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AdvaMed
Advanced Medical Technology Association

March 9, 2012

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–D–0787: Draft Guidance for Industry and Food and Drug Administration Staff; Investigational Device Exemptions for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies; Availability

Dear Sir/Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to FDA's Notice of a draft guidance entitled: *Investigational Device Exemptions for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies*.

The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed has both general comments and specific comments (included in table format) below.

General Comments

AdvaMed commends the FDA for developing the draft guidance which we believe will both facilitate and help expedite the conduct of early feasibility device studies in the U.S. The guidance adds clarity to the types of information and format FDA expects in order to grant an IDE for significant risk devices in early feasibility studies. The draft guidance also clarifies

that IDEs can be granted for early feasibility studies without the FDA considering the full clinical program plan with which the sponsor intends to achieve marketing approval. As a result, we believe the guidance will enhance manufacturers' ability to obtain the early clinical data necessary to support development of innovative products while protecting patient safety.

In Section 7 of this guidance "*Iterations during Early Feasibility Studies*" the agency describes three methods (copied below) that provide greater flexibility to make needed changes to the device or to the protocol *during* early feasibility studies:

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 than during other types of studies;

2. For anticipated changes that would require prior FDA approval, a sponsor may 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, FDA intends to utilize a new interactive review process that encourages communication with FDA during the 30-day review cycle.

These options are appreciable process advances and promote the joint FDA and industry responsibility to enhance innovation while protecting patient safety. They also have the potential to accelerate the development of innovative devices. We commend FDA's risk-based approach to flexibility during early feasibility testing of innovative devices.

We also commend FDA's discussion of the use of computational modeling and use of non-Good Laboratory Practice (GLP) study data (with deviations from GLP identified and justified) to support device evaluation strategies and IDE applications for early feasibility studies. We believe these and other test methods will be invaluable for future innovation. We further support the utilization of the device evaluation strategy plan coupled with the device iteration changes, as outlined in the guidance. This will be a very useful tool for companies developing innovative combination products.

The draft guidance also promotes early and frequent interaction with the FDA before and after the IDE submission. Industry welcomes this interactive approach and believes direct discussion with the agency, especially concerning development plans for novel devices or intended uses, is key to efficient and high quality device development. We recommend that the agency adopt an educational campaign at all levels within the agency to assure that a consistent message is communicated to industry that the FDA is available for informal and formal discussions related to IDE applications for early feasibility studies of significant risk devices. Whenever possible, FDA should reduce the IDE review time for early feasibility studies relying for example on interactive review approaches. As the agency notes in the

guidance document, "*The success of the interactive review process depends on the availability of FDA and sponsor resources to provide timely and high quality feedback*…" We understand that FDA plans to incorporate agreements reached during the Medical Device User Fee Amendments (MDUFA) negotiations on pre-submission meeting process changes in a pre-submission guidance. These changes include implementing a more structured process for managing pre-submission meetings. We recommend that the final guidance for IDEs for early feasibility device studies incorporate a reference to and be consistent with the planned pre-submission meeting guidance.

We also recommend that FDA identify and incorporate into the guidance process improvements learned from the pilot conducted in conjunction with the release of this draft guidance, especially those process improvements related to reaching consensus on follow-up periods, endpoints and the appropriate level of bench testing. It is important to identify opportunities to optimize pre-IDE meetings and interactions needed to reach consensus on these items because a lengthy, drawn out process in these areas drives decision-making regarding whether or not to conduct an early feasibility study in the U.S.

Finally, as a general comment, we recommend that important information be contained either in the body of the document or, if necessary, in footnotes. As a general rule, endnotes are not effective in communicating important information in guidance.

Specific Comments
AdvaMed's specific comments on the guidance are presented below in tabular form. Please find attached for reference a line-numbered version of the draft guidance.

In closing, thank you for the opportunity to comment on the draft guidance *Investigational Device Exemptions for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies*. Please don't hesitate to contact me if you have any questions.

Sincerely,

Tara Federici
Vice President, Technology and Regulatory Affairs

Edit #	ID #	Change	Reason
1	103 - 108	The guidance should provide for the possibility that a sponsor may present its strategies to FDA to enable inclusion of data from its early feasibility study as part of the clinical evidence supporting its marketing application.	The guidance states that early feasibility studies cannot be used as an independent study to support a marketing application in lieu of a pivotal study. However, it does not explain how data from early feasibility can be used *as part of* clinical evidence to support a marketing application. Information obtained from an early feasibility study can be potentially valuable for determining device safety and assessing effectiveness and should be able to be considered as part of the clinical evidence supporting a marketing application. The guidance should provide for this possibility.
2	121	Add to end of sentence: . . . intended clinical use <u>or used for a new indication.</u>"	It is possible the device was used for a different indication than currently intended and may behave totally different.
3	124	Please define the options available for seeking input from FDA on whether a given study can be classified as an early feasibility study.	If a pre-IDE meeting is required, it should be stated as such. If there are other options, it would help to have them listed.

