On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

FDA notes that in particular, the QMSR does not utilize certain terms, such as "Design Controls," and "Design Validation." The elements that comprise these terms are described in ISO 13485:2016, Clause 7.3 and its subclauses, which are incorporated by reference in the QMSR.

Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

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Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

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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

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Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number FDA-2011-D-0787. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number 1782 to identify the guidance you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER) by written request, Office of Communication, Outreach, and Development (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by telephone, 1-800-835-4709 or 301-827-1800, or by e-mail at ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

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Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Guidance for Industry and Food and Drug Administration Staff

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

This document is intended to provide guidance to FDA staff, clinicians, medical device innovators, and industry on the development and review of Investigational Device Exemption (IDE) applications for early feasibility studies of significant risk devices.[1] Early feasibility studies allow for early clinical evaluation of devices to provide proof of principle and initial clinical safety data. These studies may be appropriate early in device development when clinical experience is necessary because nonclinical testing methods are not available or adequate to provide the information needed to advance the developmental process. As with all clinical studies, initiation of an early feasibility study must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures.

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

[1] *Significant risk device* is defined at 21 CFR 812.3(m) as 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.

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. Regulatory Background

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 360j(g)] establishes a framework for FDA to grant devices for investigational use an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their safety and effectiveness. This exemption is known as an Investigational Device Exemption (IDE). For significant risk devices, the sponsor must first submit an IDE application and obtain FDA approval.[2]

The FD&C Act expressly recognizes that information to be included in an IDE application may vary depending on the investigation. Section 520(g)(2)(C) states:

Procedures and conditions prescribed [for granting investigational device exemptions] may appropriately vary depending on:

- the scope and duration of clinical testing to be conducted under such exemption,
- the number of human subjects that are to be involved in such testing,
- the need to permit changes to be made in the device subject to the exemption during testing conducted in accordance with a clinical testing plan required under paragraph (3)(A) [in section 520(g) of the FD&C Act], and
- whether the clinical testing of such device is for the purpose of developing data to obtain approval for the commercial distribution of the device.

As with all clinical studies of investigational devices, an early feasibility study must comply with 21 CFR part 812, including the requirements outlined below:

- Application (21 CFR 812.20): explains when a sponsor must submit an IDE application and the information that the IDE application must contain, including the investigational plan and report of prior investigations.
- Investigational Plan (21 CFR 812.25): explains what information the Investigational Plan must contain, including the purpose of the investigation, the protocol, risk analysis, description of the device, monitoring procedures, labeling, consent materials, and information about the Institutional Review Boards (IRB) reviewing the investigation.
- Report of Prior Investigations (21 CFR 812.27): explains what information the Report of Prior Investigations must contain, including reports of all prior clinical, animal, and laboratory testing of the device.
- Supplemental applications (21 CFR 812.35): explains when changes to the device and Investigational Plan must have prior FDA approval and the appropriate manner to notify FDA of changes that do not require prior approval.

[2] 21 CFR 812.20(a).

Adopting the principles set forth in section 520(g)(2)(C) of the FD&C Act, Sections 5-8 of this guidance clarify how some of these requirements should be applied to early feasibility study IDEs.

3. Definitions and Scope

For the purposes of this guidance, clinical study types are defined as follows:[3]

- An **early feasibility study** is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application). It may be used to evaluate the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility study may guide device modifications. An early feasibility study does not necessarily involve the first clinical use of a device.
- A **first in human (FIH) study** is a type of study in which a device for a specific indication is evaluated for the first time in human subjects. This document only discusses FIH studies that meet the definition of an early feasibility study.
- A **traditional feasibility study** is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Because the study of a near-final or final device design takes place later in development than an early feasibility study, FDA would expect to see more nonclinical (or prior clinical) data in a traditional feasibility study IDE application.[4] A traditional feasibility study does not necessarily need to be preceded by an early feasibility study.
- A **pivotal study** is a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.

Early feasibility studies may be conducted for multiple reasons, such as obtaining *initial* insights into:

- the clinical safety of the device-specific aspects of the procedure;
- whether the device can be successfully delivered, implanted or used;
- operator technique challenges with device use;
- human factors (e.g., difficulties in comprehending procedural steps);
- the clinical safety of the device (e.g., evaluation of device-related serious adverse events);
- whether the device performs its intended purpose (e.g., mechanical function, making intended measurements);

[3] In this guidance, the term 'feasibility' is considered synonymous with 'pilot.' For consistency purposes, 'feasibility' is the term that should be used in reference to the types of clinical studies that precede the pivotal study phase.

[4] Additional nonclinical testing could be completed concurrent with conducting the early feasibility study if needed to support the conduct of a traditional feasibility or pivotal study.

- device failures;
- patient characteristics that may impact device performance (e.g., anatomical limitations); and
- therapeutic parameters (e.g., energy applied, sizing, dose released) associated with device use.

Unlike traditional feasibility studies, which are focused on providing initial clinical safety and effectiveness information for a near final or final device design or capturing data to guide the development of a pivotal study, early feasibility studies have a broader purpose. Early clinical experience obtained from an early feasibility study increases the efficiency of the device development process, as it may be used to:

- identify appropriate modifications to the procedure or device;
- optimize operator technique;
- refine the intended use population;
- refine nonclinical test plans or methodologies; and
- develop subsequent clinical study protocols.

To determine which type of clinical study (early feasibility, traditional feasibility, or pivotal) is appropriate to pursue, certain factors, such as the novelty of the device, its intended clinical use, the stability of the device design, and the amount of test data available to support the IDE application should be considered. An early feasibility study is appropriate when device changes are expected and when, due to the novelty of the device or its intended use, a clinical study is expected to provide information that cannot be practically obtained through additional nonclinical assessments. An early feasibility study may be appropriate even if a device or a prototype of the device has previously been used clinically for the intended clinical use. Note that not all novel devices or uses warrant an early feasibility study, nor would FDA mandate that an early feasibility study be conducted. A traditional feasibility study or a pivotal study may be more appropriate if the device design is near-final or final, respectively, depending on the amount of data available to justify the study. Prior to IDE submission and to avoid preventable delays, it is advisable to contact FDA to determine whether the proposed investigation can be classified as an early feasibility study.

The guidance provided herein is specific to early feasibility study IDEs only and is not applicable to other types of clinical studies. As discussed above, excluded from the scope of this document are studies involving the first human use of a device that do not otherwise meet the definition of an early feasibility study. For example, the first human use of a non-innovative device for a well-understood clinical use could appropriately be evaluated under a traditional feasibility or a pivotal study rather than an early feasibility study.

4. Overview

FDA recognizes the value of encouraging medical device innovation to address clinical needs and improve patient care, particularly when alternative treatments or assessments are unavailable, ineffective, or associated with substantial risks to patient safety. This guidance has been developed to facilitate the early clinical evaluation of medical devices in the United States under the IDE regulations, using risk mitigation strategies that appropriately protect human subjects in early feasibility studies.

An early feasibility study IDE application must comply with section 520(g) of the FD&C Act [21 U.S.C. § 360j(g)] and 21 CFR part 812; however, the procedures and conditions prescribed for IDEs may vary depending on the type of clinical study (see Section 2).

This guidance outlines new policy regarding the application for and approval of early feasibility study IDEs. The essential elements of this policy are as follows:

1. FDA approval of an IDE application for an early feasibility study**,** including certain first in human studies**,** may be based on less nonclinical data than would be expected for a traditional feasibility or a pivotal study (see Section 5). This is because early feasibility studies are only appropriate when additional nonclinical testing would not provide the information needed to advance the developmental process. Identification of the data necessary to support an early feasibility study should be based on a thorough device evaluation strategy that describes the device procedure, performance, and basic safety-related attributes and addresses the potential failure modes (see Section 6.3). This policy is intended to facilitate initiation of clinical studies in the United States earlier in the device development process than has historically occurred.[5]

2. This guidance introduces new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study (see Section 8), while still requiring compliance with the IDE regulations in 21 CFR part 812, as follows:
   - more types of modifications that can be made under a 5-day notification without prior FDA approval, as compared with other types of studies;
   - a contingent approval process that permits changes contingent upon acceptable nonclinical test results without requiring additional FDA action; and
   - interactive review of IDE supplements and amendments.

This guidance document highlights and reviews key principles unique to an early feasibility study IDE with respect to the Report of Prior Investigations, the clinical protocol, risk mitigation strategies, and subject protection measures (see Sections 6 and 7).

Throughout this early feasibility study guidance, there are recommendations for sponsors to interact with FDA, utilizing the Pre-Submission (Pre-Sub) process to optimize the preparation and quality of early feasibility study IDE applications.[6] Appendix 1 summarizes the key elements for an early feasibility study Pre-Sub.[7]

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[5] Note that this guidance does not recommend that sponsors prematurely initiate clinical testing when further useful and appropriate nonclinical testing can be performed for the particular device the sponsor is developing.

[6] For more information on the Pre-Submission process, 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). FDA's draft guidance represents FDA's proposed approach on this topic.

[7] In the context of this guidance, the term "Pre-Sub" means a request for informal FDA feedback on information, such as a proposed non-clinical testing plan or a draft clinical study protocol, submitted prior to the formal submission of an original IDE (to initiate an early feasibility study) or IDE supplement (to request changes to the device or study protocol).

