FDA Decisions for Investigational Device Exemption Clinical Investigations

Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff

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For questions for the Center for Devices and Radiological Health regarding this document, contact the Office of Device Evaluation, Office of the Director, Investigational Device Exemptions (IDE) Staff at 301-796-5640.

For questions for the Center for Biologics Evaluation and Research regarding this document, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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Preface

Public Comment

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction and Scope

FDA seeks to encourage medical device research and innovation to address important clinical needs and improve patient care. In many cases, device development and evaluation include clinical investigation. This guidance document has been developed to facilitate the initiation of clinical investigations to evaluate medical devices under FDA's Investigational Device Exemptions (IDE) regulations, Title 21 Code of Federal Regulations (CFR) Part 812.

FDA approval of an IDE submission allows the initiation of subject enrollment in a clinical investigation of a significant risk[1] device. This guidance is intended to provide clarification regarding the regulatory implications of the decisions that FDA may render based on review of an IDE as well as a general explanation of the reasons for those decisions.

In an effort to promote timely initiation of subject enrollment in clinical investigations in a manner that protects study subjects, FDA has developed methods to allow a clinical investigation of a device to begin under certain circumstances, even when outstanding issues remain regarding the IDE submission. These mechanisms, including *Approval with Conditions*, *Staged Approval*,

[1] 21 CFR 812.3(m): A *significant risk device* means 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 purported or represented to be for a use in supporting or sustaining human life and presents 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 the health, safety, or welfare of a subject.

and communication of outstanding issues related to the IDE through *Study Design Considerations* and *Future Considerations*, are described in this guidance.[2]

FDA's decision-making for IDEs was modified with passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. No. 112-144). Section 601 of FDASIA amended Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to specify certain situations in which FDA cannot disapprove an IDE. Section 520(g)(4)(C) of the FD&C Act states that, consistent with section 520(g)(1), FDA shall not disapprove an IDE because:

> *(i) the investigation may not support a substantial equivalence or de novo classification determination or approval of the device;*
> *(ii) the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or*
> *(iii) an additional or different investigation may be necessary to support clearance or approval of the device.*

However, the Agency recognizes that some IDE sponsors may wish to ensure that the pivotal study design may support a marketing application if it is successfully executed, meets its stated endpoints, and does not raise unforeseen safety concerns. Through mechanisms such as the Pre-Submission[3] process, FDA wishes to work interactively with sponsors interested in addressing important limitations with such a study that might impair its ability to support a future marketing application.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2. IDE Decisions

FDA's regulations[4] provide for three FDA actions on IDE applications:

- Approval[5]

[2] This guidance does not offer specific information related to the design of a clinical investigation, nor does this guidance discuss the specific content that should be provided in an IDE application. For additional information on those topics, please refer to FDA's regulations (21 CFR Part 812) and to FDA's "Guidance on IDE Policies and Procedures" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm).

[3] For more information, see FDA's Guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff - Guidance for Industry and Food and Drug Administration Staff." http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

[4] 21 CFR 812.30.

- Approval with Conditions[6]
- Disapproval

FDA must inform the sponsor[7] or sponsor-investigator[8] of its decision, or must notify the sponsor that the investigation may not begin, within 30 days from the date of receipt of the IDE application, or the IDE application will be deemed approved. If an IDE application is approved or approved with conditions, the sponsor may begin subject enrollment, up to the number of subjects and investigational sites specified in FDA's decision letter, upon receipt of Institutional Review Board (IRB) approval, which may occur prior to FDA approval.

If FDA does not have outstanding issues that must be addressed to support the study of the subject cohort under the proposed investigational plan, the IDE will be approved without conditions.[9] Alternatively, if FDA has identified issues that must be addressed in a timely manner but do not preclude initiation of subject enrollment in the clinical investigation, the IDE will be approved *with* conditions. In the case of approval with conditions, approval is granted and study enrollment may begin immediately provided that, within 45 days from the date of FDA's decision letter,[10] the sponsor submits information addressing the issues identified in FDA's letter. Examples of the types of issues that may be identified in an approval with conditions letter are discussed later in this document. In certain instances, resolution of outstanding issues may be necessary before initiation of subject enrollment. In these instances, the IDE will be disapproved, meaning that the sponsor may not initiate enrollment in the clinical investigation until the sponsor responds to the issues identified in FDA's letter and receives an approval or approval with conditions letter.

