDA stating that a marketing application has been submitted and where the progress report can be located in the marketing application (i.e., PMA or 510(k) number, date of submission, volume and pages).

Withdrawing Approval of an IDE

The bases for withdrawal of approval of an IDE are listed in 21 CFR 812.30(b). Due to the seriousness of this regulatory action, ODE senior management and the IDE staff should be involved at the earliest stages of consideration of this action. If it is believed that withdrawal of approval of an IDE should be considered, it should be ensured that the following actions precede the actual issuance of a proposal to withdraw approval of the IDE application:

1. The reviewing division should have issued letters to the sponsor identifying the agency’s issues of concern. In these letters, the division should reference or include copies of any inspections or other information that is being used to support FDA’s position.
2. Involvement of the Office of Compliance should have been requested, if needed (see section “SOPs for BIMO and IDE Staff Interactions”). OC will have issued warning letter(s) to the sponsor, in accordance with their procedures, identifying issues that need to be addressed.
3. ODE should consider whether a meeting with the sponsor will help to rectify the Agency’s concerns.

If, after following the above procedures, the sponsor does not provide a satisfactory response and it is determined that no other regulatory mechanism will bring the sponsor into compliance with the regulations, the reviewing division should draft a proposal to withdraw approval of the IDE application. Note: This determination is made by the reviewing division, IDE Staff and ODE senior management. When issuing such a proposal, boilerplate G-30, Proposing Withdrawal of Approval of an IDE Application, should be used. As stated in 21 CFR 812.30(c)(2), the proposal should include a complete discussion of the reasons for this action. In accordance with this section, an IDE sponsor has the right to request a regulatory hearing under Part 16, but should do so within 10 working days of receipt of FDA's letter. If a hearing is not requested, the sponsor has 30 days in which to respond to the letter with their corrective action plan.

If the IDE sponsor does not request a regulatory hearing and the sponsor's response to the proposed withdrawal letter does not provide reasonable assurance that the corrective actions will rectify the situation, FDA may proceed with the final order withdrawing approval of the IDE. As with the proposal, the final order should include a complete statement of the reasons for withdrawal. When issuing a final order, boilerplate G-30A, Final Order Withdrawing Approval of an IDE Application, should be used.

SOPs for BIMO and IDE Staff Interactions

In the Fall of 1993, the IDE Staff and the division of Bioresearch Monitoring (BIMO) agreed that the development of standard operating procedures (SOPs) would help to maintain efficient and effective communication between the two staffs and reduce the likelihood of inconsistent actions by the two offices.

The ODE reviewing division should inform BIMO, by means of a memo through the IDE staff, whenever the division:

1. Becomes aware of questionable practices by an investigator;
2. Takes action on an IDE based on recommendations from BIMO or FDA field investigators; or
3. Is considering withdrawing approval of an IDE application.

See November 12, 1993, memo regarding SOPs for BIMO and IDE Staff Interactions for further guidance.

Exporting Unapproved Medical Devices

Exporting for Investigational Use

A manufacturer who wishes to export an unapproved device for investigational use may export the device under section 801(e)(2) or 802(c) of the act, depending on where, i.e., to what country, the device is being exported. For instance, pursuant to section 801(e)(2) of the act, an unapproved device intended for investigational use may be exported to ***any country***, if, in addition to meeting the requirements of 801(e)(1) of the act, the exporter submits 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.

Section 801(e)(1) of the act provides that a device intended for export should meet the following requirements: (1) complies with the laws of the foreign country; (2) meets the foreign purchaser's specifications; (3) is labeled for export on the shipping carton; and (4) is not sold or offered for sale in domestic commerce.

Alternatively, in accordance with section 802(c) of the act, an unapproved device intended for investigational use may be exported to ***Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa or member countries 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 under 802(c) are not required to meet the requirements of the IDE regulation, however, compliance with the basic export requirements of 802(f) of the act and the recordkeeping requirements in 802(g) of the act is required. As explained above, exportation of an unapproved device for investigational use to any country other than the countries identified above should be authorized by FDA.

Exporting for Marketing or in Anticipation of Foreign Marketing Approval

Manufacturers who wish to export unapproved medical devices either for marketing or in anticipation of marketing approval by a foreign entity, should consult with the Import/Export Staff, Office of Compliance at (301) 594-4699.