Edit #	ID #	Change	Reason
4	217	Change sentence to read: Does the information included in the Report of Prior Investigations (Section 5) meet the criteria of early feasibility study in 21 CFR 812 ~~support initiation of the study.~~	The additional question provides the background basis of the device/system in the Report of Prior Investigations with respect to first-in-man trial or first time indication for use thereby qualifying the device/system as an early feasibility trial.
5	233 - 235	Insert after development on line 235: Early feasibility may also be appropriate for those conditions with little or no treatment available.	Additional situation where early feasibility may be appropriate.
6	233 - 235	Specify the criteria the agency will consider when evaluating whether early feasibility is appropriate (i.e., criteria for determining additional nonclinical testing is not available or adequate to provide the information needed to advance device development).	Without clear criteria there is a lack of transparency and increased opportunity for missteps in the process, inequity across review divisions, and lengthier processes, all of which may lead to lack of utilization of early feasibility studies in the U.S. contrary to FDA's intent.

Edit #	ID #	Change	Reason
7	286	Add and strike the following: The rationale for providing the appropriate level of nonclinical testing ~~that would be needed to support initiation of a larger clinical study.~~	The proposed edit makes clear that the level of non-clinical testing should be appropriate to the proposed study.
8	311	Change bullet from: ~~'Minimum design-life of the device."~~ To: "Estimated minimum durability of the device.	Language is unclear. Proposed language provides clarity on requirements.
9	335	Add at end of sentence: . . . procedure, if possible or add explanation.	There will be many situations where it is not possible to know the severity and frequency of possible events.

Edit #	ID #	Change	Reason
10	371	Suggest to change from: ". . . determine the testing needed. . ." To: ". . . <u>determine the non-clinical testing needed . . .</u>"	Proposed language provides clarity on requirements.
11	377	Suggest to change from: ". . . long-term durability of the device." To: ". . . <u>estimated minimum durability of the device</u>."	Proposed language provides clarity.

Edit #	ID #	Change	Reason
12	394	Suggest adding clarifying language: ". . . testing. A rationale…" To: ". . .testing. Substitutions for the use of live animals, such as in-vitro methods (e.g., validated cell cultures), cadaveric studies, or the use of computer simulation should be considered. A rationale . . . ."	Proposed language supports the use of non-animal models and gives examples to the reader.

Edit #	ID #	Change	Reason
13	397	Suggest to replace: "The size of the animal study depends on the device and assay . . . " With: The size of the animal study depends on the device and ~~assay (i.e.,~~ how well the animal model provides anatomic, physiologic, and procedural similarities to humans~~)~~, ...	Assays are not always used for preclinical research studies. The term 'procedural goals' is a more appropriate description.

Edit #	ID #	Change	Reason
14	414 - 416	Modify sentence to read: "For early feasibility studies, although clinical data may not be available for the test device for its proposed intended use, provide relevant background clinical information, when available, ~~should be provided~~ in the Report of Prior Investigations, and which may include data or publications on: • Similar or related devices utilized for the proposed intended use; or • The subject or similar devices used for a different purpose.	Comparisons to other marketed devices may be very difficult in the case of a truly novel device.

Edit #	ID #	Change	Reason
15	475	Change from: "Human subject protection measures including informed consent and ethics committee oversight, . . ." To: Human subject protection measures including informed consent and Institutional Review Board (or ethics committee) oversight,	To be consistent with FDA regulatory language.
16	529	Add that a DMC could be composed of internal personnel as long as they are empowered with independent decision making and have adequate expertise.	Independence can be obtained either with external or internal personnel (especially in a large company). Internal DMCs are least burdensome and can lead to quicker decisions which may benefit patient safety.
17	551	Clarify if the 5-day notice is 5 business or calendar days.	Clarification.