3. IDE Approval

If FDA approves an IDE application, the sponsor may begin subject enrollment upon receipt of IRB approval[11] and in accordance with the limits described in FDA's decision letter, including

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[5] As discussed in Section 5, enrollment for an IDE application that is Approved or Approved with Conditions may in some cases be limited to a portion of the total expected enrollment (i.e., "Staged Approval") while certain outstanding questions are answered concurrently with enrollment in the clinical investigation.

[6] FDA has traditionally referred to IDE approvals that have conditions as "Conditional Approvals." FDA believes that the term "Approval with Conditions" is more appropriate because the term conveys that the IDE has been approved and may begin without awaiting further FDA review.

[7] 21 CFR 812.3(n): *Sponsor* means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

[8] 21 CFR 812.3(o): *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor. The remainder of this document uses the term "sponsor" for both sponsor and sponsor-investigator.

[9] The term "approval" in this document and in FDA's communications means approval without conditions.

[10] The remainder of this document references 45 days as the specified timeframe. Sponsors may also request an extension of this timeframe that should include a justification for why the extension is needed and will not impact study integrity or subject protection.

[11] FDA regulations do not specify when IRB review should take place, as long as it is done prior to initiation of the study. 21 CFR 812.42. Because changes are often made to the protocol as a result of FDA's review, sponsors may

the maximum numbers of U.S. subjects and investigational sites. An IDE application is approved if FDA has determined that: the sponsor has provided sufficient data to support initiation of a human clinical study; no subject protection concerns preclude initiation of the investigation; and *no* additional conditions must be met.

In some cases, FDA may determine that an outstanding issue remains that can be addressed with data that will be gathered concurrently with the enrollment of a portion of study subjects (i.e., staged approval, see Section 5). FDA may also inform the sponsor of recommended modifications to the study design that FDA believes will improve the study and may be necessary to enable the study to support a future marketing application (i.e., study design considerations) as well as other issues that FDA believes should be considered in preparing for a marketing application or a future clinical investigation (i.e., future considerations). These types of feedback are discussed in Section 7 of this document.

4. IDE Approval with Conditions

If FDA approves an IDE application with conditions, the sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA's decision letter, including the maximum numbers of U.S. subjects and investigational sites, and must submit information addressing the issues identified as conditions of approval in FDA's letter within 45 days. An IDE application is approved with conditions if FDA has determined that: the sponsor has provided sufficient data to support initiation of subject enrollment in a human clinical study; no subject protection concerns preclude initiation of subject enrollment; but additional conditions must be met to address certain outstanding issues. Previously known as "conditional approval," the phrase "approval with conditions" is now used to convey that the outstanding issues do not raise concerns that preclude FDA from granting approval for initiation of subject enrollment in the clinical investigation. Therefore, resolution of those issues is not required prior to initiation of subject enrollment in the study, except for certain issues related to the informed consent document. If FDA identifies issues with an informed consent document, FDA's letter will specifically state that they must be addressed before enrollment begins in order to ensure that informed consent is obtained in accordance with 21 CFR Part 50 - Protection of Human Subjects.[12] Outstanding issues that may lead to approval with conditions include:

- Requests for additional information or data involving non-clinical testing issues that do not need to be resolved prior to initiation of subject enrollment;
- Late-stage follow-up procedures and assessments that relate to the care of study subjects but, because they occur late in the study, can likely be addressed in response to FDA's letter prior to subjects' reaching that point in the study;
- Minor issues related to the informed consent document that must be corrected before initiation of subject enrollment but FDA can review after implementation;
- Other minor clarifications, corrections, or modifications (not related to study design) that do not need to be resolved prior to initiation of subject enrollment.

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decide to wait until they receive FDA approval, or approval with conditions, before submitting their protocol for IRB review.

[12] Informed consent issues identified in an approval with conditions letter must be corrected before enrolling subjects, but can be reviewed by FDA after study enrollment begins.