Chapter II

Regulations Affecting the IDE Program

This chapter summarizes the provisions of several new regulations that affect the IDE Program. Guidance is available for Medicare coverage of certain investigational devices (see below). In other cases, guidance is being developed and will be issued in the near future.

Medicare Program; Criteria and Procedures for Extending Coverage to Certain Devices and Related Services

In the **Federal Register** of September 19, 1995 (60 FR 48417), the Health Care Financing Administration (HCFA) announced that it would consider for Medicare coverage certain devices with an FDA-approved IDE that have been categorized as nonexperimental/investigational. For the purposes of consideration for reimbursement under the Medicare program, FDA categorized all FDA-approved IDEs into either Category A (experimental) or Category B (nonexperimental/investigational). Only those IDEs placed in Category B by FDA would be eligible for Medicare coverage consideration. The final coverage decision, however, will encompass other factors and thus will be made by HCFA

As discussed in the FDA/HCFA Interagency Agreement, an experimental (Category A) device refers to an innovative device believed to be in Class III for which “absolute risk” of the device type has not been established; i.e., initial questions of safety and effectiveness have not been resolved, and FDA is unsure whether the device type can be safe and effective. A nonexperimental/investigational (Category B) device refers to a device believed to be in Class I or II, or a device believed to be in Class III for which the incremental risk is the primary risk in question; i.e., underlying questions of safety and effectiveness of the device type have been resolved, or it is known that the device type can be safe and effective because, e.g., other manufacturers have obtained FDA approval of that device type.

For those IDEs that are either approved or conditionally approved, a HCFA categorization determination should be included in the IDE letter to the sponsor. When determining the proper categorization for an approved IDE, the reviewer should utilize the categorization checklist found in IDE Boilerplate H-1. When a reviewer determines that an IDE should be placed in Category A, the reviewer shall obtain concurrence from his/her branch chief and the IDE Staff. Alternatively, when a reviewer determines that an IDE should be placed in Category B, concurrence from only the branch chief is required.

The Health Care Financing Administration is to be copied on all approval and conditional approval letters. The Document Mail Center is responsible for ensuring that HCFA receives copies of all such letters. In addition, new boilerplates have been developed for reviewer use. These boilerplates are the HCFA Reimbursement Checklist (H-1), described above; Reconsideration of HCFA Category Determination (H-2); and Change of HCFA Reimbursement Category (H-3). The latter two boilerplates should be used when responding to a sponsor’s

request for reconsideration of a HCFA categorization determination or when revising the original HCFA categorization determination due to new information or approval of a similar device, respectively.

For further guidance, see ODE Blue Book Memo #D95-2 entitled, “Implementation of the FDA/HCFA Interagency Agreement Regarding Reimbursement Categorization of Investigational Devices.”

Emergency Research: Waiver of Informed Consent

Provisions of the Regulation

In the **Federal Register** of October 2, 1996 (61 FR 51498), FDA issued a final rule amending its informed consent regulation to harmonize with the Department of Health and Human Services’ (DHHS) policies on emergency research and to clarify when such research can proceed without obtaining an individual subject’s informed consent. The purpose of the final rule is to permit the study of potential improvements in the treatment of life-threatening conditions where current treatment is unproven or unsatisfactory, in order to improve interventions and patient outcomes. The final rule was effective November 1, 1996.

FDA recognizes that persons with life-threatening conditions who cannot either give informed consent or refuse enrollment are a vulnerable population. The lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of emergency care research. Therefore, the exception from the informed consent requirement permitted by the final rule is conditioned upon documented findings by an institutional review board (IRB).

According to 21 CFR 50.24(a), an IRB may approve a clinical investigation involving critical care research without requiring that informed consent of the research subjects be prospectively 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. Prospective subjects are in a life-threatening situation (diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted); available treatments are unproven or unsatisfactory; and collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention;
2. Informed consent is not feasible because the subject cannot consent due to their medical condition, the intervention under investigation must be administered before consent from the subject’s legally authorized representative is feasible, and subjects likely to be eligible for participation in the clinical investigation cannot be prospectively identified;

3. Participation in the research may directly benefit the subject because subjects are facing a life-threatening situation that necessitates intervention; appropriate animal and other preclinical studies have been conducted and the information derived from those studies and related evidence support the potential of providing a direct benefit to individual subjects; and the risks and benefits of the experimental treatment are reasonable compared to those associated with the patient's medical condition and standard therapy;
4. The clinical investigation could not practicably be carried out without the waiver of informed consent; (If scientifically sound research can be practicably carried out using only consenting subjects or legally authorized representatives, then the research should be conducted without involving nonconsenting subjects);
5. The investigator has committed to attempt to contact a legally authorized representative for each subject within the clinical investigation's therapeutic window and, if feasible, ask for consent within that window rather than proceeding without consent; and
6. The IRB has reviewed and approved informed consent procedures and an informed consent document for situations in which consent of a subject or a legally authorized representative is feasible.