This guidance is not intended to address all required elements of IDE applications or to provide a comprehensive tutorial on best clinical practices for investigational medical device studies. Furthermore, while this document outlines the general principles for preparing and reviewing early feasibility study IDE applications, it is not intended to provide guidance on the device-specific nonclinical information needed to justify initiation of an early feasibility study, or the specific data required to progress to other phases of clinical study for a particular device type or clinical indication. It is recommended that discussions regarding justification for study initiation take place during the Pre-Sub process.

5. Targeting approval for an Early Feasibility Study IDE Application

Because there are differences in the amount and type of information that is needed for an early feasibility study as compared to a traditional feasibility or pivotal study, the IDE application should clearly state that the proposed study is an early feasibility study and provide justification for conducting this type of study. To improve the likelihood of IDE approval, the following questions should be addressed with supporting information in the original early feasibility study IDE application:

1. What is the clinical condition to be treated or assessed by the device?
2. What is the standard of care for the clinical condition and expected clinical outcomes associated with the standard of care?
3. What are the anticipated benefits associated with use of the study device?
4. Is the information included in the Report of Prior Investigations (Section 6) adequate to support initiation of the study?
5. Does the Investigational Plan include a thorough risk analysis, sufficient risk mitigation strategies, adequate human subject protection measures, and an appropriate clinical study protocol (see Section 7)?
6. Are the potential risks associated with the device use likely to be outweighed by the anticipated benefits of the early feasibility study, that is, is initiation of the clinical study justified based on the clinical need for the device, Report of Prior Investigations and Investigational Plan?

FDA may approve an investigation as proposed, approve it with conditions, or disapprove it.[8] FDA will generally disapprove an IDE if there is reason to believe that the foreseeable risks to the study subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained.[9] When addressing benefit/risk for an early feasibility study, the concepts discussed in the FDA guidance, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm) should be considered. For early feasibility studies, in addition to the potential risks and anticipated benefits to the study subjects and the knowledge to be gained, relevant benefit/risk considerations may include the availability of safe and effective alternative therapies;

[8] See 21 CFR 812.30(a).
[9] See 21 CFR 812.30(b)(4).

prospective study subjects' tolerance for risk; risk mitigation strategies included in the clinical protocol; and information indicating that the device should perform as intended and catastrophic failure will not likely occur.

Early feasibility studies are designed to gain initial clinical insights when additional nonclinical testing methods are not available or adequate to provide the information needed to advance device development. These studies may be initiated before the design of the device is finalized and, in light of the early stage of device development and the small number of subjects, may be justified based on less evidence than for other types of clinical studies. As a result, they may carry greater unknown risk than traditional feasibility and pivotal studies. This makes human subject protection measures, such as adequate informed consent and IRB review, all the more important in an early feasibility study (see Section 7).[10] At the same time, benefits deriving from the knowledge to be gained may be substantial during the early phase of device development, particularly for innovative devices or intended uses. Even though early feasibility studies are not designed or intended to generate statistically valid results, they should be conducted for specified purpose(s), enroll the appropriate subjects, utilize meaningful endpoints, and capture relevant information so that the results can be used to further device development. Importantly, although early feasibility studies can begin before the design of the device is finalized, there still should be reason to believe that the device will function as intended.

Compared to a traditional feasibility or pivotal study, less nonclinical data would generally need to be included in the Report of Prior Investigations for an early feasibility study IDE application. For example, nonclinical testing using small sample sizes or short implant durations for *in vivo* animal studies may be sufficient to justify initiation of an early feasibility study. Under this approach, if additional and longer-term bench and animal testing are needed to support a larger clinical study of a near-final or final device design, these tests could be completed concurrently with the early feasibility study.

Some essential elements of a pivotal study, such as a prospective definition of study success and a prespecified data analysis plan, are not necessary for early feasibility study IDE applications. In addition, an early feasibility study protocol may be subject to fewer constraints as compared to a pivotal study protocol. For example, for early feasibility studies, sequential enrollment typically would not be necessary.

6. Report of Prior Investigations

The requirements in 21 CFR 812.27 apply to the Report of Prior Investigations for early feasibility study IDE applications. The information in this section is intended to clarify how certain of these requirements apply to early feasibility studies and to provide guidance on the content of the Report of Prior Investigations for an early feasibility study IDE.

The Report of Prior Investigations must include the information needed to justify a clinical investigation of a device.[11] For early feasibility studies, this information should:

[10] See 21 CFR parts 50 and 56.
[11] 21 CFR 812.27(a).

- support an expectation of acceptable clinical use (e.g., successful device placement using a benchtop model that simulates clinical conditions and/or a suitable animal model) and that the device will function as intended;
- address basic device safety, including, but not limited to, sterility, biocompatibility, software verification and validation, electromagnetic compatibility, chemical compatibility (e.g., with concomitant drugs); and
- characterize catastrophic failure modes and identify risk mitigation approaches.

When adequately justified, the information may be generated from tests utilizing non-standardized methodologies (e.g., using loading conditions that are not specified in a guidance document or voluntary standard to evaluate fatigue properties of a device for a new intended use, or using less sensitive testing equipment than specified in a standard). In determining the testing needed, the sponsor should consider the clinical significance of potential failures and the ability to predict clinical performance based on nonclinical testing. A sponsor may be able to justify deferral of certain testing until later stages of device development.

6.1 Content of the Report of Prior Investigations for an early feasibility study IDE

The information to be provided in the Report of Prior Investigations for an early feasibility study IDE application should be presented in three main sections: (1) Background, (2) Executive Summary, and (3) Detailed Reports:[12]

(1) The Background section should emphasize the unique aspects of the device design and intended patient population that will be considered when FDA evaluates whether the information provided justifies the initiation of an early feasibility study. This section should describe:
   - the clinical context for the early feasibility study:
     - the clinical condition the device is intended to treat or assess;
     - the standard of care, including the types and severity of risks and the benefits associated with current treatment options;
     - the types and severity of potential risks and the anticipated benefits that may be associated with the study device; and
     - the rationale for exposing the target population to the potential risks (i.e., whether the anticipated benefits that may be associated with the use of the study device justify the potential risks, recognizing the benefits and risks posed by current treatment or assessment options);
   - the design concept; and
   - a summary justification regarding the amount and type of information/data needed to support initiation of the early feasibility study in the specified patient population, with comment on, or comparison to, what may be expected to support the initiation of a larger clinical study.

[12] Please consult 21 CFR 812.27 for the elements that must be included in a Report of Prior Investigations.

(2) The Executive Summary section should provide a summary of the information provided and an explanation as to why this information is adequate to support study initiation. This section should include:
- a summary description of the nonclinical testing that has been performed and relevant clinical information;
- a device evaluation strategy table, as described below, that references the relevant individual test reports for the data and/or information collected to address each device or procedure-related attribute; and
- a table describing the purpose of each test or analysis, test sample description, sample size, acceptance criteria (if available), test results, any potential clinical significance of the results, and cross reference to the test reports.

(3) The Detailed Reports section should include the reports for tests conducted and additional information available to support the initiation of the early feasibility study. This section should include:
- individual reports for each bench and laboratory test, computational modeling analysis (e.g., finite element analysis), and *in vivo* animal study:
    - each test report should include the purpose, test method, sample selection, results, discussion of the acceptability of the results, and when appropriate, justification and clinical applicability of the acceptance criteria;[13]
- a summary of leveraged nonclinical information in appropriate detail, depending on the source of the information, such as:
    - individual test reports not previously submitted to FDA;
    - references to previously reviewed regulatory submissions;
    - reports in the published literature
- a summary of any relevant clinical information, with references, if available.

The following sections provide further guidance on the purpose and preparation of the key elements of a Report of Prior Investigations for an early feasibility study IDE.

6.2 Design concept

The Background section of a Report of Prior Investigations for an early feasibility study IDE should include information to clearly describe the design concept, such as the:
- device description (e.g., physical description, figures, materials of construction, software documentation), principles of operation, what the device key design features are intended to do, and how the key design features accomplish the intended objective;
- intended clinical use, designated by the medical condition or lesion type to be treated or assessed, and any associated anatomical locations and limitations;
- conditions of use/intended *in vivo* environment; and
- minimum design-life of the device (i.e., the minimum duration for which a device has been designed to function as intended).

[13] Characterization tests (i.e., testing conducted to describe the device) may not have specified acceptance criteria and it may not be possible to establish acceptance criteria until clinical data are obtained.

The device design concept provides the basis for identifying the appropriate testing and test methodologies and guides the device evaluation strategy.

6.3 Device evaluation strategy

The device evaluation strategy in the Executive Summary section of a Report of Prior Investigations should describe and justify the leveraged information and testing conducted to support initiation of an early feasibility study, with cross-references to the Detailed Reports section of a Report of Prior Investigations. The purpose of the device evaluation strategy is to facilitate FDA's understanding of the value of the leveraged information and why the information included in the Report of Prior Investigations is adequate to support IDE approval. To maximize the efficient use of sponsor and FDA resources, it is desirable for the sponsor to consult with FDA and for both parties to reach agreement on the strategy before the sponsor conducts the proposed testing. Therefore the device evaluation strategy would optimally be discussed during Pre-Sub interactions. This is particularly important when:

- the sponsor is providing less nonclinical data as compared to what would be expected for a traditional feasibility or pivotal study;
- there is no FDA guidance or voluntary standard specific to the device and intended use proposed to be studied; and/or
- certain nonclinical tests are more relevant than others in addressing basic safety and potential catastrophic failures, or to support basic device functionality.