The sponsor must submit an amendment[13] to the IDE to respond to the issues raised in FDA's approval with conditions letter within 45 days unless the sponsor has requested and FDA has granted an extension.[14] For each issue identified in FDA's letter, an acceptable response provides the specific information or modification(s) FDA requested. In some cases, the sponsor may choose to provide a scientifically valid alternative to FDA's request or a scientifically valid rationale for why the information or modification(s) is not needed. FDA will inform the sponsor of its decision within 30 days from the date of receipt of the amendment. During this time, the sponsor may continue to conduct the study. If FDA determines that the issues have been adequately resolved, it will grant approval. However, if any issues remain, FDA may again grant approval with conditions and will communicate those remaining outstanding issues to the sponsor by letter. In this case, the sponsor may continue to enroll subjects in the study provided that, within 45 days, the sponsor responds to the remaining issues identified in FDA's letter. If the sponsor's response to FDA's questions raises concerns regarding subject safety, or the sponsor does not respond, FDA may take appropriate regulatory actions to protect study subjects, including placing a clinical hold[15] on the study. If the study is placed on hold, no additional subjects may be enrolled, and previously enrolled study subjects should receive appropriate monitoring and treatment for their safety.

5. Staged Approval or Staged Approval with Conditions

This guidance defines processes, termed "staged approval" or "staged approval with conditions"[16] (which are subsets of approval and approval with conditions decisions), by which FDA may grant IDE approval or approval with conditions for a portion of the intended study cohort, enabling certain outstanding questions to be answered concurrently with enrollment in this cohort. Staged approval permits the clinical investigation to begin in a timely manner while maintaining appropriate subject protections. In some cases, the sponsor proposes a staged enrollment in the IDE application. In other cases, the sponsor requests approval for the full subject cohort but, under certain circumstances described below, FDA may decide to grant staged approval for a limited number of subjects as an alternative to disapproving the IDE.

As noted above, under staged clinical investigations, FDA will grant approval or approval with conditions for a portion of the planned subject cohort while the particular outstanding questions are addressed. FDA will grant approval with conditions if there are other issues that should be addressed within 45 days, which may include questions seeking clarification or information regarding the data that will be gathered to support future study expansion. Alternatively, if FDA and the sponsor have agreed to the additional data that will be provided and no other outstanding

[13] Beginning August 19, 2013, all submissions that respond to deficiencies from an approval with conditions or disapproval letter are designated as "IDE amendments". Prior to this date, responses to approval with conditions letters were designated as "IDE supplements".

[14] In general, FDA will not issue an approval with conditions for issues that the agency believes will require longer than 45 days to address. If FDA identifies such issues but determines that they should not preclude initiation of subject enrollment in a study, FDA may issue a staged approval, as discussed in Section 5.

[15] Section 606 of FDASIA amended section 520(g) of the FD&C Act by adding authority to place a study on "clinical hold" when, among other reasons established by regulation, the device involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation.

[16] The remainder of this section will use the term "staged approval" to refer to staged approval and staged approval with conditions.

issues remain to be addressed (i.e., under approval with conditions), a staged clinical investigation can receive approval, with enrollment limited to the number of subjects to be enrolled in the first stage.

If the benefit-risk profile based on the IDE submission is sufficiently favorable to justify enrollment of a portion of the study subjects, a staged clinical investigation may be appropriate to allow initiation of subject enrollment in a study while providing additional mitigation of risk by limiting exposure of the investigational device to a smaller subject population. Such an approach may be appropriate in the following situations:

- Additional clinical confirmation of the safety profile is obtained by reviewing initial data from subjects enrolled early in the clinical investigation before enrolling the full subject cohort.
- Additional non-clinical testing is needed to more fully characterize device performance to adequately evaluate the potential risks of the device, before permitting testing of the full subject cohort and is conducted concurrently with early enrollment in the clinical investigation.

The sponsor will be permitted to expand enrollment once an IDE supplement containing the necessary additional information is submitted to FDA and found to be acceptable. In some cases, based on the information submitted, a partial expansion of enrollment may be granted (i.e., an additional stage of enrollment rather than expansion to full enrollment) while additional data are gathered to answer FDA's outstanding questions. In such cases, as with the first stage, the sponsor will be permitted to expand enrollment once a second IDE supplement, which includes the necessary additional information, is submitted to FDA for review and found to be acceptable.