Additional protections of the rights and welfare of the subjects include:

1. Consultation (which may include consultation carried out by the IRB itself) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn. Consultation could take place via newspapers, institutional newsletters, advertisements, local radio stations, meetings, etc.;
2. Prior to the initiation of the investigation, public disclosure to the communities in which the clinical investigation will be conducted of the possible risks and expected benefits (e.g., relevant information from investigator's brochure, the informed consent document, and investigational protocol);
3. Public disclosure of sufficient information following completion of the investigation to apprise the community and researchers of the results of the investigation;
4. Establishment of an independent data monitoring committee to exercise oversight of the investigation; and
5. If consent is not feasible and a legally authorized representative is not available, the investigator must provide an opportunity for a family member to object to the subject's participation in the investigation within the therapeutic window, if feasible.

The final rule applies to all clinical investigations involving an exception from the informed consent requirements. Such research should be performed under an investigational device exemption (IDE) that is submitted and reviewed by FDA. Protocols that include subjects who are unable to provide informed consent should be submitted in a new IDE application even if an IDE for the device already exists. The new application will need to reference the existing IDE, contain a protocol for the clinical investigation that includes a description of how the investigation proposes to meet the conditions of this regulation and contain only the study-specific information required by 21 CFR 812.20 and 812.25.

ODE Procedures

When an IDE application requesting a waiver from informed consent for emergency research is received in the review division, the reviewer should immediately notify the IDE staff that the division received such an application. The IDE Staff will assist the division with the review of the application to ensure that all applicable safeguards have been satisfied and that all of the criteria identified in the regulation (see above) have been adequately addressed before the application can be approved.

The reviewing division should note that the IDE tracking sheets include a field to indicate whether or not the original IDE application included a request for exception from informed consent. It is important that the division indicate on the tracking sheets if an exception from informed consent was requested, so that ODE can properly track these applications.

Finally, the regulation requires that the sponsor of the IDE submit certain information from the IRB concerning the public disclosure of the investigation to the community where the investigation is to take place. This information is to be submitted to the IDE and to Dockets Management (21 CFR 812.47(a)). The public may request this information by submitting a request under the Freedom of Information Act (21 CFR 812.38(b)(4)).

Further guidance on this regulation is under development by the Agency.

Dating of Informed Consent Documents

In the **Federal Register** of November 5, 1996 (61 FR 57277), FDA issued a final rule amending its informed consent regulation (21 CFR Part 50) to:

- Require that the consent form signed by the subject or the subject's legally authorized representative be dated by the subject or the subject's legally authorized representative at the time consent is given (Section 50.27(a)); and
- Clarify what adequate case histories include and to clarify that the case histories should document that informed consent was obtained prior to participation in the

study (Section 812.140(a)(3)). Under this new section of the regulation, case histories include “the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician; the individual’s hospital chart(s); and the nurses’ notes.”

Disqualification of Clinical Investigators

In the **Federal Register** of March 14, 1997 (62 FR 12087), FDA issued final provisions for the disqualification of clinical investigators. These provisions apply to all cleared or approved and pending device applications containing or relying upon clinical investigations performed by disqualified investigators. Such applications include IDEs, premarket notifications (510(k)s), and PMAs.

Pursuant to the final rule, clinical investigator disqualification proceedings may be initiated if FDA has information indicating that the investigator has: (1) repeatedly or deliberately failed to comply with the requirements of 21 CFR Parts 812, 50, or 56; or (2) repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report.

Upon disqualification, FDA shall examine each approved IDE and each cleared 510(k) or approved PMA containing data reported by an investigator who has been determined to be ineligible to receive investigational devices, i.e., disqualified. The purpose of this examination is to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the clearance/approval of the marketing application.

If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under 21 CFR Part 16. Furthermore, if the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the marketing application for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval or rescind clearance of the medical device in accordance with the applicable provisions of the act and the agency’s regulations.

