Draft Guidance for Industry, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff

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FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations

DRAFT GUIDANCE

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

Preface

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Draft Guidance for Industry, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff

FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 includes 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 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 and to provide a general explanation of the reasons for those decisions.

In an effort to promote timely initiation of 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 there are outstanding issues regarding the IDE submission. These mechanisms, including *Approval with Conditions*,

[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.

Staged Approval, 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 determine whether the pivotal study design may support a marketing application if it is successfully executed and meets its stated endpoints without raising unforeseen safety concerns. To meet this interest, FDA is proposing a new, voluntary program intended to facilitate the development of trial designs that may support a marketing approval or clearance. The Agency recognizes that this type of voluntary program will not likely be suitable for all IDE sponsors and does not intend that this program become a routine step prior to submission of an IDE, nor is this program intended to replace or be a substitute for the existing Pre-Submission process.[3]

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:

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[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 draft Guidance "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff." (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm). When finalized, this guidance will represent the Agency's current thinking on this topic.

[4] 21 CFR 812.30.

- Approval[5]
- 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, with the maximum number of subjects and investigational centers 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, then 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 the clinical investigation, the IDE will be approved *with* conditions. In the case of approval with conditions, approval is granted and the study may be initiated immediately on the condition 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.

[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 subset 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.

3 IDE Approval

If FDA approves an IDE application and IRB approval is obtained,[11] the sponsor may begin subject enrollment in accordance with the limits described in FDA's decision letter, including the maximum numbers of U.S. subjects and investigational centers. FDA will approve an IDE application without conditions when the IDE sponsor has submitted data and an adequate clinical investigation plan that support initiation of the study in humans.

In some cases, FDA may determine that an outstanding issue remains which can be addressed with data that will be gathered concurrently with the enrollment of a subset 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 in order for 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 preparation 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 on the condition that, within 45 days from the date of FDA's decision letter, the sponsor submits information addressing the issues identified in FDA's letter. An IDE may be approved with conditions if FDA has determined that, despite some outstanding issues, the information provided is sufficient to justify human clinical evaluation of the device and the proposed study design is acceptable with regard to protection of study subjects. 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 the clinical investigation. Therefore, resolution of those issues is not required prior to initiation of enrollment in the study, with the exception of certain issues related to the informed consent document. If FDA identifies issues with an informed consent document, FDA's letter will specifically state that those issues 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 study initiation;

[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. Since changes are often made to the protocol as a result of FDA's review, sponsors may 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.

- Late stage follow-up procedures and assessments that relate to the care of study subjects but, because they occur late in the study, will likely be addressed prior to subjects reaching that point in the study;
- Minor issues related to the informed consent document that must be corrected before study initiation (i.e., subject enrollment) but can be reviewed by FDA after study initiation;
- Other minor clarifications, corrections, or modifications (not related to study design) that do not need to be resolved prior to study initiation.

The sponsor must submit a supplement[13] to the IDE to respond to the issues raised in FDA's approval with conditions letter, usually within 45 days, unless an extension has been requested by the sponsor and granted by FDA[14]. For each issue identified in FDA's letter, an acceptable response provides the specific information or modification(s) requested by FDA. In some cases, the sponsor may choose to provide a scientifically valid alternative to FDA's request or to provide a scientifically valid rationale for why the information or modification(s) is not needed. FDA will inform the sponsor of its decision within 30 calendar days from the date of receipt of the supplement. During this time, sponsors may continue to conduct the study. If FDA determines that the issues have been adequately resolved, FDA will grant approval without conditions. However, if any issues remain, FDA may again grant approval with conditions and will communicate the remaining outstanding issues to the sponsor by letter. In this case, the sponsor may continue to enroll subjects in the study on the condition 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 adequately 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, 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, while certain outstanding questions are answered concurrently with enrollment of a limited number of subjects in the clinical investigation. Staged approval permits the clinical investigation to begin in a timely manner while maintaining appropriate subject protections.

[13] Once an IDE is approved or approved with conditions, subsequent submissions to FDA related to the IDE are 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 study initiation, 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.

Under staged clinical investigations, FDA will grant approval or approval with conditions for a subset 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 there are no other outstanding issues to be addressed (i.e., under approval with conditions), a staged clinical investigation can receive approval without conditions, with enrollment limited to the number of subjects to be enrolled in the first stage. The size of the enrollment stages and the timing for the reporting of additional information should ideally be designed so that study enrollment does not need to be halted while interim data are reviewed.