The size of the enrollment stages and the timing for the reporting of additional information should ideally be designed so that study enrollment need not be halted while the data are reviewed. For example, if FDA wishes to see seven-day safety data on the first 30 subjects of a 300-subject study, it may be appropriate to approve the first stage for 50 subjects. In this way, enrollment can continue while FDA reviews the data from the first 30 subjects and, if appropriate, grants expansion.

Staged approval is most common for pivotal studies[17] in which many subjects will be enrolled over an extended period of time but may be applicable to other clinical investigations as well. Some additional considerations specific to staged pivotal studies include:

- The data FDA requests should not inappropriately unblind any of the relevant stakeholders, including the sponsor, investigators, or study management personnel, to critical study data or compromise the study's statistical integrity. If the requested data will necessarily do so, then a feasibility study may more appropriately answer these questions.
- Data from the full planned cohort of subjects would be expected at the time of a marketing application.

[17] Pivotal studies are discussed in more detail in the FDA guidance titled, "Design Considerations for Pivotal Clinical Investigations for Medical Devices" (available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf).

- A staged pivotal study should only be considered if the additional information that is requested is not expected to change critical elements of the clinical investigation (e.g., endpoints) or device design that would undermine data interpretation. If the information is expected to result in such changes, then a separate feasibility or early feasibility[18] study may be more appropriate. In some cases, prospectively defined adaptive design techniques, rather than a staged study, may allow for a pivotal study to accommodate pre-planned study changes based on data gathered early in the study without requiring additional feasibility data.
- FDA may determine that new feasibility data are needed prior to approving the proposed pivotal IDE to allow for a comprehensive examination of study outcomes related to the device safety profile and/or of potential benefit in a small group of subjects before a large group of subjects may be exposed to the risks of the study. In such cases, approval of a feasibility study, rather than a staged pivotal study, may be appropriate. The data from the feasibility study may be used to inform the design and support IDE approval for a future pivotal study.

6. IDE Disapproval

If an IDE application is disapproved, the sponsor may not initiate enrollment in the clinical investigation until the sponsor submits an amendment[19] to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions. Consistent with 21 CFR 812.30(b) and section 520(g) of the FD&C Act, FDA may disapprove an IDE for any of the following reasons:[20]

- There has been a failure to comply with any requirement in 21 CFR Part 812 or section 520(g) of the FD&C Act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA. (21 CFR 812.30(b)(1)).

- The application or a report contains an untrue statement of material fact, or omits material information required by 21 CFR Part 812. (21 CFR 812.30(b)(2)).

- The sponsor fails to respond to a request for additional information within the time FDA prescribes. (21 CFR 812.30(b)(3)).

- There is reason to believe that risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained (21 CFR 812.30(b)(4)). This assessment may be based on the following consideration:

[18] Feasibility studies are developmental studies not intended to provide the primary clinical evidence to support a marketing application. Early feasibility studies are discussed in the guidance document entitled "Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies" (available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf).

[19] There is no required timeframe within which a response to an IDE disapproval must be submitted.

[20] As used in this guidance, "risk" primarily refers to probable risk, rather than any possible risk.

- **Subject safety.** The investigational plan contains elements that would expose subjects to unacceptable probable risks, or fails to adequately protect study subjects from probable risks (including adequate monitoring and review of the investigation).

- The informed consent is inadequate. (21 CFR 812.30(b)(4)). The consent requires changes to adequately inform subjects of the study that FDA must review before initiating subject enrollment. If the required changes are minor and do not require FDA review before initiating subject enrollment, this may be considered a condition of approval, as discussed in Section 4.

- The investigation, as proposed, is scientifically unsound. (21 CFR 812.30(b)(4)). The investigation does not pose a reasonable scientific question or the investigation does not include the collection of data or information related to that scientific question.