Edit #	ID #	Change	Reason
18	579	Suggest adding here the point of using either 5-day notice or prospective, contingent approval as described in Appendix 2 lines 711-714.	Adds consistency between the body and the appendices.
19	590	The draft guidance introduces a new approach named "contingent approval." Line 590 specifically identifies that anticipated changes to the clinical protocol may be appropriate for contingent approval. Please provide examples in Appendix 2 or in another area of the Guidance Document on the types of clinical protocol changes that might be appropriate for contingent approval (as compared to 5-day approval).	Clarification and examples are needed to understand how the contingent approval process can be used with regard to clinical protocol changes.
20	666	Add and strike the following: An ~~A~~ illustrative portion of the device evaluation strategy provided by the sponsor is included in Table 1. Column headings are for example purposes only.	To clarify that the Table is an example only and that column headings would vary depending on the device and the evaluation strategy.

Draft Guidance for Industry and Food and Drug Administration Staff - Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: November 10, 2011

You should submit comments and suggestions regarding this draft document within **90** days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit e lectronic comments to http://www.regulations.gov[2]. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Andrew Farb, 301-769-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov.

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

Preface

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.

Table of Contents

Draft Guidance for Industry and Food and Drug Administration Staff

Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

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

1. Introduction

This document is intended to provide guidance to FDA staff, clinicians, clinical 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. However, as with all clinical studies, initiation of an early feasibility study must be justified by an appropriate risk-benefit analysis and adequate human subject protection measures.

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

- 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 basic safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot be readily 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. As compared to an early feasibility study, more nonclinical (or prior clinical) data are necessary for approval to initiate a traditional feasibility study[2]; however, 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 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 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);
- 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.

Early feasibility studies are not designed or intended to generate definitive data to independently support a marketing application in lieu of a pivotal clinical trial. Further, unlike traditional feasibility studies, which are focused on providing initial 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 non-clinical 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 readily provided 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. Please note that not all novel devices or uses warrant an early feasibility study. Either 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 does 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.

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

2. 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 Federal Food, Drug, and Cosmetic Act (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 3).

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

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 4). This is because early feasibility studies are only appropriate where additional nonclinical testing is not available or adequate to 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 and procedure-related attributes and addresses the potential failure modes (see Section 5.2.1). This policy is intended to facilitate initiation of clinical studies in the United States earlier in the device development process than has historically occurred, when appropriate.[3]

2. This guidance introduces new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study while still requiring compliance with the IDE regulations in 21 CFR Part 812 (see Section 7), 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;
    - interactive review of IDE supplements.

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 5 and 6). This guidance is not intended to address all required elements of IDE applications, generally, 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. Pre-submission discussions with FDA are necessary to optimize the preparation and quality of early feasibility study IDE applications.

3. Regulatory background

Section 520(g) of the FD&C Act 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.[4]

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), 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.

Adopting the principles set forth in section 520(g)(2)(C) of the FD&C Act, Sections 4-7 of this guidance clarify how some of these requirements should be applied to early feasibility study IDEs.

4. 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 IDE application as compared to a traditional feasibility or pivotal study IDE application, 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 by the sponsor, with supporting materials, 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. Does the information included in the Report of Prior Investigations (Section 5) support initiation of the study?
4. Does the Investigational Plan include a thorough risk/benefit analysis, sufficient risk mitigation strategies, adequate human subject protection measures, and an appropriate clinical study protocol (see Section 6)?
5. Is initiation of the clinical study justified based on the responses to the aforementioned questions?

Under 21 CFR 812.30(a), FDA may approve an investigation as proposed, approve it with conditions, or disapprove it. FDA may disapprove an IDE application if it finds that any of the grounds in 21 CFR 812.30(b) exist. The ground for disapproval provided at 21 CFR 812.30(b)(4) is of particular importance for early feasibility studies:

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

Early feasibility studies are designed to gain initial clinical insights and not data to independently support a marketing application. They may be initiated based on less evidence than for other types of clinical studies and before the design of the device is finalized because they are only appropriate where additional nonclinical testing is not available or adequate to provide the information needed to advance device development. As a result, early feasibility studies 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 6). At the same time, benefits deriving from the knowledge to be gained may be substantial, particularly for innovative devices or intended uses during the early phase of device development. Even though early feasibility

studies are not designed or intended to generate statistically valid results, they should be scientifically sound (e.g., enrolling the right subjects and utilizing meaningful endpoints) so that the results can be used to further device development. Importantly, as early feasibility studies can begin before the design of the device is finalized, there still should be reason to believe that the device will be effective.

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 prior to permitting 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, and documentation in case report forms might be limited to highly relevant data fields.

5. 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.

The Report of Prior Investigations must include the information needed to justify a clinical investigation of a device.[5] For early feasibility studies, this information should:

- 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, electromagnetic compatibility, chemical compatibility (e.g., with concomitant drugs, chemicals, cleaners); and
- characterize catastrophic failure modes and risk mitigation approaches.