If the benefit-risk profile is sufficiently favorable to justify enrollment of a portion of the study subjects, a staged clinical investigation may be appropriate to allow initiation of 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 or the potential for benefit is obtained by reviewing initial data from subjects enrolled early in the clinical investigation before enrolling the entire 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 entire 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.

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 that are specific to staged pivotal studies include:

- Successful support of a marketing application under staged approval is not expected until the full planned cohort of subjects is studied.

[17] Pivotal studies are discussed in more detail in the FDA draft guidance titled, "Design Considerations for Pivotal Clinical Investigations for Medical Devices" (available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm265553.htm). When finalized, this guidance will represent the Agency's current thinking on this topic.

- A staged pivotal study should only be considered if the additional information that is requested is not expected to result in changes to important elements of the clinical investigation (e.g., endpoints, sample size, stopping rules) or device design. If the information is expected to result in changes to important elements of the study or device design, then a separate feasibility[18] study may be more appropriate. In some cases, prospectively defined adaptive design techniques may allow for a pivotal study to accommodate pre-planned study changes based on data gathered early in the study without the need for additional feasibility data.
- FDA may determine that new feasibility data are needed prior to approval of the proposed pivotal IDE, in order to allow for a comprehensive examination of the study outcomes related to the device safety profile in a small group of subjects prior to exposing a large group of subjects to the risks of the study. In such cases, rather than granting approval for a staged pivotal study, FDA may choose to grant approval of the IDE for a limited number of subjects on the condition that the sponsor considers the study to be a feasibility study. The data from the feasibility study may be used to inform the design and support IDE approval for a future pivotal study.
- The data requested by FDA should not inappropriately unblind any of the relevant stakeholders, including the sponsor, investigators, or study management personnel, to critical study data. If the requested data will necessarily unblind these stakeholders to critical study elements, then a feasibility study may be more appropriate to answer these questions.

6 IDE Disapproval

If an IDE application is disapproved, the sponsor may not initiate 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)).

[18] Feasibility studies are developmental studies not intended to provide the primary clinical evidence to support a marketing application. A draft 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/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm) discusses the types of feasibility studies. When finalized, this guidance will represent the Agency's current thinking on this topic.

[19] If an IDE has not yet received approval or approval with conditions, subsequent submissions to FDA related to the IDE are designated as "IDE amendments." 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.

- The sponsor fails to respond to a request for additional information within the time prescribed by FDA. (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:
    - **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, and must be reviewed by FDA prior to study initiation.

- 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 therapies or diagnostic devices 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 not a 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, for studies that the sponsor intends to use in support of a marketing application, the sponsor and other stakeholders may benefit from awareness of the modifications that FDA believes are needed to achieve this objective. Therefore, FDA will convey such considerations to the sponsor to provide greater clarity and predictability. In addition, FDA will convey certain 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 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 whether FDA believes that additional modifications are needed in order for the study to do so. Similarly, for feasibility studies that are 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 if important issues relevant to a determination of safety or effectiveness have emerged since the time of the IDE approval. In such cases, FDA will acknowledge the change in our recommendations, document the rationale for the change, and discuss with the sponsor how the identified issues relate to safety and effectiveness. FDA's determination will be supported by the appropriate management concurrence.

- **Study Design Considerations.** If FDA identifies concerns that are unrelated to subject safety but which the Agency believes should be addressed in order for the study to support the sponsor's stated goals (e.g., a future marketing application or future study), FDA intends to note these concerns in the "Study Design Considerations" section of FDA's letter.[21] Where FDA provides a suggested approach to address a study design consideration, FDA will adhere to the least burdensome principle, meaning the suggested approach will constitute a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA. Sponsors are not required to modify the investigational plan to address study design considerations. If FDA recommends major modifications to the investigational plan, FDA may recommend that the sponsor submit a Pre-Submission[3] to discuss the study design before submitting modifications under the IDE. If FDA has minor suggestions for improvement of the study that do not impact subject safety or the ability of the study to support a future marketing application or future study (e.g., a suggestion regarding analysis of a tertiary or minor secondary endpoint), FDA may communicate those suggestions via email.