Section 6.3.1 describes a systematic method for presenting the device evaluation strategy for an early feasibility study. This method involves identifying the key information necessary to justify initiation of the study based on a risk assessment, taking into consideration the anticipated benefits that may be associated with the device.

Even if testing has been done in accordance with a guidance document or voluntary standard, a justification should be provided to explain why the testing specified in the guidance or standard applies to the device and its intended use. This may involve a modification of the device evaluation strategy process described in Section 6.3.1, focusing on the unique aspects of the device or intended use as compared to those specifically addressed by the guidance or standard.

Section 6.3.2 presents an option for obtaining early FDA feedback on a comprehensive device evaluation strategy that extends beyond the early feasibility phase.

6.3.1 Device evaluation strategy for an early feasibility study

The device evaluation strategy for an early feasibility study should be based on a risk/benefit assessment.[14] In general, for an early feasibility study, the evaluation strategy should be focused on identifying the information needed to address significant safety concerns and support basic device functionality.

The device evaluation strategy is best outlined in a table, with the following column headings:

[14] At the early feasibility stage, a descriptive assessment may be more informative than a formal failure modes and effect analysis (FMEA), which provides a quantitative ranking of risks.

- *Column 1, Device Attribute*: Each procedure-related function, performance-related function, and basic safety-related feature required for the device to achieve the desired performance (i.e., benefit).
  Note: For the purpose of the device evaluation strategy, a function is defined as the ability of the device to accomplish a goal and a feature is defined as an essential property of the device.
- *Column 2, Potential Failure Modes*: For each Device Attribute, 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.
- *Columns 3 and 4, Potential Device and Clinical Effects of Failure*: For each Potential Failure Mode, the potential effects of the failure mode on the device and/or study subject (i.e., risks).
- *Column 5, Device Design Information*: For each Potential Failure Mode, the design characteristics intended to provide the function or feature or to address or mitigate the potential failure mode. Relevant anticipated benefits associated with the design characteristics may be highlighted in this column.
- *Columns 6 and 7, Leveraged Nonclinical Information and Supportive Clinical Information*: For each Attribute and/or Potential Failure Mode, the information from internal or external sources to supplement the assertions that:
  a) the function or feature will be attained; and/or
  b) the failure mode will not likely occur or will not be catastrophic if it does occur.
- *Column 8, Nonclinical Device Testing*: The bench, laboratory, analytical, and/or animal testing of the study device (i.e., the device that will be used in the clinical study) to complete the evaluation of the attribute and the potential failure mode(s).
- *Column 9, Clinical Study Mitigation Strategies*: For each Potential Clinical Effect of Failure, the mitigation strategies included in the clinical protocol intended to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute.
  Note: Although the Clinical Study Mitigation Strategies are a subset of the risk mitigation strategies included in the risk analysis section of the Investigational Plan, they should be presented within the device evaluation strategy table to emphasize their applicability to specific failure modes and effects of failure.

Table 1 defines the device evaluation strategy column headings and Table 2 describes the information recommended for inclusion in a device evaluation strategy table.

Table 1: Column Definitions for a Device Evaluation Strategy Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
				Knowledge Base				
Device Attribute	Potential Failure Modes	Potential Effects of Failure		Device Design Information	Supportive Information		Nonclinical Device Testing	Clinical Study Mitigation Strategies
		Potential Device Effects of Failure	Potential Clinical Effects of Failure		Leveraged Nonclinical Information	Supportive Clinical Information		
Each individual device function or feature required for the device to achieve the overall desired performance. Note: A function is the ability of the device to accomplish a goal and a feature is an essential property of the device.	The failures that might occur and could result in consequences (effects) to the device or study subject if the function or feature is not attained.	The potential effect(s) of the failure mode on the device.	The potential effect(s) of the failure mode on the study subject.	The design characteristics intended to provide the function or feature or to address or mitigate the potential failure mode, and the anticipated benefits of these characteristics. And, if applicable, relevant information considered in the design of the device (i.e., design input) to support the assertions that: a) the function or feature will be attained; and/or b) the failure mode will not likely occur or will not be catastrophic if it does occur.	Nonclinical information leveraged from internal or external sources to support the assertions that: a) the function or feature will be attained; and/or b) the failure mode will not likely occur or will not be catastrophic if it does occur.	Relevant clinical experience obtained from internal or external sources for a similar device or indication to support the assertion that: a) the function or feature will be attained; and/or b) based on an evaluation of the clinical effects of failure, the failure mode will not likely occur or will not be catastrophic if it does occur.	Bench, laboratory, analytical, and/or animal testing of the study device (i.e., the device that will be used in the clinical study) to complete the evaluation of the attribute and the potential failure mode(s), considering the information in Columns 3-7 and 9.	Mitigation strategies included in the clinical protocol intended to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute.

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Table 2: Information To Be Included In The Device Evaluation Strategy Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
				Knowledge Base				
Device Attribute	**Potential Failure Modes**	**Potential Effects of Failure**		**Device Design Information**	**Supportive Information**		**Nonclinical Device Testing**	**Clinical Study Mitigation Strategies**
		Potential Device Effects of Failure	**Potential Clinical Effects of Failure**		**Leveraged Nonclinical Information**	**Supportive Clinical Information**		
List each procedure-related function needed for the device to be used successfully. List each performance-related function or feature needed for acceptable device performance. List each necessary basic safety-related feature.	For each attribute, list the failure modes that could result if the attribute is not attained.	For each failure mode, list the potential effects of the failure mode on the device.	For each failure mode, list the potential effects of the failure mode on the study subject.	List the design characteristics intended to: a) provide the function or feature, identifying any anticipated benefits that may be associated with the characteristics; or b) address or mitigate the potential failure mode. And, if applicable, identify and reference the relevant information considered in the design of the device (i.e., design input) to support the assertions that: a) the function or feature will be attained; and/or b) the failure mode will not likely occur or will not be catastrophic if it does occur.	Identify and reference the nonclinical information leveraged from internal or external sources to support the assertions that: a) the function or feature will be attained; and/or b) the failure mode will not likely occur or will not be catastrophic if it does occur. Explain and justify how the specific aspects of the testing or analysis are relevant to the evaluation of the attribute or failure mode under consideration.	Identify and reference any relevant clinical experience obtained from internal or external sources for a similar device or indication to support the assertion that: a) the function or feature will be attained; and/or b) based on an evaluation of the clinical effects of failure, the failure mode will not likely occur or will not be catastrophic if it does occur. Explain and justify how the specific aspects of the clinical experience are relevant to the evaluation of the attribute or failure mode under consideration.	List and reference the testing and/or analyses on the study device (i.e., the device that will be used in the clinical study) to evaluate the attribute and the potential associated failure mode(s). For tests or analyses intended to address multiple attributes, identify the specific aspects of the testing or analysis relevant to the evaluation of the attribute or failure mode under consideration.	Identify any applicable mitigation strategies that will be utilized during the clinical study to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute.

The process of constructing the device evaluation strategy table can be divided into four parts:

1) **Device Deconstruction** – identify the attributes needed for the device to achieve the design goals (Column 1), the potential failure modes (Column 2), and the effects of failure (Columns 3 and 4).
2) **Knowledge Base and Mitigation Strategies** – describe what is known from the device design (Column 5), leveraged nonclinical and clinical information from internal or external sources (Columns 6 and 7), and the clinical study mitigation strategies (Column 9) applicable to the attributes and failure modes.
3) **Evidence Gaps** – identify gaps in the existing information indicating that additional testing may be needed to justify study initiation, considering the Knowledge Base and focusing on the following:
    a. attributes most important for the intended use;
    b. potential failure modes most likely to be associated with catastrophic failures; and
    c. basic safety requirements (e.g., biocompatibility).
4) **Filling the Gaps** – identify in Column 8 the bench, laboratory, analytical, and/or animal testing to complete the evaluation of the device attributes and the potential associated failure modes, considering the following:
    a. Evidence Gaps;
    b. clinical context for the early feasibility study [see Section 6.1(1)];
    c. potential types, frequency, and severity of the clinical effects of failure that may be associated with the device or procedure; and
    d. Mitigation Strategies.

Any implications of the unique aspects of the device or the proposed intended use should be emphasized in the device evaluation strategy table. Similarly, the items listed under the Evidence Gaps (3a-c), above should be highlighted in the table.

Submitting the draft device evaluation strategy table in a Pre-Sub will maximize efficiency. In the draft table, the Nonclinical Device Testing (Column 8) may include proposed or completed testing, but reaching consensus with FDA on the appropriate testing prior to completion is preferable. Pre-Sub discussions on the device evaluation strategy table may focus on the following:

- whether Columns 1-4 (the Device Deconstruction) are complete,
- the applicability and usefulness of the information in Columns 5-7 and Column 9 (the Knowledge Base and Mitigation Strategies),
- whether the right information was considered when identifying the Evidence Gaps, and
- whether the additional proposed (or completed) testing described in Column 8 (Filling the Gaps) will likely complete the evaluation of the attribute or failure mode.

These discussions should continue under the early feasibility IDE, when the device evaluation strategy table has been further refined, and should focus on whether the information and data provided adequately address the specific attributes or failure modes.