When adequately justified, the information may be generated from tests utilizing non-standardized methodologies (e.g., evaluating fatigue properties using loading conditions different from those specified in a guidance document or voluntary standard or using less sensitive testing equipment than specified in a guidance or 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.

The Report of Prior Investigations for an early feasibility study IDE application should include three main sections: (1) background, (2) an executive summary, and (3) detailed reports.

(1) The background section should describe:

- the clinical context for which the testing is being conducted:

    - the clinical condition the device is intended to treat or assess and the current standard of care; and
    - the rationale for exposing the target population to potential risks (e.g., description of the types and severity of risks posed by current treatment or assessment options and scientific data to support potential benefits);
- the design concept;
- the device evaluation strategy for the early feasibility study; and
- the rationale for providing less nonclinical testing than would be needed to support initiation of a larger clinical study.

(2) The executive summary should include:

- a description of the nonclinical testing that has been performed and relevant clinical information;
- a table describing the purpose of each test or analysis, acceptance criteria (if available), test results, and any potential clinical significance of the results.

(3) Individual test reports should be provided for each bench and laboratory test, computer 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.[6] A summary of any relevant clinical information, with references, if available, should also be provided.

5.1. Design concept

Identification of appropriate testing and test methodologies should be based on the device design concept. An early feasibility study IDE application should include information to clearly describe the design concept, such as:

- Device description (e.g., physical description, figures, materials of construction, software documentation)
- Intended function
- Intended patient population
    - Intended clinical use, designated by the medical condition or lesion type to be treated or assessed
    - Anatomical location and limitations
- Conditions of use/intended *in vivo* environment
- Directions for use
- How the intended function is achieved (i.e., key design features for the mechanism of action)
- Minimum design-life of the device.

This information is needed to guide the device evaluation strategy.

5.2. Device evaluation strategy

The device evaluation strategy in the Report of Prior Investigations is intended to describe and justify the appropriate testing to support initiation of the clinical study. The guidance below describes one appropriate method for presenting the device evaluation strategy for an early feasibility study as well as an option for obtaining early FDA feedback on the overall device evaluation strategy beyond the early feasibility phase.

5.2.1. Device evaluation strategy for the early feasibility study

The device evaluation strategy for the early feasibility study should be based on an appropriate risk assessment.[7] In some cases, the appropriate testing to evaluate a device for use in an early feasibility study may not be found in an FDA guidance or a voluntary standard. 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 column headings as presented and explained below. To complete the table, the sponsor starts with listing the necessary attributes for the device (Column Number 1). Next, for each attribute, the sponsor should list the types of problems or failures that might result if the device does not function properly (Column Number 2). The specific effects of the failure modes can be device-related or clinical, and should be listed separately (Column Numbers 3 and 4). The identified failure modes and effects of failure guide the information the sponsor needs to assess each device function (Column Number 5).

Device Evaluation Strategy Table Headings and Explanations:

Column Heading	Explanation	Context
Column 1: Device/Procedure Related Attribute	The intended or defined performance of the product.	
Column 2: Potential Failure Modes	Difficulties or failures that might be encountered that could result in consequences (effects) to the patient or device.	If the device does not have an adequate [column 1], there could be a problem with [column 2].
Column 3: Potential Effect(s) of Failure (Device)	The initial effect(s) of the failure mode on the device.	If there is a problem with [column 2], [column 3 or 4] could occur and should be documented.
Column 4: Potential Effect(s) of Failure (Clinical)	The effect(s) of the failure mode on the patient.	If there is a problem with [column 2], [column 3 or 4] could occur and should be documented.
Column 5: Information/Data	A list of information/data (e.g., bench, laboratory, analytical, animal) that should be obtained to evaluate the individual device attribute.	To evaluate the adequacy of the device's [column 1] the following information should be obtained: [column 5].

When identifying the appropriate testing to evaluate basic safety, it is necessary to consider the potential frequency, severity, and nature of the clinical effects of failure that may be associated with the device or procedure. For an early feasibility study, the focus of testing should be on identifying and minimizing the potential for adverse events associated with basic safety risks (e.g., non-biocompatibility, incompatibility between components, and catastrophic failures). With respect to device functionality, the device evaluation strategy should indicate those attributes most relevant for the intended use and appropriate testing to evaluate those attributes. For highly innovative devices, FDA recognizes that appropriate

nonclinical test methodologies to assess some critical parameters may not be available, and therefore, these would need to be evaluated clinically.

The device evaluation strategy should be updated as new information emerges about the potential risks and the appropriate and necessary assessment of the device.

The following table is an example of a portion of an acceptable device evaluation strategy for a permanently implanted metallic device.