  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
    - 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 communicated to the sponsor that FDA believes the sponsor should consider in preparation for a marketing application or a future clinical investigation but which FDA does not believe are necessary for the sponsor to address for 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. Examples of typical future considerations include discussion of:

[21] If changes to the study design are needed in order to protect study subjects, these concerns 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.

- Known limitations of the IDE clinical investigation with regard to 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 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 to Approved IDEs

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

- To request approval for or to notify FDA of changes to the clinical investigation or the investigational device;[22]
- To provide the annual or final IDE reports to FDA;
- To report to FDA on unanticipated adverse device effects as required per 21 CFR 812.150 (b)(1), or other information related to the ongoing clinical investigation; or
- To request approval for Compassionate Use or to notify FDA of an Emergency Use.[23]

For IDE supplements that require FDA approval, the FDA decision process 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. A notable difference

[22] The guidance document entitled "Changes or Modifications During the Conduct of a Clinical Investigation," (available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm082145.htm) discusses the types of changes that require FDA approval and those that qualify for notification.

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

between FDA's review of such supplements and the review of an original IDE submission is that FDA disapproval of the supplement 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 original IDE clinical investigation remains approved and may continue.[24] For IDE supplements that are notifications or 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.

10 Pre-Decisional IDE Review Process

The Pre-Decisional IDE process discussed in the following section is a process within the Center for Devices and Radiological Health (CDRH). The Center for Biologics Evaluation and Research (CBER) does not intend to add the Pre-Decisional IDE Review Process to its current IDE program. CBER commits to providing complete and meaningful feedback through the Pre-Submission process as outlined in the draft guidance "The Pre-Submission Program and Meetings with FDA Staff."[3]

To provide sponsors with information regarding study designs that will support market approval or clearance, we have developed a novel process for IDE sponsors to collaborate with FDA in the design of high quality clinical trials that may support marketing applications if the studies are successfully executed and meet the stated endpoints without raising unforeseen safety concerns. This process, called a "Pre-Decisional IDE," is a voluntary approach to enable sponsors to obtain timely feedback from review staff on a near-final IDE application, with the opportunity for a mid-cycle interaction with the review team to promote a clearer understanding and quicker resolution of major issues with device or subject safety as well as study design. In contrast to the Pre-Submission process, Pre-Decisional IDEs will include data and full study protocols and reports where appropriate, and will be reviewed in a similar manner as an IDE, allowing for more complete and meaningful feedback from review staff. An overview of the Pre-Decisional IDE process in flowchart form is provided in Appendix A.

FDA believes this process could result in faster approval of IDE submissions that may support market approval or clearance, and help to address several commonly reported challenges in the initiation of clinical trials, such as delays in IRB approvals and reimbursement from third party payers. Ultimately, this process is intended to lead to faster enrollment and completion of trials for selected devices. Another objective of this process is to promote more efficient allocation of FDA and sponsor resources, with submission of higher quality IDE applications and higher quality data generated from the studies.

The Pre-Decisional IDE process is completely voluntary and can be submitted prior to a planned original IDE, IDE amendment (e.g., in response to a previous disapproval letter), or

[24] 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.

IDE supplement, which requests approval to initiate a pivotal study. Due to resource constraints, eligibility for this process will be limited to pivotal studies for which an IDE is required. Sponsors intending to study non-significant risk devices, or conduct feasibility or research studies, or studies without US sites can utilize the Pre-Submission process to obtain feedback from the Agency.

The Pre-Decisional IDE Process

Submission

To participate in this voluntary program, the sponsor should submit the application, clearly labeled as a "Pre-Decisional IDE," to the appropriate Document Control Center (DCC).[25, 26] The application should also include potential dates and the sponsor's preference (meeting or teleconference) for a mid-cycle interaction to discuss FDA's initial feedback on the application. The application should follow the format and contain all of the content required for an IDE (see 21 CFR 812.20, 812.25, and 812.27). In addition, for the purposes of this program, the Report of Prior Investigations should include a description of the Device Evaluation Strategy employed to address the risks of the investigational device identified in a risk assessment and the potential for benefit for the identified patient population. This systematic and comprehensive approach is intended to provide FDA with a more complete picture of how the sponsor has reached the conclusion that sufficient information has been gathered to support the initiation of human clinical trials. See Appendix B for more detailed recommendations for presentation of this information.