The Division of Bioresearch Monitoring, OC is preparing a guidance document on this regulation.

Investigational Device Exemptions; Treatment Use

Treatment use of investigational devices is addressed by a new Treatment IDE regulation (21 CFR 812.36). This regulation parallels the Treatment IND regulation, and in so doing, facilitates

broader availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible. Under this new regulation, patients faced with a serious or life-threatening disease/condition for which no alternative device exists may receive investigational devices outside of the controlled clinical trial.

This regulation is discussed in detail in Chapter III under “Treatment Use of Investigational Devices.”

Section 201 of the FDA Modernization Act

Section 201 of the FDA Modernization Act of 1997 requires FDA, within one year of enactment of the new law, to establish regulations to provide procedures and conditions that would allow certain device or protocol changes to be made under an existing IDE without requiring FDA approval of a supplement. Changes that would be permitted without FDA approval are:

- (1) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in basic principles of operation and that are made in response to information gathered during the course of the investigation; and
- (2) changes or modifications to clinical protocols that do not affect:
 - (a) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;
 - (b) the scientific soundness of the investigational plan; or
 - (c) the rights, safety, or welfare of the human subjects involved in the investigation.

A change or modification as described above may be made if (i) the sponsor of the investigation determines, on the basis of credible information (to be defined by FDA) that the above applicable conditions are met; and (ii) the sponsor submits to FDA, not later than 5 days after making the change or modification, a notice of the change or modification.

The implementing regulation for this section of the law is currently under development.

Chapter III *Expanded Access to Unapproved Devices*

According to the statute and FDA regulations, an unapproved medical device may normally only be used on human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity, or to help a patient suffering from a serious disease or condition for which there exists no other alternative therapy. Below is a discussion of the four main mechanisms by which FDA may make unapproved devices available to patients/physicians faced with circumstances such as those described. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (See section 561 of the Federal Food, Drug, and Cosmetic Act). FDA plans to modify existing guidance in minor ways, as needed, to track the language in the new law.

Emergency Use of Unapproved Medical Devices

Procedures governing the emergency use of an investigational device are covered in two separate documents: the IDE regulation (21 CFR Part 812) and FDA's "Guidance for the Emergency Use of Unapproved Medical Devices," (hereinafter referred to as the Emergency Use Guidance) which appeared in the **Federal Register** of October 22, 1985 (50 FR 42866).

The IDE regulation recognizes that 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. Therefore, the regulation permits deviations from the investigational plan when necessary to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.35(a)). Prior approval for shipment or emergency use of the investigational device is not required, but the use should be reported to FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed (as discussed below), and patient outcome information.

In addition to the IDE regulation, emergency use is also addressed in an FDA guidance document. The Agency issued the Emergency Use Guidance because the IDE regulation does not address emergency use comprehensively (e.g., by not defining the term "emergency use," identifying the patient protection measures that should be followed in such situations, or addressing emergency use of devices not covered by an IDE). This guidance defines an unapproved medical device as a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e)(the act) or an approved IDE under section 520(g) of the act (21 U.S.C. 360j(g)). As discussed in the Guidance, an unapproved device should normally only be used in human subjects if it is approved for clinical testing under an IDE and if it is used by an investigator for the sponsor in accordance with the terms and conditions of the application.

Emergency use of an unapproved device, however, may also occur when: (i) an IDE for the device does not exist, (ii) when a physician wants to use the device in a way not approved under the IDE, or (iii) when a physician is not an investigator under the IDE.

The Emergency Use Guidance document was intended to address these *emergency* situations. As stipulated in the guidance, a physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that:

1. The patient has a life-threatening condition that needs immediate treatment.[†]
2. No generally acceptable alternative treatment for the condition exists; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

1. Informed consent from the patient or a legal representative;
2. Clearance from the institution as specified by their policies;
3. Concurrence of the IRB chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the IDE sponsor, if an approved IDE exists for the device.

Although not provided for under this guidance, often times a physician, who is faced with an emergency situation as described above, will contact FDA to discuss his/her patient's condition. In this situation, ODE acts in an advisory role, rather than in an approving role. The ODE employee who receives the call should discuss the emergency use criteria with the physician, but the responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician. If the physician decides to proceed with the emergency use of the device, the ODE employee should advise the physician of the above patient protection procedures to be followed before the emergency use occurs and fill out the Emergency Use Checklist. This checklist helps to ensure

[†] As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity. This is consistent with the new law.

that the criteria for emergency use have been met and that the physician has been informed that he/she is expected to follow as many patient protection procedures as possible. After discussing the situation with the physician and completing the checklist, it should be filed in the Emergency Use Report File located in the Program Operations Staff.