Table 1: Device Evaluation Strategy Example

Device/Procedure Related Attribute	**Potential Failure Modes**	**Potential Effects of Failure**		**Information/Data**
		Device	**Clinical**	
Implant integrity	Structural failure of implant	• Metallic fracture	• Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures	• Discussion on design concept to optimize integrity • Comparison of design to marketed devices • Strength testing • Stress/strain analysis
	Corrosion	• Metallic fracture	• Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures	• Comparison of materials to the sponsor's own marketed devices
Appropriate biological response	Loss of device function	• None	• Necrosis	• Comparison of design and materials to marketed devices • Acute and medium-term implantation in an appropriate animal model

This example presumes that, based on the device design and intended use, failure due to a loss of implant integrity is unlikely to lead to serious adverse clinical effects of failure (i.e., that it would be a non-catastrophic failure), so only basic information is needed regarding structural integrity and corrosion. An appropriate biological response is a basic safety requirement, and although comparison of the design and materials to marketed devices provides useful supportive information, implantation in an animal model is needed to adequately assess this critical attribute. For both attributes in this example, less information/data is necessary than for a pivotal study.

5.2.2. Overall device evaluation strategy (optional)

Though not required for IDE approval, it may be valuable to submit a pre-IDE to obtain FDA feedback on the overall device development plan by identifying the types of information or levels of testing that may be needed to progress beyond the early feasibility study.

In the device evaluation strategy table described above, subheadings may be included under the Information/Data column, as presented in Table 2, to describe the additional information/data for each device/procedure-related function needed to support:

- initiation of a traditional feasibility study;
- initiation of a pivotal study; and
- a marketing application.

Table 2: Overall Device Evaluation Strategy

Device/Procedure Related Attribute	Potential Failure Modes	Potential Effects of Failure		Information/Data			
		Device	Clinical	Early Feasibility/FIH	Traditional Feasibility *	Pivotal	Marketing

* It may not be necessary to conduct a traditional feasibility study following an early feasibility study.

An example of an overall device evaluation strategy can be found in Appendix 1.

5.3. 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 are not required for IDE approval. As outlined in Section 5.2, FDA encourages sponsors to consider the relationship between an attribute or device failure mode and its 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 chronic implants in which the boundary and loading conditions are known, CM may be used to predict the long-term durability of the device.
- For chronic 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.

5.4. 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. The size of the animal study depends on the device and assay (i.e., 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.

In vivo animal studies to evaluate medical devices are generally required to follow Good Laboratory Practices (GLP) for animal care and study conduct as specified in 21 CFR Part 58. However, non-GLP study data may be used to support an early feasibility study IDE application if the deviations from GLP are identified and justified and do not compromise the validity of the study results. For example, i f 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 non-GLP studies should include independent monitoring and assessments with full disclosure of study findings, including the raw data.

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.

5.5. Prior clinical information

For early feasibility studies, although clinical data may not be available for the test device for its proposed intended use, relevant background clinical information should be provided in the Report of Prior Investigations, and may include 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, if available, 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 clinical data are available, a clinical study report should be provided.

6. 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 an IDE application, the study should be clearly designated as an early feasibility study that is not intended to capture data that would be sufficient to support a marketing application. The proposed study should reflect the novelty of the device and medical need. Use of the pre-IDE process to discuss the Investigational Plan with FDA is highly recommended.

6.1. Risk analysis and mitigation

The Investigational Plan must include a thorough risk analysis which describes the type and potential severity of risks to the subjects, how they will be minimized, and a justification that the risks are reasonable in relation to the expected benefits.[8] The risk analysis should take the availability of alternative therapies or analyses into consideration.

The Investigational Plan should also include appropriate risk mitigation strategies, such as:

- adequate informed consent, as required by 21 CFR Part 50 Subpart B (see Section 6.3.1);
- use of study sites that have a sufficient level of clinical expertise and support to manage adverse events that may arise and to 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 relevant study inclusion and exclusion criteria;
- limiting the sample size to a number appropriate for an early feasibility study (e.g., 5-10 subjects);
- appropriate 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);
- initial device use in subjects with more favorable anatomical characteristics as compared to the population 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 the device use); and
- description of a pre-specified plan for periodic patient outcome assessments (e.g., as frequently as after each use of the device) and reporting prior to enrollment of additional patients.