- There is reason to believe that the device as used is ineffective. (21 CFR 812.30(b)(4)). This assessment may be based on the following consideration:

  - **Inadequate potential for benefit.** Available data suggest the device is ineffective for the use that will be evaluated in the proposed study, or no information has been provided to suggest the device as used may result in patient benefit and the generation of knowledge adequate to justify the risks. For example, for a therapeutic device, the submission does not provide a scientifically plausible explanation for how the proposed mechanism of action of the device could have an impact on the outcome of interest, or for a diagnostic device, no data have been provided showing that the device is informative concerning the condition of interest. The amount of information or data to support scientific plausibility of the proposed use of the device will depend on the level of risk associated with the device/procedure and the alternatives available to the intended patient population. For a device with lesser risk, a scientific explanation for how the device could lead to patient benefit may be sufficient. However, for a device that poses more substantial risks to subjects, especially when alternative commercially available therapies, diagnostic devices or surgical procedures exist, initial evidence to support the likelihood of patient benefit would generally be necessary. If the study proposes to evaluate a significant risk device in patients for whom no alternatives exist, and/or if there is no way to evaluate the potential for benefit in a reasonable nonclinical model, FDA may allow limited enrollment as a feasibility study or staged pivotal study.

- It is otherwise unreasonable to begin or to continue the investigation owing 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) monitoring and review of the investigation. (21 CFR 812.30(b)(5)). This assessment may be based on the following consideration:

- **Device safety.** The data and information provided are insufficient to adequately characterize the safety profile of the device such that, based on the data provided thus far, human clinical investigation is not considered reasonable. A specific safety concern may relate to the need for additional basic device evaluation (e.g., biocompatibility, mechanical durability, drug or biologic component characterization, electrical safety, software validation, or biological response in an animal model) or additional information regarding the methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device.

7. Information Conveyed in FDA Communications

Consistent with section 520(g) of the FD&C Act, FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing application. However, if FDA believes modifications to the study are needed to achieve this objective, FDA will convey such considerations to the sponsor to provide greater clarity and predictability. In addition, FDA will convey to the sponsor considerations that FDA believes will be important for future submissions related to the proposed investigation. These considerations are communicated in the following ways:

- **Study Design Assessment.** For pivotal studies, FDA's decision letter will specify whether FDA believes that (1) the study design is adequate and may support a future marketing approval or clearance, if it is successfully executed and meets its stated endpoints without raising unforeseen safety concerns; or (2) additional modifications are needed in order for the study to do so.[21] Similarly, for feasibility studies designed to support a future pivotal study, FDA's decision letter will specify whether FDA believes the study design is adequate to support the study goals.

  If FDA determines that a pivotal study design is adequate and may support a future marketing application, FDA intends to consider changes to its assessment of the study design only if the sponsor materially changes the device or the study design or important issues relevant to a determination of safety or effectiveness have emerged since it approved the IDE. In such cases, FDA will acknowledge the change in its assessment, document the rationale for the change, and discuss with the sponsor how the identified issues relate to safety and effectiveness. Appropriate management concurrence will support FDA's determination.

- **Study Design Considerations.** If FDA identifies concerns unrelated to subject safety which the Agency believes should be addressed to enable the study to support the

[21] An IDE disapproval or approval decision is a "significant decision" under section 517A of the FD&C Act ("517A decision"). Factors unrelated to the approvability of the IDE, such as the study design assessment, study design considerations, and future considerations, may be appealed but are not considered significant decisions under 517A. For more information on 517A decisions and non-517A decisions, see FDA's draft guidance "Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm352248.htm; when final, this guidance will represent the Agency's current thinking on this topic.

sponsor's stated goals (e.g., a future marketing application or future study), FDA intends to communicate these "study design considerations" to the sponsor.[22] Where FDA provides a suggested approach to address a study design consideration, FDA will adhere to the least burdensome principle, meaning that it will suggest only those modifications it deems necessary to successfully address outstanding issues related to approval/clearance of a future marketing application or study. Sponsors are encouraged but not required to address study design considerations. Sponsors who choose to propose changes to address the identified study design considerations must obtain approval from FDA prior to implementation (See Section 9). If FDA recommends major modifications to the investigational plan, FDA may recommend that the sponsor submit a Pre-Submission to discuss the study design before submitting modifications under the IDE.