For the early feasibility IDE, the level of detail to include in each row of the device evaluation strategy table should be proportional to the importance of the attribute to the intended use, the potential severity of the failure modes, and whether the method of assessing the attribute or failure mode is generally understood. A summary of Knowledge Base and Mitigation Strategies

information should be included in the rows of the table for the most critical attributes for achieving the intended function of the device and for the potentially catastrophic failure modes. Descriptive information should be included for novel methods of assessment. Conversely, for less critical attributes, less clinically relevant failure modes, and standardized methodologies, it may be adequate to simply identify the applicable information or tests without providing descriptive information in the table. A comprehensive presentation of all leveraged information and completed testing should be included in the Detailed Reports section of the Report of Prior Investigations. Interaction between the sponsor and FDA is encouraged to establish consensus on the most important attributes and to determine the appropriate level of detail that should be included in the rows of the table.

It is understood that there may be uncertainty regarding some elements of the device evaluation strategy, depending on the novelty of the device or intended use. The device evaluation strategy table should be updated as new information emerges about the potential risks and the appropriate assessment of the device.

Depending on the device and intended use, it may be appropriate and acceptable to defer some device testing until after the early feasibility study, if the testing will not provide additional meaningful information regarding basic device safety or functionality. For some devices or intended uses, particularly for highly innovative devices, FDA recognizes that appropriate nonclinical test methodologies to assess some critical parameters may not be available or are impractical to complete, and therefore, these parameters would need to be evaluated clinically.

An example of a portion of a draft device evaluation strategy table for a hypothetical permanently implanted, percutaneously delivered, covered metallic device is presented in Appendix 2.

6.3.2 Overall device evaluation plan (at the sponsor's discretion)

It may be useful to obtain FDA feedback on the overall device evaluation plan. The plan would identify the types of information or levels of testing that may be needed to progress beyond an early feasibility study and propose the timing of deferred or additional testing.

The additional information/data that may be used to support progression to each of the planned developmental phases (e.g., traditional feasibility study, pivotal study, marketing application) can be listed in Column 8 (Nonclinical Device Testing) of the device evaluation strategy table. It should be noted that not all developmental phases may be necessary for every new device or intended use.

6.4 Bench and laboratory testing and computational modeling

For early feasibility studies, the full battery of tests that would be expected for evaluation of a final device design is not required for IDE approval. As outlined in Section 6.3 FDA encourages sponsors to consider the relationship between a device attribute or failure mode and the anticipated clinical consequences to determine the testing needed to support the IDE application. This approach may be used when justifying the device evaluation strategy, including the use of preliminary results or deferral of certain testing at the early feasibility phase of device development.

Computational modeling (CM) can be used for a variety of purposes to support the initiation of an early feasibility study. For example:

- For long-term implants in which the boundary and loading conditions are known, CM may be used to predict the long-term durability of the device.
- For long-term implants in which the boundary and loading conditions are not well-defined, CM may be useful for iterative design modifications, where simulations can be used to optimize the device design or enhance the design of prototypes.
- For certain test scenarios, which cannot be evaluated using other nonclinical methods or clinically, CM may be used. For example, to aid in assessing MRI safety, CM may be used to simulate certain worst-case MRI conditions that cannot be replicated in an animal model and cannot be tested ethically in humans.

Discussions with FDA regarding protocols for complex and novel testing are strongly encouraged.

6.5 In vivo animal studies

In vivo animal studies provide unique anatomic and clinical pathologic information on the local and systemic responses to device use. An animal study may be conducted to support the initiation of an early feasibility study when an animal model is needed to further assess basic safety or device functionality beyond the information provided from non-animal testing.

An animal study should involve the use of a validated animal model, when available, for which the results are likely to predict risks in humans. In cases in which a validated animal model is unavailable, a focused animal study to address a limited range of safety issues may be conducted to complement the non-animal testing. A rationale for addressing questions typically answered by animal studies with alternative methods or data should be provided in the IDE application.

Animal studies should not be viewed as an alternative to adequate bench testing, and whenever possible, protocols should apply the principles of reduce, replace, and refine. For example, substitutions for the use of live animals, such as *in vitro* methods (e.g., validated cell culture experiments), cadaveric studies, or the use of computer simulation may be considered. The size of the animal study depends on the device and how well the animal model provides anatomic, physiologic, and procedural similarities to humans. Recognizing the inherent variability of results, animal studies should be large enough to show consistent results. Short-term animal studies may be adequate for the initiation of an early feasibility study. However, additional animal study data may be needed to support a larger clinical study with a near-final or final device design.

Good Laboratory Practices (GLP) for animal care and study conduct as specified in 21 CFR part 58 assure the quality and integrity of safety data to support IDE applications. Non-GLP study data may be used to support an early feasibility study IDE application only if the deviations from GLP are identified and justified and do not compromise the validity of the study results.[15] For example, if an independent quality assurance unit is not utilized, a sponsor should describe how bias was mitigated and how the study was verified to be authentic and complete. Both GLP and

[15] See 21 CFR 812.27(b)(3).

non-GLP studies should include independent monitoring and assessments with full disclosure of study findings.

Discussions with FDA on study protocols, including the evaluation of operator technique, safety outcomes, and the effects of the biological system on the device, are encouraged prior to the initiation of *in vivo* animal studies.

6.6 Prior clinical information

For all IDEs, a summary of any prior clinical studies of the device used for the proposed intended use must be provided in the Report of Prior Investigations.[16] For early feasibility studies, although clinical data may not be available for the test device for its proposed intended use, any relevant background clinical information should also be provided. Relevant information includes data or publications on:

- similar or related devices utilized for the proposed intended use; or
- the subject device or similar devices used for a different purpose.

This information may come from clinical use outside of the United States and may be used to support proof of principle and/or to address the likelihood of potential failure modes that may be observed during the early feasibility study. If such information is available, it should be summarized in a format appropriate for the type of information (e.g., clinical study reports, summaries of publications with copies of the citations, individual experience with the device or prototype outside of a clinical study).

7. Investigational Plan

The requirements in 21 CFR 812.25 apply to the Investigational Plan for early feasibility study IDE applications. The information in this section is intended to clarify how certain of these requirements apply to early feasibility studies. In the IDE application, the study should be clearly designated as an early feasibility study. The proposed study should reflect the novelty of the device and medical need. Use of the Pre-Sub process to discuss the Investigational Plan with FDA is highly recommended.

Note that small clinical trials to determine device feasibility are specifically excluded from the definition of "applicable device clinical trials" requiring registration on www.ClinicalTrials.gov.[17] FDA is interpreting this exception to apply to early feasibility studies.

7.1 Risk analysis and mitigation

The Investigational Plan must include a thorough risk analysis which describes the type and estimated severity of risks to the subjects, how risks will be minimized, and a justification that the risks are reasonable in relation to the expected benefits.[18] The risk analysis should include the anticipated benefits and potential clinical effects of failure identified in the device evaluation strategy, as well as risks independent of the device that may be related to the underlying disease,

[16] See 21 CFR 812.27.
[17] 42 U.S.C. 282(j)(1)(A)(ii).
[18] See 21 CFR 812.25 and 812.30(b)(4).

comorbidities, or inherent to the procedure, and benefits unique to the device concept. For example, a risk analysis may include the risks associated with use of anesthetic and contrast agents and the benefits of a less invasive intervention.

For an early feasibility study, the methods to minimize risks may include the use of standard approaches, with additional mitigation strategies to protect individual study subjects and future study participants during the ongoing early feasibility study. Examples of both standard and additional risk mitigation strategies include:

- use of study sites that have sufficient expertise and resources to manage adverse events and provide appropriate alternative therapies if needed;
- identification of qualified investigators with adequate training to conduct the early feasibility study;
- a plan to capture human factors information during the course of the study to modify the procedures or device as necessary based on the information obtained;
- specifying appropriate study inclusion and exclusion criteria;
- limiting the sample size to a reasonable number for an early feasibility study (e.g., 5-10 initial subjects);
- follow-up assessments at regular intervals to monitor subject safety and device effectiveness (i.e., potentially more frequent than for a traditional feasibility or pivotal study);
- timely reporting of serious adverse events (e.g., after each occurrence rather than only in a periodic progress report);
- timely reporting of device performance parameters, which help determine whether the device functions as intended (e.g., measurements of deliverability, stability, handling, visualization, patency, integrity);
- non-sequential enrollment, that is, initial device use in subjects with more favorable anatomical characteristics as compared to the population otherwise eligible for the early feasibility study (e.g., selecting subjects that meet study eligibility requirements but do not have anatomic features that may increase the difficulty of device use); and
- a pre-specified plan for periodic patient outcome assessments and reporting prior to enrollment of additional patients (e.g., as frequently as after each use of the device).

7.2 Clinical protocol

The Investigational Plan for an early feasibility study must present objectives that reflect the purpose of the clinical study.[19] The study protocol should include study endpoints, endpoint assessment methods, and adverse event definitions as appropriate for an early feasibility study. The study protocol must also clearly describe the methodology to be used in the investigation.[20] This should include a comprehensive description of the subjects to be enrolled in the study. When identifying the appropriate study population, subject risk tolerance (based on the severity of the underlying condition and limitations of alternative treatment options) and the ability to utilize the standard of care if the study device does not function as intended should be considered. The subjects may have different clinical characteristics as compared to the population to be included in a future pivotal study (e.g., the early feasibility cohort may have more comorbidities, or a more advanced stage of disease). However, to ensure that the study

[19] 21 CFR 812.25(a).
[20] 21 CFR 812.25(b).

will provide information useful for the device development process, and to avoid exposing subjects to risks in the absence of any anticipated benefit, the study should avoid enrolling subjects for whom success is unlikely due to general health issues.