6.2. Clinical protocol

The Investigational Plan for early feasibility studies must present objectives that reflect the purposes of the clinical study.[9] 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.[10]

This should include a description of the subjects to be included in the study. 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). In addition, the study protocol must include an analysis of the protocol demonstrating that the investigation is scientifically sound.[11] Thus, to ensure that the study will provide information useful for the device development process, and to avoid exposing subjects to risks in the absence of any potential benefit, the study should avoid enrolling subjects for whom success is unlikely due to general health issues. The protocol generally does not need to include the same level of detail as a pivotal study protocol, as previously discussed in Section 5; however, it needs to ensure adequate capture of adverse clinical events and device performance information.

6.3. Human subject protection measures

Human subject protection measures including informed consent and ethics committee oversight,[12] should be tailored to the subject population and the risk profile of the device under investigation.

6.3.1. Informed consent

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. For example, subjects must be told that the study involves research and must be provided an explanation of the purposes of the research,[13] 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 is less nonclinical data than would be required for a larger study). The novelty of the device or procedure should also be described in language understandable to the subject.

As discussed above, due to the reduced amount of information needed to commence an early feasibility study, these studies may carry greater inherent risk, especially 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.[14] 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 personal benefit to the study subject, future patients with the disease or condition may benefit from the information obtained during the early feasibility study. However, the consent form should not include language that could lead subjects to overestimate the chance of personal benefit.

6.3.2. 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 consider whether the

risks to the subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may be expected to result, as well as ensure that risks to the subjects are minimized to the extent possible.[15]

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 safety analysis of the preceding subjects.

6.4. Monitoring

6.4.1. Monitoring procedures

Detailed monitoring procedures, appropriate for an early feasibility study, must be included in the Investigational Plan under 21 CFR 812.25(e). For information on standard monitoring procedures see FDA's draft guidance, "Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring[3]."[16] The monitoring procedures for early feasibility studies may deviate from the standard monitoring procedures and should be tailored to the particular study being conducted.

6.4.2. Data monitoring committee (DMC)

FDA's guidance, "Establishment and Operation of Clinical Trial Data Monitoring Committees[4]."[17] 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 on in the course of the study and would provide an additional layer of human subject protection. Use of a DMC could be helpful and may be proposed by a sponsor as an element of its risk mitigation strategy, particularly for studies where additional independent oversight would be of value.

7. 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-IDE 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[5]."[18]regarding changes to a device or clinical protocol apply to all types of investigational studies. However, this early feasibility guidance adopts a new policy, interpreting the requirements differently for these studies.

To facilitate timely device and/or clinical protocol modifications during an early feasibility study this guidance announces 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 than during other types of studies;
2. For anticipated changes that would require prior FDA approval, a sponsor may 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, FDA intends to utilize a new **interactive review** process that encourages communication with FDA during the 30-day review cycle.

Please note that certain changes must be reported in the annual progress report to the IRB required by 21 CFR 812.150(b)(5).[19] In addition, the changes may be subject to IRB review procedures under 21 CFR 56.110.

7.1. 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 days of making the change.[20] A sponsor may make changes with 5-day notice if: (i) the changes to device development do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of the investigation; or (ii) the changes to the clinical protocol do not affect the (a) 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 rights, safety, or welfare of the human subjects involved in the investigation.[21] The information to be included in such a notice is described in 21 CFR 812.35(a)(3)(iv).

For early feasibility studies 5-day notices may be used in the following manner:

Device developmental changes that do not constitute a significant change in design or basic principles of operation are appropriate for 5-day notices. For early feasibility studies, we would consider a broader range of changes not to be significant than we would for other types of studies. This is in part because the evaluation of early feasibility studies does not depend on statistically significant analyses of data collected or on pooling data among study subjects. However, the changes should be expected not to adversely affect device performance or pose additional risk to the study subjects. The types of changes that may be considered for 5-day notices may be prospectively identified within the IDE application to facilitate timely implementation of potential improvements.

For changes to an early feasibility study clinical protocol, sponsors should particularly focus on the requirements for 5-day notice that the changes not: (1) alter the relationship of likely subject benefit and risk relied upon to approve the protocol, or (2) affect the rights, safety or welfare of study subjects.[22] 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,[23] 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.

Appendix 2 includes examples of the types of changes that may be appropriate for 5-day notification during an early feasibility study.

7.2. Changes requiring FDA approval[24]

The first step in obtaining FDA approval of changes during the early feasibility study should be informal discussion with FDA 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. This guidance adopts the following new approaches for obtaining timely FDA approval of changes to early feasibility studies: 1) contingent approval and 2) interactive review.

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 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 and document 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 potential device iterations and can prospectively identify the appropriate testing plan and acceptance criteria for each type of change, a proposal that covers all the changes may be provided in the original early feasibility IDE application or in a single supplement. 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. For modifications to the clinical protocol, this could include pre-defining several clinical parameters and acceptable values for each that may be added or removed during the study to allow investigators to determine the most relevant parameters for future evaluation of the device. 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.