Examples of potential study design considerations (if unrelated to subject protection) include suggestions related to:

- Primary and important secondary endpoints and study success criteria
- Randomization and control plan
- Blinding (masking)
- Follow-up duration and assessments
- Statistical plan, including:
  - Statistical method for analysis of key endpoints
  - Sample size and power
  - Missing data handling
  - Type-1 error control
  - Interim analyses and stopping rules
  - Poolability
- Case report forms
- Enrollment criteria
- Core labs and independent adjudication committees

- **Future Considerations.** Future considerations are issues or recommendations that FDA believes the sponsor should consider in preparing for a marketing application or a future clinical investigation but which FDA does not deem necessary to address to enable the current study to support its stated goals. Future considerations are intended to provide helpful, non-binding advice to sponsors regarding important elements of the future application that the IDE may not specifically address. Future considerations communicated to the sponsor are not intended to list all additional issues that the sponsor should consider in preparing for a future submission. Examples of typical future considerations include discussion of:

  - Known limitations of the IDE clinical investigation in supporting certain claims or indications. For example, FDA may remind the sponsor that, due to a specific exclusion criterion, any approved/cleared indications for use based on the clinical

[22] Any changes to the study design needed to protect study subjects will be communicated as deficiencies that may result in IDE disapproval (as discussed in section 6) and will not be communicated as study design considerations.

investigation will be limited to that particular population rather than a broader population.

- Specific non-clinical testing that, while not necessary to support approval of the IDE, will be needed to support the marketing application. For example, FDA may have accepted shorter term device durability testing to support IDE approval but may wish to remind the sponsor that longer term testing will be needed to support a marketing application.

8. Informed Consent Document

The process of informing potential study subjects of, among other things, the possible risks, benefits, and alternatives associated with participation in the clinical investigation is a necessary element of proper study conduct. FDA closely reviews the informed consent document as part of the IDE review. In order to support approval of the IDE, the informed consent document must meet the requirements of 21 CFR Part 50. Changes to address minor issues related to the informed consent may be addressed as a condition of approval as discussed in Section 4. Changes to address major issues will generally require FDA review prior to implementation and may be grounds for disapproval (see Section 6). Additional information on informed consent can be found on FDA's website: A Guide to Informed Consent – Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm).

9. Supplements, Reports, and Amendments to IDEs

In general, reports are intended to provide notification or updates for FDA's routine monitoring of a clinical investigation, while supplements are intended to seek FDA's approval for something new or different.

Supplements

Supplements to IDEs are submitted for several reasons, including the following:

- To request approval for changes to a clinical investigation(e.g., to the investigational protocol or informed consent), including those proposed in response to study design considerations FDA previously identified;
- To request approval for changes to the investigational device (e.g., device design or manufacturing) ;
- To notify FDA that changes to the investigation or the device that do not require prior approval have been made (i.e., 5-day notice);[23]

[23] The guidance document entitled "Changes or Modifications During the Conduct of a Clinical Investigation," (available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm082145.htm) discusses the types of changes that require FDA approval and those that qualify for notification. For additional guidance on the use of 5-day notices in early feasibility studies, please see the guidance document entitled "Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies" (available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf).

- To request approval for a new study (e.g., a pivotal study) under the same IDE as an earlier study (e.g., a feasibility study) for the same device studied for the same indication;
- To request that the study be expanded in terms of number of approved subjects and/or investigational sites. This may be based on the sponsor's providing data that were requested under a staged approval;
- To request approval to terminate enrollment and/or follow-up in a manner different from that described in the approved investigational protocol;
- To notify FDA when a study has been suspended and subsequently to request approval to resume a suspended study;
- To request approval for a compassionate use, [24] live case demonstration, or other protocol deviation; and
- To request an extension of time for responding to an FDA letter or for meeting a reporting requirement.

The FDA decision process for supplements is similar to that described for original IDE submissions, with the same decision options (i.e., approval, approval with conditions, and disapproval) and review and response timelines. Similar to original IDE applications, an IDE supplement will receive a single decision for the entire supplement (i.e., approval, approval with conditions, or disapproval). If a supplement is approved with conditions or disapproved, the sponsor's response to the deficiencies identified in FDA's letter is designated as an amendment to that supplement.