After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. If no IDE exists, the physician should submit a follow-up report on the use of the device to the IDE Staff. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

For more information on emergency use of investigational devices, see 50 FR 42866 and 21 CFR 812.35(a).

Individual Patient Access to Investigational Devices Intended for Serious Diseases

As discussed above, the IDE regulation and the Emergency Use Guidance address those situations in which an investigational or unapproved device, respectively, is needed to save the life of a patient or to prevent irreversible morbidity. FDA recognizes, however, 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 condition (hereinafter referred to as “compassionate use”). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur.

Unlike emergency use of an unapproved device, 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 alternative 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. (These measures were previously discussed under the Emergency Use Guidance.)

The sponsor should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. (IDE boilerplate G-16A has been developed for reviewers to use when addressing this type of request.) 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 serious disease or condition for which no alternative therapy adequately meets the 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 of Investigational Devices

Provisions of the Regulation

In the **Federal Register** of September 18, 1997 (62 FR 48940), FDA established procedures to allow for the treatment use of investigational devices. These procedures are intended to facilitate the availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible, i.e., before general marketing begins, and to obtain additional data on the device's safety and effectiveness. These procedures apply to patients with serious or immediately life-threatening diseases or conditions for which no comparable or satisfactory alternative device, drug, or other therapy exists.

Under the final rule, treatment use of an investigational device will be considered when:

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 available to treat or diagnose 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 all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

Procedures

If a sponsor is considering submitting a treatment IDE, the sponsor should consult with the appropriate review division in order to determine if the device/indication would meet the criteria for approval. Note that treatment IDEs are limited to those devices/indications which meet the criteria defined above. According to 21 CFR 812.36, requests for treatment use should be submitted as a supplement to the existing IDE and should include:

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 the use of the device, including either a list of the available regimens that ordinarily should be tried before using the device or an explanation of why the use of the device is preferable to the use of available marketed treatments;
4. A description of clinical procedures, laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk;
5. Written procedures for monitoring the treatment use and the name/address of the monitor;
6. Instructions for use and all labeling for the device as required under section 812.5(a) and (b);
7. Information relevant to the safety and effectiveness of the device for the intended treatment use;
8. A statement of the sponsor's commitment to meet all applicable responsibilities under Parts 812 and 56 and to ensure compliance of all participating investigators with Part 50;
9. An example of the investigator agreement to be signed by all investigators 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 that the price is based on manufacturing and handling costs only.

As with all IDEs, treatment IDEs may begin 30 days after FDA receives the application, unless FDA notifies the sponsor earlier than 30 days that the treatment use may or may not begin. The Agency may approve the treatment use as proposed, approve it with modifications/conditions, or disapprove it. FDA may withdraw approval of the treatment IDE if it is determined that the above criteria are no longer met.

In order to protect the rights, safety, and welfare of human subjects involved in the clinical trial, while at the same time facilitating the development of beneficial device therapies, FDA included certain safeguards in the Treatment IDE process. Some of these measures were already in place as part of the IDE regulation, while other safeguards were specifically designed for treatment use. Safeguards for this process include: the distribution of the device through qualified experts; maintenance of adequate manufacturing facilities; the submission of reports pursuant to 21 CFR 812.150; and compliance with the regulations governing informed consent and institutional review boards. Sponsors should review these sections of the regulation when preparing a Treatment IDE application to ensure that these issues are properly addressed.

When an IDE supplement requesting approval for treatment use is received in the reviewing division, the reviewer should immediately notify the IDE Staff. The IDE Staff will assist the division with the review of the application to ensure that all applicable safeguards have been satisfied and that all of the criteria identified in the regulation (see above) have been adequately addressed before the application can be approved. Three boilerplate letters are available for responding to requests for treatment use: G-46 for approval, G-47 for conditional approval, and G-48 for disapproval.

ODE review divisions should note that the IDE tracking sheets include a reason-for-submission code for Treatment IDE supplements. It is important that the division indicate on the tracking sheets that the application was a Treatment IDE, so that these applications can be properly tracked.