Appendix 2 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. The sponsor should submit an official request for the modifications that incorporates the

information previously communicated to FDA and prior FDA feedback. During 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.

8. Next steps in clinical evaluation

After obtaining clinical information from an early feasibility study, the type of subsequent clinical evaluation will depend on the stability of the device design, the availability of adequate data to justify the next study, and the purpose of that 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, sponsors may submit an IDE supplement including a request for expansion of the early feasibility study to FDA. 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. At this point, further informal communications with FDA are important to help determine the most appropriate study, which will ultimately depend on the amount of nonclinical and clinical data available to the sponsor to justify the 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.

9. Conclusion

Early feasibility studies provide early device safety data and clinical verification of the proof of principle. 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 towards 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-IDE process will be instrumental in the successful implementation of this guidance.

Appendix 1: Device Evaluation Strategy Example

The following hypothetical example of an acceptable proposal further illustrates the concepts described in Section 6.2.2.

A sponsor approaches FDA with a proposal to evaluate an innovative, metallic implant to treat a disease common in the elderly in an early feasibility study. The device is unique in that delivery of the treatment

will be through a novel catheter design, rather than through the standard procedure that involves open surgery. There are some aspects of the new device that are similar to an approved device.

The sponsor has described the design concept in detail to support the sponsor's device evaluation strategy. In order to obtain FDA feedback regarding the sponsor's longer-term evaluation plans, the sponsor has included proposals for the information/data needed to support progression to each of their planned developmental phases in addition to that needed to support initiation of the early feasibility study under a pre-IDE submission.

A portion of the device evaluation strategy provided by the sponsor is included in Table 1.

Device/ Procedure Related Function	Potential Failure Modes	Potential Effects of Failure		Information/Data			
		Device	Clinical	Early Feasibility/FIH	Traditional Feasibility*	Pivotal	Marketing
Implant integrity	Structural failure of implant	Metallic fracture	• Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures	• Discussion on design concept to optimize integrity • Comparison of design to marketed devices • Strength testing • Stress/strain analysis	• Early feasibility clinical data If device modified: • Strength testing on modified device, if appropriate • Stress/strain analysis on modified device, if appropriate	• Limited number of cycles for durability testing • Bench testing and fatigue analysis on final device design • Clinical data	• Full number of cycles of durability testing • Clinical data
	Corrosion	Metallic fracture	• Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures	• Comparison of materials to marketed devices	Corrosion testing	If device modified: Assessment of modifications on corrosion potential, with new testing if necessary	Clinical data
Appropriate biological response	Loss of device function	None	Necrosis	• Comparison of design and materials to marketed devices • Acute and medium-term implantation in an appropriate animal model	• Early feasibility clinical data If device modified: • Repeat acute and medium-term animal study, if appropriate	• Longer–term implantation in a validated animal model • Feasibility clinical data	Clinical data

Table: Device Evaluation Strategy Example

* It may not be necessary to conduct a traditional feasibility study following an early feasibility study.

As shown in the Early Feasibility Information/Data column, the sponsor proposes to address the need for device structural integrity for their early feasibility study through discussion of the design concept and other relevant experience, supplemented by basic strength testing and a stress/strain analysis. The new device design has similarities to a device that is in clinical use; thus, some information can be leveraged to support the assessment of the structural integrity of the new device. The sponsor indicates that a loss of device integrity would not lead to a catastrophic failure and that subjects would be closely monitored to allow detection of any loss of device integrity.

The sponsor proposes that similar testing and analyses would be needed to support a traditional feasibility study, with the addition of corrosion testing and clinical data from the early feasibility study. Progression to a pivotal study would include submission of limited durability testing results, which will be supplemented by fatigue analysis (i.e., a finite element analysis) of, and additional bench testing on, the final device design. Complete durability testing would be needed to support a marketing application. The clinical data would further support the implant integrity in the marketing application.

An animal study in a validated animal model to evaluate the potential for catastrophic failure of the device acutely and in the medium term is proposed to justify the initiation of an early feasibility study. A longer-term animal study would be completed to demonstrate complete healing at later time points.

Appropriate changes in the device evaluation strategy will be made as information is obtained from the early feasibility study.

Appendix 2: Device iteration example

The following is a hypothetical scenario that illustrates the concepts described in Section 7 regarding device iteration during an early feasibility study.

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 novel catheter design, 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. Based on these assessments, they will consider device and clinical protocol modifications.