A notable difference between FDA's review of supplements requesting changes and the review of an original IDE submission is that FDA disapproval of a supplement requesting changes to an approved study does not imply that the IDE study itself is disapproved. For example, if a supplement to an approved IDE requests approval for changes to the clinical investigation, and that supplement is disapproved, the sponsor may not implement the requested changes. However, the previously approved clinical investigation remains approved and may continue.[25]

Reports

Reports to IDEs are submitted for several reasons, including the following:

- To provide biannual investigator/site/IRB reporting information required for studies approved with an investigational site waiver;
- To provide annual reports to FDA and, if requested by FDA, to provide more frequent interim reports;
- To notify FDA of a failure to obtain informed consent;
- To notify FDA of an Emergency Use;
- To report to FDA on the outcome of an approved compassionate use or live case;
- To report to FDA on unanticipated adverse device effects as required per 21 CFR 812.150 (b)(1);

[24] The guidance entitled "Guidance on IDE Policies and Procedures," (available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080202.htm), discusses Compassionate and Emergency Uses.

[25] If the supplement was submitted to address a safety issue in the study, FDA may determine that the study should be placed on clinical hold.

- To notify FDA of completion of enrollment;
- To notify FDA of completion of a study (including all patient follow-up);
- To provide the final IDE report to FDA;
- To notify FDA of other information, as appropriate, related to the ongoing clinical investigation.

For IDE reports, FDA will respond to the sponsor within 30 days if FDA has questions or requests for additional information; otherwise, FDA may close the submission without issuing a formal response letter to the sponsor. In such cases, FDA will generally inform the sponsor via email that the submission has been closed. If a report is deficient, the sponsor's response to the deficiencies identified in FDA's communication is designated as an amendment to that report.

Amendments

Any response to a deficiency letter is an Amendment to the submission for which the deficiency letter was sent. Amendments may be submitted to each of three parent document types: Original IDEs, IDE Supplements, and IDE Reports. Importantly, multiple Amendments will be accepted until all of the deficiencies have been resolved.

10. Examples

The following are generic examples of how different IDE decision mechanisms may be employed.

10.1. Example 1

A sponsor submits an original IDE application to conduct a 30-subject feasibility study for a permanently implanted device to treat a serious chronic medical condition. The study is intended to provide data to support a future pivotal study.

FDA's review results in the following conclusions:

- The data provided are sufficient to support a feasibility clinical evaluation under the rigorous monitoring plan proposed.
- Because questions remain regarding the consequences of the long-term presence of the device, longer-term animal data that include histology may be needed before a pivotal study exposing a large number of subjects to the device can be approved.
- The sponsor's proposed follow-up assessments do not include a particular evaluation that, while not a subject safety issue, is important for assessing the device's performance.
- The informed consent document does not communicate a potential risk relevant for this study.

FDA determines that none of the concerns should preclude the sponsor from initiating the feasibility study, provided that the informed consent document is amended. Therefore, FDA issues an approval with conditions letter to the sponsor. The letter states that the sponsor may initiate enrollment in the study, using an informed consent document that is modified to include

the potential risk discussed above on the condition that, within 45 days from the date of FDA's letter, the sponsor submits the modified consent form to FDA for review.

In addition, FDA's letter notes that FDA believes changes to the study design are needed to enable the feasibility study to support a future pivotal study. An attachment to FDA's letter includes a study design consideration suggesting that the sponsor modify the follow-up assessments to include the evaluation noted above. The attachment also includes a future consideration related to the likely need for a longer-term animal study prior to initiating a future pivotal study to collect additional safety data, unless the sponsor is able to provide additional data or a scientifically valid rationale for why such a study is not needed.

The sponsor submits an amendment to the IDE to respond to FDA's approval with conditions letter within 45 days. In addition to addressing the informed consent issue, the submission provides a modified clinical protocol addressing the study design consideration noted in FDA's letter. FDA approves the IDE without conditions. FDA's approval letter notes that FDA believes the study design is adequate to support the study goals.

10.2. Example 2

A sponsor submits an original IDE application to request approval of a 300-subject pivotal study at 10 sites to evaluate the safety and effectiveness of a permanently implanted device to treat a serious chronic medical condition.

FDA identifies the following issues that must be addressed before initiating subject enrollment in a study:

- Inadequate non-clinical durability testing to evaluate a potential failure mode.
- Enrollment criteria do not exclude subjects with severe renal insufficiency in a study that requires contrast-enhanced imaging and for whom the device is contraindicated. This subgroup has an unacceptably high risk of serious adverse events and should not be enrolled in the study.