Application Screening

Once received and assigned a number (Pre-Decisional IDEs will receive a number beginning with Q, similar to other pre-submissions), the application will be screened. In order to appropriately allocate FDA resources, within 5 calendar days of receipt of the application, the lead reviewer will evaluate whether the application is eligible and sufficiently complete for substantive review, as defined by the criteria in Appendix C. If any of these critical items is missing or inadequate for review, the lead reviewer will contact the sponsor and offer two options: the sponsor can either request that the application be converted to a Pre-Submission, or the Pre-Decisional IDE can be withdrawn and resubmitted with the missing information. If the application is converted to a Pre-Submission, the sponsor will be asked to provide specific questions upon which FDA feedback is desired. Upon receipt of this information, FDA will schedule the Pre-Submission meeting or teleconference, if requested, or proceed with review and preparation of written feedback. Note that consistent with the Pre-Submission Program, FDA intends that its review and feedback will be limited to the specific questions raised; no data will be evaluated.[3]

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[25] Submissions to CDRH should be sent to: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

[26] Section 745A(b) of the FD&C Act, added by section 1136 of FDASIA, provides statutory authority to require an eCopy after issuance of final guidance. FDA issued final guidance on this topic, "eCopy Program for Medical Device Submissions," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. Pre-Decisional IDE applications, as a type of pre-submission, must include a valid eCopy and two paper copies.

Substantive Review with Mid-Cycle Interaction

Once the Pre-Decisional IDE is accepted for review, a 30-day review clock will start. At this time, the lead reviewer should contact the sponsor to schedule the meeting or teleconference (as requested by the sponsor) to occur within 15 days after the close of the 30-day review period, or at a mutually agreeable date shortly thereafter. During the 30-day review period, the review team should conduct a full review of the information submitted.

At the end of the 30-day review period, CDRH should provide to the sponsor via email comments which have received division management concurrence that reflect the significant issues identified in the review. These comments should focus on concerns that, if the application were submitted as an actual IDE, would result in a disapproval decision (see Section 6 above); would be a condition of approval (see Section 4 above); and/or would constitute study design considerations (see Section 7 above) that FDA believes would not support a market approval or clearance either independently or as a component of a larger clinical study program.

Other less significant study design concerns or recommendations and future considerations (see Section 7 above) may be communicated if applicable and as time permits. If not communicated at this stage, such concerns should be included in FDA's later comprehensive comments, as described below. The concerns described above may not be communicated in the form of formal deficiencies, but should be in sufficient detail that the sponsor can understand the nature of FDA's concerns and to facilitate in-depth discussion.

The meeting or teleconference with the sponsor should be a maximum of 90 minutes in duration and the sponsor may recommend the topic(s) to be discussed, based on the initial feedback provided after the 30 day review period. Also the sponsor should provide draft meeting minutes.[27] To facilitate timely communication of FDA's comprehensive feedback following the meeting, the draft minutes should be provided within 7 days of the meeting.

Following the meeting, the sponsor has the option to request that the Pre-Decisional IDE be converted to an actual IDE, in which case FDA would issue a decision letter including the deficiencies and recommendations provided in the initial feedback. To request such a conversion, the sponsor should submit a letter to the appropriate DCC within 7 days of the meeting or teleconference, requesting that the previously submitted Pre-Decisional IDE be converted to an IDE. FDA intends to issue a letter within 15 days of receipt of the conversion request. If any new information, including a modified study protocol, is provided as part of the conversion request, a standard IDE review will commence and a decision will be communicated within 30 days of receipt of the conversion request.

In the absence of a conversion request, within 15 days of the meeting or teleconference, FDA should provide comprehensive written feedback on the Pre-Decisional IDE. This feedback

[27] For additional information, see the FDA draft guidance, "The Pre-Submission Program and Meetings with FDA Staff" (available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm), which, when finalized, will represent the Agency's current thinking on this topic.

should list the deficiencies and recommendations identified during the review, and taking into account any clarifications from the meeting or teleconference with the sponsor.[28] If information submitted in the subsequent IDE is consistent with that provided in the Pre-Decisional IDE and any new data submitted in the IDE application do not raise new issues materially affecting safety or effectiveness, FDA intends to adhere to the feedback and decisions reached during the Pre-Decisional IDE review. FDA intends that modifications to our feedback will be limited to situations in which FDA concludes that the feedback given previously does not adequately address important issues materially relevant to a determination of safety or effectiveness that have been identified since the time of the Pre-Decisional IDE. In such cases, FDA should acknowledge a change in our advice, document the rationale for the change, and the determination should be supported by the appropriate management concurrence.