In their original IDE application the sponsor seeks contingent approval for several types of changes. They propose the following specific iterative changes that they would like FDA approval for implementing as they complete their pre-specified device evaluation plan:

- improvements in maneuverability, including:
    - modifying the shape of the nose cone of the introducer (e.g., make sharper or more blunt); 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);
- adding, moving, or changing the radiopaque bands on the catheter to improve visibility; and

- modifying the operator interface console.

The sponsor and FDA reach concurrence on the test plan to evaluate the proposed changes through informal discussions that are subsequently documented in the original IDE submission. Although some of these changes may have been appropriate for 5-day notices, obtaining prospective, contingent approval provides the sponsor with more predictability in the regulatory process for their device modification plans.

With help from their principal investigator, the sponsor identified other types of changes that may be needed for their device and clinical protocol during the conduct of their early feasibility study and discussed these with FDA under a pre-IDE. The sponsor includes the following table in their original IDE to describe their plan.

Table: 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**
Addition of surface coating to catheter if lubricity is needed to improve access*	If a surface coating is added, need to 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)
Change specific features of the device to be consistent with device approved for use under another IDE for a similar indication*	Modification to improve catheter resistance to kinking, with the type of modification and appropriate testing to be identified prior to supplement submission	Changes identified as necessary during the early feasibility study for which the testing needed would be different from that previously used or where it is difficult to determine reasonable acceptance criteria for the testing
Changes in the device preparation for use	Changing the device to accommodate a broader range of subject anatomies (i.e., type of modification and therefore type of appropriate testing not identified in the original IDE)	Change from percutaneous access to an open cutdown or to use of a vascular conduit
Addition of use of approved ancillary device intended to improve the safety of the procedure*	Other device modifications identified during the clinical study for which an appropriate testing plan and acceptance criteria can be identified	
Use of off the shelf tools (i.e., that were not identified in the original IDE) to perform bailout procedures		
Modification to subject		

selection to limit, rather than expand, the criteria*		
Modify procedural imaging modalities*		
Reducing follow-up assessments if early data support change (i.e., show 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.

Many of the types of changes that might be appropriate for 5-day notification during this early feasibility study would not normally be acceptable for studies enrolling a larger number of subjects or in a study intended to collect data to independently support a marketing application. However, for this early feasibility study, the changes proposed to the device and clinical protocol would not adversely alter the risks for the study subjects. The developmental device changes would be appropriate for 5-day notification 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, because enhanced subject protection measures are in place for the early feasibility study;
- the validity of the data or information resulting from the completion of the approved protocol because the such data or information will not be pooled;
- the relationship of likely patient risk to benefit relied upon to approve the protocol; or
- the scientific soundness of the study because there are no statistical hypotheses to be tested in the early feasibility study.

During the course of the sponsor's early feasibility study, the sponsor made some of the anticipated changes, but also identified an additional modification that had not been predicted in the original IDE submission which the sponsor described to FDA informally. The sponsor requested contingent approval of a change in a material used in the construction of the device based on obtaining acceptable results for this material using same types of testing used to evaluate the original device design. To formally request this change, the sponsor submitted an IDE supplement that described the change and evaluation plan. FDA and the sponsor reached a consensus regarding the proposal during the 30-day review time for the

supplement, and FDA granted approval of the modification contingent on the sponsor's successful completion of the proposal and reporting of the change and supporting information to FDA within 10 days of implementing the change. The sponsor evaluated the modified device according to the test plan, obtained acceptable results, implemented the change and submitted their test report to FDA 7 days after making the change.

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[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.

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

[3] 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.

[4] 21 CFR 812.20(a).

[5] 21 CFR 812.27(a).

[6] Characterization tests (i.e., testing conducted to describe the device) may not have specified acceptance criteria.

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

[8] See 21 CFR 812.25 and 812.30(b)(4).

[9] 21 CFR 812.25(a).

[10] 21 CFR 812.25(b).

[11] 21 CFR 812.25(b).

[12] See 21 CFR Parts 50 and 56.

[13] 21 CFR 50.25(a)(1). For more information on Informed Consent see, "A Guide to Informed Consent - Information Sheet[6]."

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

[15] 21 CFR 56.111(a)(1) and (2).

[16] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf[7]

[17] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf[8]

[18] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082145.htm[9]

[19] See 21 CFR 812.35(a)(4).

[20] 21 CFR 812.35(a)(3).

[21] 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).

[22] See 21 CFR 812.35(a)(3)(ii).

[23] 812.35(a)(3)(ii)(A) and (B).

[24] See 21 CFR 812.35(a)(1)