To allow for appropriate flexibility with respect to patient selection and data interpretation, the early feasibility study protocol generally does not need to include the same level of detail as a pivotal study protocol (see Section 5), but it needs to ensure adequate capture of adverse clinical events and device performance information.

7.3 Human subject protection measures

Any early feasibility study involving human subjects must comply with FDA human subject protection requirements, including obtaining informed consent and Institutional Review Board (IRB) (or ethics committee) oversight.[21] These measures should be tailored to the subject population and the risk profile of the device under investigation.

7.3.1 Informed consent

Sponsors, investigators, and IRBs should pay particular attention to the adequacy of informed consent in early feasibility studies. The informed consent process for early feasibility studies, as for all clinical investigations, must adhere to the requirements described in 21 CFR part 50 subpart B – Informed Consent of Human Subjects. An informed consent form for early feasibility studies must comply with the requirements in 21 CFR 50.25 and should address the distinctive aspects of an early feasibility study. For example, subjects must be told that the study involves research and must be provided an explanation of the purposes of the research,[22] including that the proposed investigation is an early feasibility study (e.g., a small study of an innovative device or innovative clinical use of a device for which there may be less nonclinical data than would be required for a larger study). The novelty of the device or procedure must also be described in language understandable to the subject.[23]

As discussed above, an early feasibility study may carry greater unknown risk as compared to traditional feasibility and pivotal studies. Subjects must be made aware during the informed consent process that there may be unforeseeable risks associated with participation in the study due to limitations in available data and experience with the device.[24] A description of any benefits to the subject or to others which may reasonably be expected from the research must be provided during the informed consent process in accordance with 21 CFR 50.25(a)(3). For example, the form should note that even if there is limited or no expected personal benefit to the study subject, future patients with the disease or condition may benefit from the information obtained during the early feasibility study. The consent form should not include language that could lead subjects to overestimate the chance of personal benefit.

Additional guidance on the information to include in an informed consent form for an early feasibility study can be found in Appendix 3.

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[21] See 21 CFR parts 50 and 56.

[22] 21 CFR 50.25(a)(1). For more information on Informed Consent see, "A Guide to Informed Consent - Information Sheet," at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm.

[23] 21 CFR 50.20.

[24] See 21 CFR 50.25(b)(1).

7.3.2 Institutional Review Boards

As with all clinical investigations, early feasibility studies must adhere to the requirements for study oversight by an IRB, as described under 21 CFR part 56. For example, IRBs must determine if the risks to the subjects are minimized to the extent possible, and consider whether the risks to the subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may be obtained.[25]

IRBs must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year, as required by 21 CFR 56.109(f). It is likely that more frequent oversight by the IRB to assure human subject protection may be appropriate for early feasibility studies. This may include, for example, continuing review on a more frequent basis than annually, continuing review after a small target number of subjects have been studied, and/or graduated enrollment based upon a safety analysis of the preceding subjects.

7.4 Monitoring

7.4.1 Monitoring procedures

Detailed monitoring procedures, appropriate for an early feasibility study, must be included in the Investigational Plan, as required by 21 CFR 812.25(e). For more information on standard monitoring procedures, see FDA's draft guidance, "Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf). FDA's draft guidance represents FDA's proposed approach on this topic. Due to the limited number of study sites and subjects, and the expected close oversight of each study subject, the monitoring procedures for early feasibility studies may deviate from standard procedures and should be tailored to the particular study being conducted.

7.4.2 Data monitoring committee (DMC)

FDA's guidance, "Establishment and Operation of Clinical Trial Data Monitoring Committees," (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf) notes that:

> [E]arly studies are often exploratory in nature; they are frequently not randomized or controlled and therefore accumulating results are known to the investigators and sponsor. Issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting. Nevertheless, for difficult situations in which the potential scientific gain from continuing a study must be evaluated in the context of ethical considerations for ensuring subjects' rights and welfare, particularly in settings such as those described above, DMCs may be helpful to investigators, sponsors, and IRBs by providing independent, objective expert counsel.

For certain early feasibility studies, a DMC composed of clinicians, scientific experts, and individuals with ethical expertise may be helpful in evaluating data relatively early in the course of the study and would provide an additional layer of human subject protection. Use of a DMC

[25] 21 CFR 56.111(a)(1) and (2).

could be proposed by a sponsor as a risk mitigation strategy element, particularly for studies where additional independent oversight would be of value.

8. Iterations during early feasibility studies

Because modifications to the Investigational Plan are expected during early feasibility studies, discussions with FDA to facilitate timely implementation of changes are particularly important throughout the Pre-Sub and IDE processes. The requirements outlined in 21 CFR 812.35 and explained in, "Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082145.htm), regarding changes to a device or clinical protocol apply to all types of investigational studies. However, this guidance describes new policy, interpreting the requirements differently for early feasibility studies.

To facilitate timely device and/or clinical protocol modifications during an early feasibility study, this guidance introduces the following approaches:

1. Permitting a broader array of modifications to the device and the clinical protocol under 5-day notification without prior FDA approval during an early feasibility study as compared to other types of studies;
2. For anticipated changes that would require prior FDA approval, allowing a sponsor to seek **contingent approval** beforehand, which would permit changes contingent upon acceptable nonclinical test results without requiring additional FDA action;
3. For early feasibility study IDE supplements and amendments, utilizing a new **interactive review** process that encourages communication with FDA during the 30-day review cycle.

Note that annual progress reports to the FDA are required by 21 CFR 812.150(b)(5) for studies of significant risk devices. Some minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information are not required to be submitted in supplemental applications but must be identified in these annual progress reports. [26]

8.1 Changes requiring FDA notification (5-day notice)

For all IDEs, a sponsor may make certain changes to an investigational device or clinical protocol during the study without prior FDA approval of a supplemental application by submitting a notice to FDA within 5 working days of making the change.[27] A sponsor may make changes with 5-day notice if: (i) the changes to the device are made in response to information gathered during the course of the investigation, and the changes do not constitute a significant modification in design or basic principles of operation; or (ii) the changes to the clinical protocol do not affect: (a) the validity of the data or information, or the relationship of likely patient risk to benefit relied upon to approve the protocol, (b) the scientific soundness of the plan, or (c) the

[26] See 21 CFR 812.35(a)(4).
[27] 21 CFR 812.35(a)(3).

rights, safety, or welfare of the human subjects involved in the investigation.[28] The information to be included in such a notice is described in 21 CFR 812.35(a)(3)(iv).

Device developmental changes that do not constitute a significant change in design or basic principles of operation are generally appropriate for 5-day notices. For early feasibility studies, FDA would consider a broader range of changes not to be significant as compared to other types of studies. This is in part because the evaluation of an early feasibility study does not depend on statistical analyses of data collected or the pooling of data among study subjects, which would require the use of a consistent device design. However, the changes should be expected not to adversely affect device performance or pose additional risk to the study subjects.

For changes to an early feasibility study clinical protocol, the most relevant requirements for application of the 5-day notification option are that the changes: (1) not alter the relationship of likely subject benefit and risk relied upon to approve the protocol, and (2) not affect the rights, safety or welfare of study subjects.[29] Since, as discussed above, early feasibility studies are expected to have enhanced risk mitigation strategies and patient protection measures directed toward each study subject, sponsors should explain how these instruments provide additional support when considering changes appropriate for implementation under a 5-day notice. The other criteria, specifically that changes to the clinical protocol not affect the validity of the data or the scientific soundness of the investigational plan,[30] should generally be much easier to meet for early feasibility studies than for other studies, because these studies are not intended to obtain statistically valid data or test statistical hypotheses.

The types of changes that may be considered for 5-day notices may be discussed during Pre-Sub interactions and prospectively identified within the IDE application to facilitate timely implementation of device and clinical protocol modifications. For changes that are appropriate for implementation under a 5-day notice, the contingent approval process (described below), in which the information needed to justify a change is identified, may be used as an alternative approach.

Appendix 4 includes examples of the types of changes that may be appropriate for 5-day notification during an early feasibility study.

8.2 Changes requiring FDA approval

The first step in obtaining FDA approval of changes during the early feasibility study should be informal discussion with FDA, using the Pre-Sub process when appropriate, to identify the proposed modifications, the reasons for the modifications (e.g., adverse events observed during the clinical study), the purpose of the modifications, and the evaluations needed to support use of a modified device and/or changes to the clinical protocol.

Following the informal discussion, there are two new approaches for obtaining timely FDA approval of changes to early feasibility studies: 1) contingent approval and 2) interactive review.

[28] 21 CFR 812.35(a)(3)(i) and (ii). These changes must be supported by credible information as defined at 21 CFR 812.35(a)(3)(iii). 21 CFR 812.35(a)(3).
[29] See 21 CFR 812.35(a)(3)(ii).
[30] 21 CFR 812.35(a)(3)(ii)(A) and (B).

1) Contingent approval. When device iterations or changes to the clinical protocols are anticipated, identified, and explained prospectively, the contingent approval process may be used. This process may be informally discussed during Pre-Sub interactions and formally proposed during the original early feasibility study IDE application or in IDE supplements.

   In order to obtain contingent approval, during the 30 day review cycle the sponsor and FDA should reach final concurrence on the nonclinical test plan and associated acceptance criteria to evaluate the anticipated changes. Once these are agreed upon, FDA may approve the anticipated changes contingent on the sponsor's successful completion of the test plan and the reporting of the test data to FDA within 10 calendar days of implementing the change.