The Treatment IDE regulation is effective on January 16, 1998. For further guidance on Treatment IDEs, see the **Federal Register** of September 18, 1997 (62 FR 48940) or contact the IDE Staff at (301) 594-1190.

Continued Access to Investigational Devices

As discussed in ODE's Blue Book Memorandum entitled, "Continued Access to Investigational Devices During PMA Preparation and Review," (hereinafter referred to as the Continued Access Policy) 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:

1. A public health need for the device; or

2. 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.

The reviewer should consider all of the above factors, in addition to ODE’s progress in the review of the marketing application, when determining whether to approve, approve with modifications, or disapprove the proposed request for the extended investigation. The above factors should also be considered when determining the appropriate rate of enrollment, the number of investigators, and the number of investigational sites for the extended investigation. A sponsor’s past compliance with applicable FDA regulations should also be considered when making these decisions. For example, sponsors who have been negligent in their monitoring responsibilities or who have other unresolved compliance problems would not be permitted to participate in an extended investigation.

It is important to recognize that there is significant overlap between the treatment IDE regulation and the Continued Access Policy. As discussed in the preamble to the treatment IDE final rule, 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.

For further information, see ODE Blue Book Memorandum #D96-1 entitled, “Continued Access to Investigational Devices During PMA Preparation and Review.”

Expanded Access Mechanisms for Unapproved Devices

Expanded Access Mechanism	Regulatory Authority	Criteria for Use	When Can It Be Used?	Number of Patients to be Treated	FDA Approval Needed?	How is FDA Approval Obtained?	Patient Protection Measures
Emergency Use	“Guidance for the Emergency Use of Unapproved Medical Devices” 50 FR 42866 21 CFR 812.35(a)	1. Life-threatening condition [†] ; 2. No alternative; and 3. No time to obtain FDA approval.	Before or after initiation of clinical trial	Limited to few patients	No; submit report to FDA following device use	Not applicable	1. Independent assessment by uninvolved doctor; 2. IRB chairperson’s concurrence; 3. Institutional clearance; and 4. Informed consent
Compassionate Use	21 CFR 812.35(a)	1. Serious disease or condition and 2. No alternative.	During clinical trial	Individual patient or small groups of patients	Yes	IDE supplement with: 1. Explanation of circumstances constituting need for the device; 2. Reasons alternatives not acceptable; 3. Deviations from protocol, if any; and 4. Patient protection measures.	1. Independent assessment by uninvolved doctor; 2. IRB chairperson’s concurrence; 3. Institutional clearance; and 4. Informed consent.
Treatment IDE	21 CFR 812.36	1. Life-threatening or serious disease; 2. No alternative; 3. Controlled clinical trial; and 4. Sponsor pursuing marketing approval.	During clinical trial	Wide access; depends on patient/physician need	Yes	Trt IDE supplement with: 1. Intended Use, protocol, and patient selection criteria; 2. Rationale for trt use 3. Methods used to evaluate device use and minimize risks; 4. Monitoring plan; 5. Summary of S&E data 6. Instructions for use and device labeling; 7. Commitment to patient protection; 8. Investigator agreement; and	1. IRB approval and 2. Informed consent.

Expanded Access Mechanisms for Unapproved Devices

Expanded Access Mechanism	Regulatory Authority	Criteria for Use	When Can It Be Used?	Number of Patients to be Treated	FDA Approval Needed?	How is FDA Approval Obtained?	Patient Protection Measures
						9. Price, if will be sold.	
Continued Access	<p>“Continued Access to Investigational Devices During PMA Preparation and Review”</p> <p>ODE Blue Book IDE Memorandum #D96-1</p>	<ol style="list-style-type: none"> 1. Public health need; <u>or</u> 2. Preliminary evidence that device will be effective <u>and</u> no significant safety concerns. 	After completion of clinical trial	Same rate of enrollment as study	Yes	<p>IDE supplement with:</p> <ol style="list-style-type: none"> 1. Justification for extended study; 2. Summary of S & E data and risks posed by the device; 3. Proposed enrollment rate; 4. Clinical protocol; and 5. Progress towards marketing approval. 	<ol style="list-style-type: none"> 1. IRB approval and 2. Informed consent.

‡As a matter of practice, FDA has expanded the criteria of “life-threatening condition” to include serious conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.

For questions or further information regarding the above table, contact the IDE Staff at (301) 594-1190.