Following receipt of FDA's complete feedback, the sponsor may choose one of the following options:

- submit the formal IDE application. You should identify which parts of the application are identical to that submitted in the Pre-Decisional IDE, and include a section in which FDA's feedback provided on the Pre-Decisional IDE has been addressed;
- submit a focused response to specific issues from the original Pre-Decisional IDE for which a follow-up discussion would be useful. If received within 30 days of FDA's feedback on the original Pre-Decisional IDE, FDA will accept the response as a supplement and provide comments by email within 30 days from receipt of the additional information. Requests for additional feedback on specific issues from the original Pre-Decisional IDE that are not submitted within 30 days after FDA's feedback should be submitted to FDA as a Pre-Submission (please reference the Pre-Decisional IDE number in the Pre-Submission); or
- submit a focused response to FDA's feedback and a request to repeat the Pre-decisional IDE process as described above (beginning after the acceptance review); resources permitting, FDA intends to grant a request to repeat the Pre-decisional IDE process only once to avoid multiple Pre-Decisional IDE cycles.

11 Examples

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

11.1 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.

[28] FDA's written feedback will be based primarily on the information provided in the original pre-decisional submission. FDA does not intend, under the pre-decisional IDE, to conduct an in-depth review of new information, data, or protocol changes that were provided during or immediately following the meeting or teleconference with the sponsor.

FDA's review results in the following conclusions:

- The data provided are sufficient to support 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 will contain recommendations. FDA's letter will inform the sponsor of a study design consideration which suggests that the sponsor modify the follow-up assessments to include the evaluation noted above. Lastly, FDA's letter includes a future consideration related to the likely need for a longer-term animal study prior to initiation of 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 a supplement 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 which addresses the study design consideration noted in FDA's letter. FDA approves the IDE without conditions. In the IDE approval letter, the sponsor is reminded of the future consideration communicated in FDA's previous letter.

11.2 Example 2

A sponsor submits an original IDE application to request approval for 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 study initiation:

- 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, which is contraindicated for these subjects. This subgroup has an unacceptably high risk of serious adverse events and should not be enrolled in the study.

FDA also identifies the following issues with the study design, which FDA believes should be addressed in order for the study to support a marketing application:

- The sponsor proposed an historical control but FDA believes a concurrent randomized control group is needed because the historical control data that are available 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 because there are essential longer-term safety and effectiveness questions regarding this device.
- Inadequacies regarding definitions associated with the safety endpoint.
- Additional details needed in the protocol regarding the statistical analysis plan.

Based on the first two concerns, FDA disapproves the study. FDA's letter conveys the four study design considerations, which the sponsor is not required to 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 also 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 that preclude the sponsor from initiating the study. FDA determines that the durability test data that were provided strongly suggest good long-term performance of the device and are sufficient to support study of the device in a small group of subjects. However, the data are not adequate to fully address the identified deficiency and longer term non-clinical durability testing should be conducted before the entire study cohort is exposed to the risks of the study. Regarding the study design considerations, 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 in order for the study to support a marketing application.

FDA issues a staged approval letter that allows the sponsor to begin enrollment in the study, for up to 50 subjects at 2 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 to the sponsor that FDA believes the current study design is unlikely to support a marketing application. The study design considerations section of FDA's letter explains why FDA believes that a historical control will not be sufficient and why 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 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, if 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 to provide the results from the durability testing and requests approval to enroll up to 300 subjects. FDA finds the results acceptable and grants approval for the sponsor to enroll the entire study cohort. FDA's approval letter again informs the sponsor that FDA believes the study design is adequate and may support a future marketing application if the study is successfully executed and meets its stated endpoints without raising unforeseen safety concerns.

11.3 Example 3 (variation on Example 2)

A sponsor submits a Pre-Decisional IDE application for 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. During the 30-day review, FDA identifies the same concerns described in Example 2. These concerns are provided to the sponsor via email prior to the Pre-Decisional IDE meeting. During the meeting, FDA and the sponsor discuss the sponsor's plan for addressing FDA's concerns. Within 65 days after the initial submission, the sponsor is provided with a list of FDA's concerns, including the need for longer term durability testing prior to full enrollment. Shortly thereafter, the sponsor submits an original IDE application which specifically responds to FDA's Pre-Decisional IDE concerns.