   If the sponsor deviates from the conditions of FDA's approval, the contingent approval would no longer be valid, and the sponsor would need to renegotiate the test plan with FDA and obtain a new contingent approval. Alternatively the sponsor could seek approval through the submission of a 30-day IDE supplement.

   If the sponsor is able to anticipate multiple changes to the clinical protocol or potential device iterations, a proposal that covers these changes may be provided in the original early feasibility IDE application or in a single supplement. For device modifications, the sponsor would need to prospectively identify the appropriate testing plan and acceptance criteria for each type of change to allow for contingent approval of all of the proposed changes. For example, if a sponsor anticipates iterations of the materials of construction based on clinical data generated during the early feasibility study, they may present their strategy in a single IDE supplement and receive approval for the iterative plan, contingent on successful completion of the test plan for each material type. Within 10 days of implementing each change, an IDE supplement should be submitted to provide the data and to report to FDA the current device iteration being used in the study.

   For the clinical protocol, the sponsor could propose changing several clinical parameters during the early feasibility study to determine the most relevant parameters for future evaluation of the device. If the sponsor can adequately justify the use of each parameter within the initial IDE submission or in an IDE supplement, the approval of the changes would be contingent only on reporting to FDA, within 10 days of implementing each change, that the changes were made. This report should include a copy of the clinical protocol currently being used. For other changes to the clinical protocol, it may be necessary to collect additional information (e.g., outcomes for the initial patients treated) to support the changes. In this case, FDA concurrence with the information to be collected and the results needed to support the change would need to be obtained prior to FDA granting contingent approval. The approval would be contingent on reporting the information, in addition to providing a copy of the protocol currently being used.

   Appendix 4 includes examples of the types of changes that may be appropriate for contingent approval during an early feasibility study.

2) Interactive review. Interactive review involves the continuation of informal discussions with FDA during the 30-day IDE supplement review cycle. This process may be used in situations where the sponsor has completed nonclinical testing to evaluate device modifications, or where changes to the clinical protocol do not meet the criteria for a 5-day notice, and FDA decides that the additional information needed to address outstanding questions can be provided and reviewed within the 30-day review cycle.

   For this process, the sponsor should submit an IDE supplement that requests the modifications and addresses any prior FDA feedback. During the interactive review, FDA may request, and the sponsor may provide, additional information to enable the approval of the supplement within 30 days. The success of the interactive review process depends on the availability of FDA and sponsor resources to provide timely and high quality feedback, as well as the acceptability of the test results.

9. Design controls

The current good manufacturing practice requirements of the quality system regulation (21 CFR part 820) govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. An approved IDE exempts a device from the good manufacturing practice requirements under section 520(f) of the FD&C Act except for the requirements found in 21 CFR 820.30 (design controls).[31]

When complying with the requirements of 21 CFR 820.30 under an IDE, a device manufacturer shall establish and maintain a plan that describes or references the design and development activities specific to the medical device being designed or manufactured. This plan does not need to be submitted in the IDE application. The design plan shall describe or reference the following design and development activities in accordance with 21 CFR 820.30.

- Definition of responsibility for the implementation of the design and developmental activities;
- Identification and description of the interfaces with different groups or activities that provide or result in input to the design development process;
- Verification that the design outputs that are essential for the proper functioning of the device were identified;
- Formulation of a plan to conduct design reviews to assess the progress of the design, and confirm the design is ready to move to the next phase of development;
- Assurance that the design outputs met the design input requirements as part of the design verification;
- Completion of a design validation to show that the approved design met the predetermined user needs and intended uses;

[31] See section 520(g)(2)(A) of the FD&C Act; 21 CFR 812. 1. See also http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051602.htm.

- Performance of a risk analysis and consideration of risk throughout the design process;
- Documentation and control of design changes occurring during pre-production and post-production of the device; and
- Documentation of the design transfer into production specifications.

Appropriate documentation and establishment of the aforementioned elements of the device design plan will facilitate meeting the design control requirements in 21 CFR 820.30 as the device design evolves.

10. Next steps in clinical evaluation

After obtaining clinical information from an early feasibility study, the type of subsequent clinical evaluation will depend on whether changes in the device design are expected, the availability of adequate data to justify the next study, and the purpose of the clinical study. Early feasibility studies involve the investigation of devices that may be in a rapid phase of device iteration. If clinical information is needed after device modification and further device iterations are expected, a sponsor may submit an IDE supplement including a request for expansion of the early feasibility study. Once approved, the sponsor may enroll additional subjects in the early feasibility study. If the device design is near-final or final, and the results of the early feasibility study support the initial safety of the device and proof of principle, it may be more appropriate for the sponsor to pursue either a traditional feasibility study or a pivotal study. Progression to a traditional feasibility or pivotal study should be requested under an IDE supplement and should include the information needed to justify initiation of the larger study. The approval of any IDE supplement will ultimately depend on the availability of nonclinical and clinical data to justify initiation of the specific type of study requested.

Informal communications with FDA are important to help determine the most appropriate next step in the clinical evaluation of a device.

11. Conclusion

Early feasibility studies may be used to provide proof of principle and initial clinical safety data. Data from an early feasibility study may lead to device modifications and be used to refine the bench, analytical, and *in vivo* animal studies and future clinical study protocols.

Conducting an early feasibility study under an IDE provides a unique opportunity to obtain clinical experience with a new or modified device or new clinical use, while utilizing appropriate subject protection measures and good clinical study practices. Vital clinical information can be captured and used to optimize the device design, design evaluation, and clinical investigation plans.

Initiation of an early feasibility study and progression toward a pivotal study benefit from a flexible process that relies on sound nonclinical assessments and appropriate risk-based rationales. A high degree of interaction between FDA and the sponsor and use of the Pre-Sub process will be instrumental in the successful implementation of this guidance.

Appendix 1: Suggested topics for a Pre-Sub for an early feasibility study IDE

Although use of the Pre-Sub process is not a requirement, interactions between the FDA and sponsor are encouraged to enhance the predictability of the early feasibility study IDE review process. Based on the recommendations outlined in the guidance, the following topics may be useful to discuss during Pre-Sub interactions prior to the submission of the original IDE application:

1. Design concept

2. Clinical context
   a. Clinical condition the device is intended to treat or assess
   b. The standard of care, including the types and severity of risks and the benefits associated with current treatment options
   c. The types and severity of potential risks and the anticipated benefits that may be associated with the study device
   d. The rationale for exposing the target population to the potential risks (i.e., whether the anticipated benefits that may be associated with the use of the study device justify the potential risks, recognizing the benefits and risks posed by current treatment or assessment options)

3. Rationale for early feasibility study, considering:
   a. Novelty of the device or its intended clinical use
   b. Stability of the device design
   c. Whether additional nonclinical testing would likely provide the information needed to further device development

4. Nonclinical testing plan
   a. Draft device evaluation strategy for the early feasibility study
   b. Draft device evaluation strategy for device development beyond the early feasibility phase, if the sponsor wishes to obtain FDA feedback that may assist with future submissions
   c. Summary justification regarding the amount and type of information/data needed to support initiation of the early feasibility study in the specified patient population, with comment on, or comparison to, what may be expected to support the initiation of a larger clinical study
   d. Protocols for complex and novel nonclinical (e.g., bench, animal and computational modeling) testing or analyses, when available

5. Investigational plan
   a. Clinical study protocol summary
   b. Summary of risk analysis and mitigation strategies
   c. Informed consent language regarding the early feasibility nature of the study

6. Anticipated design iterations and clinical protocol changes and proposals for using the strategies outlined in the guidance

7. Projected device development timeline (e.g., significant regulatory and testing milestones)

Appendix 2: Device evaluation strategy example

The following hypothetical example illustrates the concepts described in Section 6.3.

A sponsor approaches FDA with an early feasibility study proposal to evaluate an innovative, covered, metallic implant to treat a disease common in the elderly. The device is unique in that delivery of the treatment will be through a catheter, rather than by open surgery (the standard of care). The expected benefits of this approach include less bleeding, fewer major adverse events, less pain, shorter hospital stay, and faster recovery as compared to the open surgery. There are aspects of the new device that are similar to a device approved for a different indication.

In a Pre-Sub, the sponsor describes the design concept and provides a draft device evaluation strategy table as described in Tables 1 and 2 of Section 6.3. Portions of the table are presented in Tables 3-5 for a procedure-related function, a performance-related function, and a basic safety-related feature.

The procedure-related functions for this device include the ability to:

- access the target site;
- deploy the implantable portion of the device; and
- withdraw the delivery system.

For the 'the ability to access the target site' attribute, the potential failure modes are:

- the inability to safely advance the system to the target site; and
- implant dislodgement from the delivery system.

Table 3 outlines the information for the attribute 'the ability to access the target site' and the potential failure mode of 'the inability to safely advance the system to the target site.'

Some of the performance-related functions and features include:

- implant integrity;
- fixation effectiveness; and
- patency.

For the 'implant integrity' attribute, the potential failure modes are:

- corrosion; and
- structural failure of the implant.

Table 4 outlines the information for the attribute 'implant integrity' and the potential failure mode of 'corrosion.'

The basic safety-related features include:

- biocompatibility;
- sterility; and
- MR compatibility.