FDA also identifies the following study design issues it believes should be addressed to enable the study to support a marketing application:

- The sponsor proposed an historical control but FDA believes a concurrent randomized control group is needed because available historical control data are not representative of the current standard of care.
- The sponsor proposed a 3-month follow-up duration, but FDA believes the primary endpoints should be evaluated at 6 months due to essential longer-term safety and effectiveness questions regarding this device.
- There are inadequacies regarding definitions of parameters associated with the safety endpoint.
- The protocol needs to include additional details regarding the statistical analysis plan.

Based on the first two concerns, FDA disapproves the study. An attachment to FDA's letter conveys the four above-stated study design considerations, which the sponsor need not address.

In response to FDA's letter, the sponsor submits an amendment to the IDE that includes additional durability test data and a modified clinical protocol. Modifications to the protocol include changes to the enrollment criteria to exclude the specific sub-population of concern. The amendment specifically responds to each deficiency. Additional changes were made to address FDA's study design considerations. Specifically, the sponsor has proposed a longer follow-up duration but continues to believe that a historical control is appropriate.

FDA's review of the amendment does not identify any issues precluding the sponsor from initiating the study. FDA determines that the durability test data provided strongly suggest good long-term device performance and are sufficient to support study of the device in a small group of subjects. However, the data are not adequate to fully FDA's concern and longer term non-clinical durability testing should be conducted before the full subject cohort is exposed to the risks of the study. Furthermore, while the revised study design partially addresses FDA's concerns, based on the information provided, FDA continues to believe that a concurrent randomized control group is needed to enable the study to support a future marketing application.

FDA issues a staged approval letter allowing the sponsor to begin study enrollment of up to 50 subjects at five sites. FDA's letter informs the sponsor that, concurrent with enrollment in the study, the sponsor should conduct longer-term durability testing. The results of this testing will be needed to support expansion of the study. FDA's letter also indicates that FDA believes the current study design is unlikely to support a marketing application. The study design consideration included in an attachment to FDA's letter explains why FDA believes that a historical control will not suffice and a concurrent control group is likely needed.

The sponsor submits a Pre-Submission to discuss a new proposal for a concurrent control. FDA and the sponsor work together to develop minor modifications to the sponsor's proposal to address FDA's concerns.

The sponsor submits a supplement[26] to the IDE to modify the study design as discussed in the Pre-Submission. FDA approves the IDE supplement. FDA's approval letter informs the sponsor that FDA believes the study design provided in the submission is adequate and may support a future marketing application, assuming that the study is successfully executed and meets its stated endpoints without raising unforeseen safety concerns. The enrollment continues to be limited to 50 subjects while the durability testing is ongoing.

Two months later, with 37 subjects enrolled in the study, the sponsor submits an IDE supplement providing durability testing results and requests approval to enroll up to 300 subjects. FDA finds the results acceptable and grants the sponsor approval to enroll the full subject cohort.

1.3 Example 3 (variation on Example 2)

A sponsor submits an original IDE application to request approval of a 300-subject pivotal study at 10 sites to evaluate the safety and effectiveness of a permanently implanted device to treat a

[26] Because none of the changes proposed in the example submission is in response to deficiencies, it is designated as a supplement and not an amendment.

serious chronic medical condition. FDA identifies the same concerns described in Example 2. In contrast to Example 2, the sponsor chooses not to address the study design considerations provided in the attachment to FDA's letters. FDA's approval letters (for the initial stage and the subsequent full enrollment) inform the sponsor that FDA believes the current study design is unlikely to support a marketing application. The study design considerations provided explain the modifications that FDA believes are needed to enable the study to support a marketing application. The sponsor, however, chooses to conduct the study as currently designed.

11. Conclusions

FDA recognizes the public health benefit of permitting clinical investigations of medical devices to proceed in a timely and efficient manner while ensuring proper subject protections. When determining whether to approve an IDE application, FDA considers many factors, as discussed in this document. Where appropriate, FDA seeks to offer flexibility in how to address outstanding issues (e.g., approval with conditions, staged approval, and future considerations) to allow clinical investigations to commence without unnecessary delay while ensuring that human subjects are adequately protected.