FDA issues a staged approval letter that allows the sponsor to begin enrollment in the study, for up to 50 subjects at 2 sites. FDA's letter informs the sponsor that, concurrent to enrollment in the study, the sponsor should conduct longer term durability testing (which the sponsor has already begun based on the Pre-Decisional IDE feedback). FDA's approval letter informs the sponsor that FDA believes the study design provided in the submission is adequate to support a future marketing application.

One month later, with 10 subjects enrolled in the study, the sponsor submits an IDE supplement to provide the results from the durability testing and requests approval to enroll up to 300 subjects. FDA finds the results acceptable and grants approval for the sponsor to enroll the entire study cohort. FDA's approval letter again informs the sponsor that FDA believes the study design is adequate to support a future marketing application.

11.4 Example 4 (variation on Example 2)

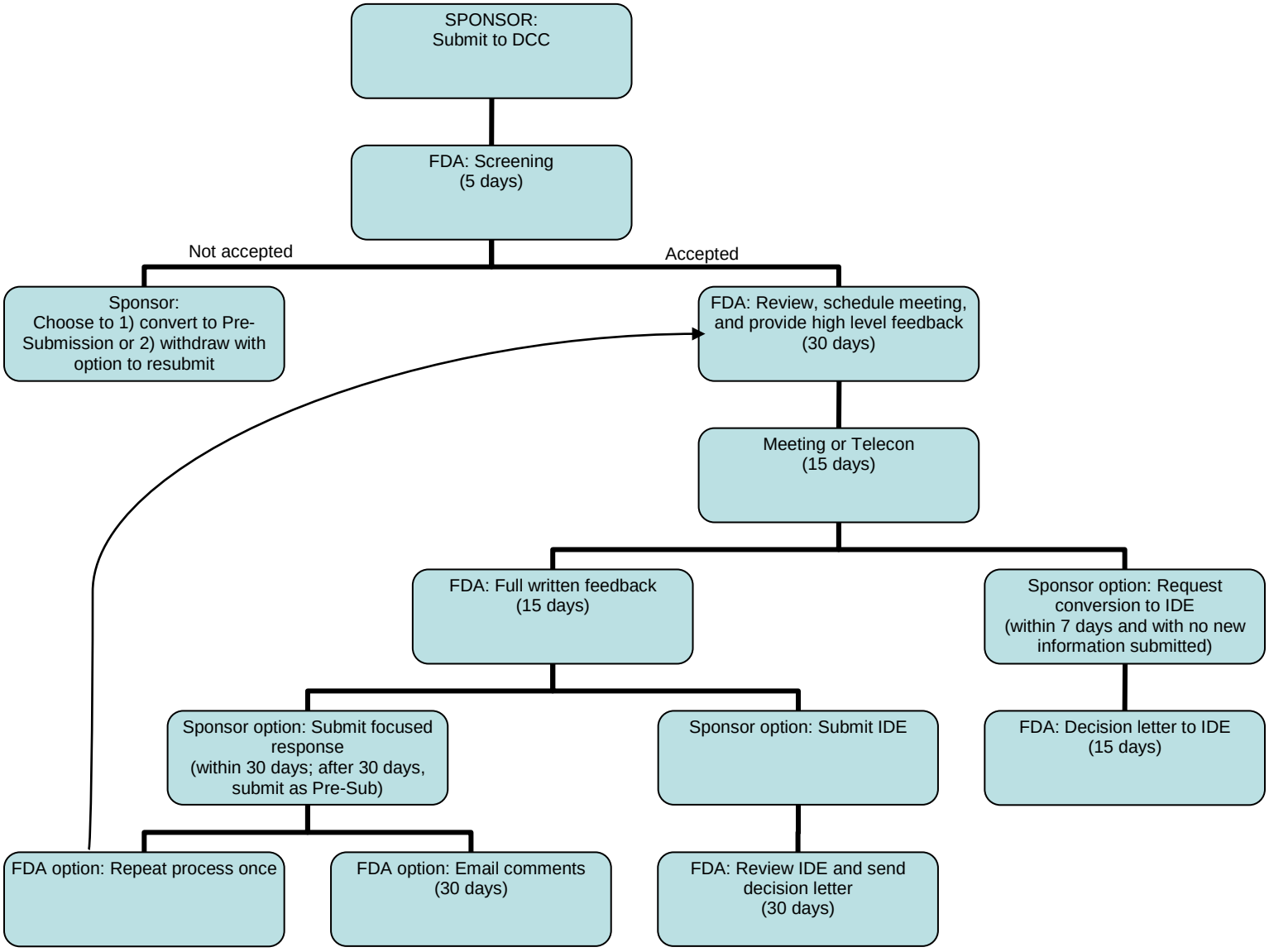
A sponsor submits an original IDE application to request approval for a 300 subject pivotal study at 10 sites to evaluate the safety and effectiveness of a permanently implanted device to treat a serious chronic medical condition. FDA identifies the same concerns described in Example 2. In contrast to Example 2, the sponsor chooses not to address the study design considerations provided in 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 section of