For the 'biocompatibility' attribute, the potential failure mode is 'non-biocompatibility.' Table 5 outlines the information for the attribute 'biocompatibility' and the potential failure mode of 'non-biocompatibility.'

Table 3: Device Evaluation Strategy Table, Procedure-Related Function – Ability to Access

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
		Potential Effects of Failure			Supportive Information			
Device-Related Attribute *Device function or feature required for the device to achieve the overall desired performance*	**Potential Failure Modes** *The failures that might occur and could result in consequences (effects) to the device or study subject, if the function or feature is not attained*	**Potential Device Effects of Failure** *The potential effect(s) of the failure mode on the device*	**Potential Clinical Effects of Failure** *The potential effect(s) of the failure mode on the study subject*	**Device Design Information** *Relevant design characteristics intended to provide the function or feature or to address or mitigate the potential failure mode, and other information considered in the design of the device*	**Leveraged Nonclinical Information** *Nonclinical information leveraged from internal or external sources*	**Supportive Clinical Information** *Relevant clinical experience obtained from internal or external sources for a similar device or indication*	**Nonclinical Device Testing** *Proposed testing of the study device (i.e., the device that will be used in the clinical study) to complete the evaluation of the attribute and the potential failure mode(s), considering the information in Columns 3-7*	**Clinical Study Mitigation Strategies** *Mitigation strategies included in the clinical protocol intended to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute*
Ability to access the implantation site	Inability to safely advance the system to the target site	- Delivery system damage - Implant damage	- Embolism - Procedural failure - Tissue damage at access site	Design characteristics: - Unique tip to minimize tissue trauma - Enhanced flexibility to accommodate tortuous anatomy - Safety features to prevent completion of deployment steps out of sequence Relevant information considered in the design of the device: - Use of same delivery mechanism as our similar device with a known clinical performance (without catastrophic failures), approved to treat a different disease process in the same anatomic location	- Volume 2, Section 1 of the Pre-Sub describes nonclinical testing conducted on our similar device Reference to this information is appropriate because the study device has the same delivery mechanism as the approved, similar device.	- Volume 2, Section 2 of the Pre-Sub describes the clinical use of our similar device Reference to this information is appropriate because the new intended use does not involve targeting a new anatomical implantation site and therefore would not likely negatively affect the ability of the study device to access the implantation site.	The following tests will be conducted on the study device: - Acute and 30-day animal study (see study protocol in Volume 3, Section 1) - Simulated use testing (see protocol in Volume 3, Section 2) - Tensile bond strength - Torsional bond strength	For all events - Timely detection, treatment, and reporting of adverse events For 'Embolism' - Clinical evaluations and imaging post-procedure for early detection of distal organ damage to allow for early treatment and to identify the need to change the procedure or device - Embolic protection device use For 'Procedural failure' - Pre-operative imaging to confirm appropriate anatomy - Plan to treat subjects with the current standard of care if the delivery system cannot be advanced For 'Tissue damage at access site' - Pre-operative imaging to confirm appropriate anatomy

Table 4: Device Evaluation Strategy Table, Performance-Related Function – Implant Integrity

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
		Potential Effects of Failure			Supportive Information			
Device-Related Attribute	**Potential Failure Modes**	**Potential Device Effects of Failure**	**Potential Clinical Effects of Failure**	**Device Design Information**	**Leveraged Nonclinical Information**	**Supportive Clinical Information**	**Nonclinical Device Testing**	**Clinical Study Mitigation Strategies**
Implant integrity	Corrosion	- Component separation - Fracture - Movement from intended implant location	- Foreign body embolization - Loss of biocompatibility - Effectiveness failure (specify) due to component separation - Effectiveness failure (specify) due to implant movement - Trauma to adjacent structures	Design characteristics: - Electropolished metallic components to improve corrosion resistance Relevant information considered in the design of the device: - Use of same metallic components and surface finishing as our similar, approved device with acceptable corrosion resistance	- Volume 2, Section 3 of the Pre-Sub describes nonclinical testing conducted on our similar device with known corrosion resistance Reference to this information is appropriate because the risk of corrosion is similar to the previously approved device. The study device will be exposed to an *in vivo* environment that has the same relevant characteristics (e.g., body fluid contact, externally applied forces), has a similar design and is constructed with the same metal, using the same manufacturing methods.	- Volume 2, Section 4 of the Pre-Sub describes the clinical use of our approved device Reference to this information is appropriate because the new device will be exposed to the same *in vivo* environment.	No device-specific testing needed prior to initiation of the early feasibility study	For all events - Timely detection, treatment, and reporting of adverse events For 'Foreign body embolization, trauma to adjacent structures and all other clinical effects of failure' - No additional mitigation strategies beyond timely detection, treatment, and reporting of adverse events - For 'Loss of biocompatibility' - Assess inflammatory biomarkers post-procedure - Monitoring of subjects for signs and symptoms of allergic reactions to allow for early treatment For 'Effectiveness failure (specify) due to implant movement or component separation' - Imaging studies at regular intervals to evaluate device position - Plan to implant additional devices if the original device moves from the targeted implant site

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Table 5: Device Evaluation Strategy Table, Basic Safety-Related Feature – Biocompatibility

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
Device-Related Attribute	**Potential Failure Modes**	**Potential Effects of Failure**		**Device Design Information**	**Supportive Information**		**Nonclinical Device Testing**	**Clinical Study Mitigation Strategies**
		Potential Device Effects of Failure	**Potential Clinical Effects of Failure**		**Leveraged Nonclinical Information**	**Supportive Clinical Information**		
Biocompatibility	Non-biocompatibility	No device effects	Adverse biological response	Relevant information considered in the design of the device: - Use of materials with histories of clinical use	No leveraged nonclinical information Although the metallic component is identical to one of our approved devices, there are additional materials used in the construction of the device, and therefore, biocompatibility testing on the study device is needed.	No leveraged clinical information	The following tests will be conducted to support the initiation of the early feasibility study: - Testing in accordance with Part 1 of ISO 10993 (see Volume 3, Section 3) - Acute and 30-day animal study (see study protocol in Volume 3, Section 4) The specific aspects of biocompatibility that will be assessed in the animal study are acute systemic and subchronic toxicity, *in vivo* thrombogenicity, hemolysis and local irritation. These will be assessed through complete necropsy and target tissue gross and histologic evaluation.	For all events - Timely detection, treatment, and reporting of adverse events - For 'Adverse biological response or loss of biocompatibility' - Assess inflammatory biomarkers post-procedure - Monitoring of subjects for signs and symptoms of allergic reactions to allow for early treatment

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To help support the device evaluation strategy, the sponsor identifies the novel and most clinically relevant attributes (i.e., those that support an expectation of acceptable clinical use or are associated with basic device safety) and those that could be affected by differences in their study device as compared to existing devices. The sponsor explains why certain potential failure modes would not likely be associated with catastrophic failures, discusses the likelihood and severity of the potential clinical effects of failure, emphasizes the unique anticipated benefits of their novel technology, and details how the mitigation strategies can be used to minimize harm to study subjects. The sponsor also describes their rationale for deferring some nonclinical testing.

The FDA interacts with the sponsor to reach agreement on the comprehensive list of device-related attributes and the potential failure modes that could occur if the desired functions or features are not achieved. They then discuss whether the proposed bench, laboratory, analytical, and animal testing of the study device should be adequate to complete the evaluation of the attributes and the potential failure modes, considering the information provided in Columns 5-7 of the device evaluation strategy table.

The sponsor plans to modify the device design based on the information obtained from the early feasibility study. The sponsor elaborates on the planned testing to be completed for the modified device, prior to progressing beyond the early feasibility study. For example, to justify the initiation of the early feasibility study, an animal study is planned to evaluate the potential for catastrophic failure of the device acutely and in the intermediate-term. To support initiation of a pivotal trial, the sponsor proposes a long-term animal study, which will be carried out concurrently with the traditional feasibility study, to demonstrate complete healing at the implant site. The sponsor will update their overall device evaluation strategy table as information is obtained from their nonclinical testing and early feasibility study.

The sponsor continues to interact with the FDA as they complete the nonclinical testing of their device. The Pre-Sub interactions regarding the device evaluation strategy enhance the predictability of the review process by increasing the likelihood that the Report of Prior Investigations will be adequate to help support IDE approval.

Appendix 3: Supplemental guidance for the preparation of an early feasibility study informed consent document

The informed consent process for early feasibility studies, as for all clinical investigations, must adhere to the requirements described in 21 CFR part 50 subpart B – Informed Consent of Human Subjects. The outline below presents the general informed consent requirements listed in 21 CFR 50.25. The specific recommendations relevant to an early feasibility study are found under each applicable general consent requirement. Some of these recommendations may be appropriate for other types of clinical studies, but are particularly relevant for early feasibility studies.

Note that the recommendations below are not presented in plain language. When drafting an informed consent form, appropriate wording should be used to effectively communicate the information to the potential study subject.

Introduction

General consent requirement:

__ a statement that the study involves research

Early feasibility consent recommendations:

include a statement that this is an early feasibility study and explain the significance of such studies

describe the consent process and the purpose of the consent process

Note: It may be appropriate to have a patient advocate present during the consent process and/or have an independent individual, other than the investigator, be responsible for explaining the study.