FDA's letters explain the modifications that FDA believes are needed in order for the study to support a marketing application. The sponsor, however, chooses to conduct the study as currently designed.

12 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 outstanding issues can be addressed (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.

Appendix A – Overview of the Pre-Decisional IDE Process



Appendix B
Elements of a Device Evaluation Strategy

The Device Evaluation Strategy is intended for assessment of both the risks and the anticipated benefits of the device. First, this strategy should be used to convey how the sponsor has considered each of the potential risks of the device, the available information from nonclinical testing and/or prior clinical studies, and mitigation strategies incorporated within the proposed pivotal study protocol to reach a conclusion that evaluation of the device in a pivotal study setting is appropriate. Second, this approach should provide insight into the information supporting the sponsor's conclusion that the anticipated benefits outweigh the risks to the study subjects.

This information can be provided in any format, narrative or tabular. The Tables below are provided for illustrative purposes only. The left column of Table 1 below provides the steps that should be followed as part of this process, with the right column providing an illustrative example of how each step might be addressed for a particular device.

Table 1 – Device Evaluation Strategy - Risks

Based on a risk assessment:	Example *(Note that this example is intended to be illustrative and should not be considered as a template for multiple device types.)*
• List necessary attributes for the device (i.e., each procedure-related function, performance-related function, and basic safety-related feature required for the device to achieve the desired performance)	o Attribute: structural integrity of the device is maintained in vivo
• For each attribute, list the types of problems or failures that might occur and could result in consequences to the device or study subject if the function or feature is not attained.	o Failure mode: device may fracture at critical construction joint
• For each potential failure mode, list the potential effects of the failure mode on the device and/or study subject	o Effect of failure: loss of structural integrity; ongoing inflammation at site of fracture; reduction in body function at and surrounding the implant site
• For each failure mode and effect of the failure:[1]	
• identify the design characteristics intended to provide the function or feature, or to address or mitigate the potential failure mode;	o Design characteristics – materials with demonstrated long-term durability used in device; finite element analysis used to design device with minimized sources of stress at construction joint

• identify the available information to support the assertions that the function or feature will be attained and/or that the failure mode will not likely occur, or will not be significant if it does occur; and	o Available information: chronic durability testing (bench), computational modeling to assess probability of device fracture and ability of device to function when fractured; animal study to evaluate actual in vivo forces and tissue reaction to fractured device
• identify the mitigation strategies in the clinical protocol intended to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute	o Clinical protocol: includes clinical visits and imaging at appropriate follow-up timepoints to screen for device fracture; patient information instructs patient to return to physician for follow-up if pain at implantation site beyond initial recovery or experiences loss of function

[1] Note that for any particular failure mode, more than one type of information may be appropriate to address the problem, either because no one approach (bench vs. animal vs. clinical feasibility study) fully addresses the problem or because one piece of information does not provide adequate assurance that the failure mode has been mitigated.

The left column of Table 2 below outlines the steps that should be followed to address the anticipated benefits of the device in the proposed study. The middle and right columns provide two examples of how these steps might be addressed for a particular device. In Example 1, the device is similar to other previously cleared or approved devices, where the mechanism of action and the clinical effectiveness is well understood. In this example, the sponsor points to available literature on the device type and specific testing on the subject device to support the anticipated benefits. In Example 2, the available information on the device (or device type) is limited as this is a novel device intended to treat a patient population with very limited alternatives. In this example, the sponsor points to the lack of significant safety concerns from prior testing, and the fact that the patient population has few satisfactory alternatives to support why the anticipated benefits outweigh the risks.

741 **Table 2 – Device Evaluation Strategy – Anticipated benefits**

	Example 1 *(Note that this example is intended to be illustrative and should not be considered as a template for multiple device types.)*	Example 2 *(Note that this example is intended to be illustrative and should not be considered as a template for multiple device types.)*
• List the anticipated benefits of the device	o Anticipated benefits of the ABC device include: o Less invasive procedure with shorter hospital stay o Faster recovery and rehabilitation time o Fewer repeat hospitalizations for re-treatment	o Anticipated benefits of the XYZ device include: o Chance of improved outcomes when drug treatments have failed o Ability to discontinue drug therapy and avoid related side effects
• Identify the available information to support each anticipated benefit	o Available information includes: o Literature establishing this type of procedure as requiring a shorter hospital stay o Literature and prior studies conducted by our company have established recovery time of 48-96 hours compared to approximately 1 week for the surgical alternative. o Device is a modified design, but operates using the same mechanism of action as a prior approved device. Animal studies have demonstrated a similar effect on accepted effectiveness measures, which should equal similar or improved outcomes regarding need for repeat hospitalizations.	o Available information includes: o Mechanism of action for the device as an approach to treat the disease is scientifically plausible based on available literature o Animal studies did not raise any overt safety concerns, but did not demonstrate device treatment might be effective. Animal model is not well understood or validated as predictive and may explain apparent lack of effectiveness. o Small pilot study suggested adverse events similar in frequency and severity to drug therapy in the intended patient population (failed drug therapy)

• List the potential alternatives to treatment or diagnosis with the subject device in the patient population to be studied	o Available alternatives: o Surgery – longer recovery and initially higher adverse event rate, but good long-term effectiveness o Medical therapy – lesser effectiveness, but ability to discontinue or make modifications if side effects problematic	o Available alternatives: o None, other than to continue drug therapy that is not providing benefit to the patient and may be causing significant side effects

Appendix C
Factors for Participation in the Pre-Decisional IDE Process

Address the following for a proposed Pre-Decisional IDE. The Pre-Decisional IDE should not be accepted if any item is marked "No," and sponsors should be referred to the Pre-Submission process.		Yes	N/A	No
1.	An IDE is required for the study (*i.e., the study is not an NSR study, an exempt study, or will be conducted wholly outside of the United States)*	☐		☐
2.	Submission is for a pivotal study (*a study intended to support, in part or alone, a marketing submission)*	☐		☐
3.	Submission contains a Device Evaluation Strategy (see Appendix 3)	☐		☐
4.	If a prior Pre-Submission was submitted for the same device, submission includes a copy of FDA's feedback and addresses the main points of FDA's prior feedback. (*Note that whether the response to FDA's prior feedback is adequate is a review issue and should not be a reason to refuse to accept the Pre-Decisional IDE.)*	☐	☐	☐
5.	Submission contains test reports for nonclinical testing *(A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, and conclusions.)* *May be N/A if the nonclinical testing is incorporated by reference to a prior approved or cleared submission (IDE, 510(k), or PMA) or study is to evaluate a commercially available device.*	☐	☐	☐
6.	Submission includes the battery of nonclinical tests typically needed for the device type, such as: bench testing, animal studies, biocompatibility testing, sterilization information, EMC/electrical safety testing, software validation; or a reference to where this information is available (e.g., prior submission)	☐	☐	☐
7.	Each nonclinical test is complete, as defined by the protocol (except for certain chronic tests where FDA typically accepts interim timepoints to allow study initiation)	☐		☐
8.	If prior clinical studies have been conducted on the device, the submission includes the study protocol or study report	☐	☐	☐

9.	Submission contains the following critical elements of the investigational plan					
	a.	Objective of the study		☐		☐
	b.	Study population (inclusion/exclusion criteria)		☐		☐
	c.	Study design, including proposed control population, if applicable		☐		☐
	d.	Proposed study endpoints		☐		☐
	e.	Ascertainment/measurement methods for study endpoints		☐		☐
	f.	Proposed follow-up (for primary analysis timepoint and any longer-term follow-up planned)		☐		☐
	g.	Statistical plan, which includes:				
		i.	Primary and secondary (if applicable) hypotheses	☐		☐
		ii.	Proposed sample size with statistical justification	☐		☐
		iii.	Statistical methods to evaluate primary and secondary endpoints	☐		☐
	h.	Informed consent document		☐		☐
	i.	Sample case report forms		☐		☐