Purpose of the Study

General consent requirement:

__ an explanation of the purposes of the research

Early feasibility consent recommendations:

Generic early feasibility study information

describe an early feasibility study, that is, a study of an innovative device or innovative clinical use of a device in a small number of patients

explain that the study is designed to gain initial insights into the basic safety and device functionality

explain that there may be unforeseeable risks associated with participation in an early feasibility study due to limitations in available data and experience with the device

Specific information regarding the proposed investigation

name the device and the number of patients to be enrolled

provide a brief description of the underlying medical condition, the device (including the innovative device features) and what the device is intended to do

explain how different the device or procedure is from currently available therapies

provide information on whether this study involves the first human use of the device or whether there has been previous clinical use of this or a similar device for the same or a different intended use

Study Procedures

General consent requirement:

__ a description of the procedures to be followed

Early feasibility consent recommendation:

include a description of all procedures and follow-up requirements

General consent requirements:

__ identification of any procedures which are experimental

__ the expected duration of the subject's participation

Early feasibility consent recommendation:

indicate how the procedures and follow-up in the study differ from the standard of care

Risks

General consent requirement:

__ a description of any reasonably foreseeable risks or discomforts to the subject

Early feasibility consent recommendations:

Note: This section should reflect the risk analysis and risk mitigation strategies in the clinical protocol.

include a statement to indicate that not all risks associated with the use of the study device are currently known

list reasonably foreseeable risks, but indicate that there may not be information to fully predict the frequency and severity of these risks

describe risk mitigation strategies (e.g., if the investigational treatment is unsuccessful, the patient may still be eligible for treatment with the current standard of care)

Benefits

General consent requirement:

__ a description of any anticipated benefits to the subject or others

Early feasibility consent recommendations:

without overestimating the chance of personal benefit, describe any anticipated benefits to the subject which may reasonably be expected

disclose that there may be little information to support a likelihood of personal benefit

indicate that even if there is limited or no personal benefit to the study subject, future patients with the disease or condition may benefit from the information obtained during the early feasibility study

Alternative Treatments

General consent requirement:

__ a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject

Early feasibility consent recommendation:

describe the benefits, risks, and limitations of current treatment options

Other Information

General consent requirements:

__ a statement describing the extent to which confidentiality of the subject's records will be maintained and that notes that FDA may inspect the records

__ for research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of or sources of further information

__ an explanation of whom to contact for answers to questions about the study and the subject's rights and whom to contact in the event of a research-related injury
__ a statement that participation is voluntary and that subjects may refuse to participate or discontinue participation at any time without penalty or loss of benefits, and whom to contact if they wish to withdraw

Early feasibility consent recommendation:

if applicable, include a statement that an investigator(s) has a proprietary interest in the test article and identification of the person the study subject can speak to about potential financial conflicts

Additional elements, when appropriate:

General consent requirements:

__ a statement that the procedure or treatment may involve unforeseeable risks to subject, or to the embryo or fetus should the subject become pregnant
__ anticipated circumstances under which the investigator may terminate the subject's participation without regard to the subject's consent
__ any additional costs to subject as a result of participation
__ consequences of a subject's decision to withdraw and procedures for withdrawal
__ a statement that significant new findings developed during the course of research which may relate to the subject's willingness to participate will be provided to the subjects
__ the approximate number of subjects involved in the study

Early feasibility consent recommendations:

clearly indicate the consequences of withdrawal if, for example:

- withdrawal results in termination of therapies, testing, or monitoring; or
- transfer to an another health care provider is required

if early termination of treatment and/or withdrawal from the study might adversely affect the subject, describe the specific procedures that are recommended to ensure the subject's safety and why these procedures are important to the subject's welfare

if continued follow-up is recommended to ensure the subject's safety following withdrawal, explicitly inform the subject of the potential adverse effects of premature termination and the need for continued follow-up

include a statement indicating that information will be provided to the study subject that may relate to the subject's willingness to participate

Appendix 4: Device iteration example

The following is a hypothetical scenario that illustrates the concepts described in Section 8 regarding device iteration during an early feasibility study.

Using the Pre-Sub process, a sponsor approaches FDA with a proposal to evaluate an innovative device in an early feasibility study to treat a disease common in the elderly. The device is unique in that delivery of the treatment will be through a catheter, rather than through the standard procedure which involves open surgery. The sponsor proposes to enroll up to 10 subjects at up to 3 investigational sites. The sponsor will evaluate the device performance and clinical outcomes after each subject is treated, and prior to enrolling the next subject.

In the Pre-Sub, the sponsor describes several potential device changes that may be implemented during the early feasibility study. The sponsor proposes the following specific iterative changes for which they will request contingent approval under the original early feasibility IDE, if the information obtained during the clinical study suggests that these device modifications are needed to optimize the device design:

- improvements in maneuverability, including:
    - modifying the shape of the nose cone of the introducer (e.g., increase or reduce tapering); and
    - making the sheath stiffer or more flexible;
- changing the length of the catheter to allow for the use of alternative access sites;
- modifying the hemostatic valve by changing material properties or device dimensions to improve hemostasis or reduce friction;
- implementing ergonomic changes in the handle that do not affect the overall function of the device (e.g., changing texture of knobs or handle); and
- modifying the operator interface console.

During the Pre-Sub discussions, the sponsor and FDA reach agreement on the test plan to evaluate the proposed changes, including the acceptance criteria to be included in the original IDE application. Although some of these changes may be appropriate for 5-day notices, obtaining prospective, contingent approval under the original IDE will provide the sponsor with more predictability in the regulatory process for their device modification plans.

The sponsor, with help from the principal investigator, identifies other types of changes that may be needed for their device and clinical protocol during the conduct of their early feasibility study. In the original IDE application, the sponsor seeks FDA concurrence on their proposed approaches for implementing these changes, as outlined in Table 6.

Table 6: Regulatory process for anticipated modifications

Changes that may be appropriate for 5-day notification	**Changes that may be appropriate for contingent approval**	**Changes that may be appropriate for 30-day interactive IDE supplement**
Add a previously characterized surface coating to the catheter if lubricity is needed to improve access*	If a surface coating is added, modify the distribution, thickness or area covered by the coating	Expand the subject selection criteria (e.g., inclusion of younger subjects than defined in the original protocol)
Adding, moving, or changing the radiopaque bands on the catheter to improve visibility.	Improve the catheter resistance to kinking, with the type of modification and appropriate testing to be identified prior to supplement submission	Change from percutaneous access to open surgical access
Changes in the device preparation for use	Change the device to accommodate a broader range of subject anatomies (type of modification and therefore type of appropriate testing not identified in the original IDE)	
Add the use of an approved ancillary device (e.g., use of a longer introducer sheath) intended to improve the safety of the procedure*	Add new types of imaging studies to monitor device performance, if the modalities specified in the original protocol are found to be inadequate and if the new imaging procedure is supported through a risk assessment	
Modify the subject selection criteria to limit, rather than expand, the criteria*		
Modify procedural imaging modalities*		
Reduce follow-up assessments if early data support the change (i.e., the clinical data indicate that the change would not affect the safety of the subjects)*		
Change case report forms to capture additional information		

* These types of changes would not generally be appropriate for 5-day notification in a pivotal study due to their possible effect on the scientific soundness of the investigational plan and/or data validity.

FDA considers the proposed approaches to be reasonable.

The developmental device changes proposed for the 5-day notification process are considered appropriate in this case because they:

- are reasonably defined such that appropriate testing and expected outcomes are known;
- do not constitute significant changes in the basic principles of operation; and
- are not considered significant because they would not adversely affect the interpretability of the results of an early feasibility study, and would not be expected to adversely affect device performance or to be associated with additional risk to the study subjects.

Similarly, the clinical protocol changes would be appropriate for 5-day notification because the changes do not affect:

- subject safety, rights, or welfare;

- the validity of the data or information resulting from the completion of the approved protocol, because the data or information will not be pooled; or
- the relationship of likely patient risk to benefit relied upon to approve the protocol.

The additional subject protection measures included in the early feasibility study protocol augment patient safety.

FDA recognizes that more types of changes are appropriate for 5-day notification during this early feasibility study than would normally be acceptable for a study enrolling a larger number of subjects or requiring a stable device design and clinical protocol to allow for pooling of the data from study subjects. For example, reducing the follow-up assessments would not likely be appropriate under a 5-day notice for a pivotal study; prior clinical studies would have been used to identify the appropriate follow-up assessments to ensure that consistent data are captured for each study subject. For this early feasibility study illustration, since the optimal study subject follow-up has not been defined, the sponsor plans to require laboratory testing on days 3, 7 and 14, but may find that, based on the results from the initial 5 subjects, the 7-day assessment is not informative and can be safely omitted. As the safety of subsequent study subjects would not be compromised with this change, FDA agrees that such a change during this study could be made with a 5-day notification.

During the course of the early feasibility study, the sponsor makes some of the anticipated changes, but also identifies an additional modification that had not been predicted in the original IDE submission. The sponsor proposes contingent approval for a change in a material used in the construction of their device based on obtaining acceptable results with the same types of nonclinical testing used to evaluate the original device design. To formally request this change, the sponsor submits an IDE supplement that describes the change and evaluation plan, including the acceptance criteria for the testing. FDA and the sponsor reach a consensus regarding the proposal during the 30-day review time for the supplement, and FDA grants approval of the modification, contingent on the successful completion of the test plan and reporting of the change and supporting information to FDA within 10 days of implementing the change. The sponsor evaluates the modified device according to the test plan, obtains acceptable results, implements the change and submits their test report to FDA 7 days after making the change.