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Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions

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Guidance for Investigational Device Exemption Sponsors, Sponsor-Investigators and Food and Drug Administration Staff

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For questions about this document regarding CDRH-regulated devices, contact the Office of Device Evaluation, Office of the Director, Investigational Device Exemptions (IDE) Staff at 301-796-5640. For questions about this document for CBER-regulated devices, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

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Preface

Public Comment

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA is committed to improving U.S. patient access to new devices by strengthening and streamlining the clinical trial enterprise so that medical device clinical trials are conducted in the U.S. in an efficient and cost-effective manner, while maintaining appropriate patient and research participant protections.

The purpose of this guidance is to provide greater clarity for FDA staff and investigational device exemption (IDE) sponsors and sponsor-investigators[1] regarding the principal factors that FDA considers when assessing the benefits and risks of IDE applications for human clinical studies.

[1] Sponsor and sponsor-investigator are defined in 21 CFR 812.3.

Consistent with applicable laws and regulations, FDA may disapprove an IDE application if, among other reasons, "[t]here 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."[2] In many cases, the Agency believes that effective risk management, including the application of risk controls, which includes risk mitigation measures, can result in a favorable IDE benefit-risk determination.

FDA recognizes that in assessing risks and anticipated benefits, the medical device total product lifecycle should be considered, and that earlier stages of device development and investigational clinical study are typically associated with greater *uncertainty* (i.e., a lower level of evidence). A primary goal of this guidance is to clarify the factors that FDA considers when assessing risks and anticipated benefits as significant contributors to the decision to approve IDE studies, and how uncertainty may be offset by a variety of *risk mitigation* measures which can ensure appropriate patient and research participant protections in investigational research settings. For proposed IDE studies, at earlier stages of device development, FDA considers appropriate mitigation measures for anticipated possible risks and unanticipated risks, whereas in later stages, FDA considers whether risk mitigation measures focus on the most probable risks.

Another important goal of this guidance is to characterize benefits in the context of investigational research, which includes direct benefits to the subject and benefits to others (to the extent there are indirect benefits to subjects such as knowledge to be gained from the study or information that may contribute to developing a treatment).

As with the benefit-risk framework for evaluating marketing applications, FDA assessment of benefits and risks for an IDE application takes into account the contextual setting in which the study is being proposed, including but not limited to characterization of the disease or condition being treated or diagnosed, the availability of and risks associated with alternative treatments or diagnostics. When available, information characterizing subject tolerance for risk and their perspective on benefit may provide useful context during this assessment. See for more information FDA Guidance, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf).

FDA believes use of this benefit-risk framework will facilitate the incorporation of evidence and knowledge from different domains—clinical, nonclinical, and patient—to support a comprehensive, balanced decision-making approach. FDA envisions this will facilitate a common understanding between FDA and sponsors/sponsor-investigators by highlighting which factors are critical in the benefit-risk assessment for a specific application, and clearly explaining how these factors influence FDA's decisions. This guidance document will also help improve the predictability, consistency, and transparency of the review process for IDE applications.

[2] 21 CFR 812.30(b)(4).

FDA's guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

II. SCOPE

This guidance document explains the principal factors that FDA considers when assessing benefits and risks of original IDE applications, IDE amendments and IDE supplements for human clinical investigations of certain medical devices to determine safety and effectiveness. The approach discussed in this guidance is applicable to studies subject to the IDE requirements in 21 CFR part 812, including postmarket studies. In general, IDE applications are required for clinical investigations of significant risk devices to determine safety and effectiveness.[3] This guidance applies to both diagnostic and therapeutic devices. This guidance is not intended to provide recommendations regarding device-specific data or study requirements.

III. INFORMED CONSENT AND IDE DECISIONS

The purpose of the IDE regulations, as set forth in Title 21 CFR part 812, is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to maintain optimum freedom for scientific investigators in their pursuit of this purpose.[4] Title 21 CFR part 812 applies to all clinical investigations of devices to determine safety and effectiveness with some exceptions, as described in 21 CFR 812.2(c).

FDA approval of an IDE application prior to study initiation is typically required for a clinical investigation conducted in the U.S. of a significant risk device that is not approved or cleared for the indication being studied.[5] As defined in 21 CFR 812.3(m), a significant risk device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

[3] 21 CFR 812.2 and 20.
[4] 21 CFR 812.1.
[5] See section 520(g) of the Federal Food, Drug and Cosmetic Act (FD&C Act) and 21 CFR 812.2(b) for conditions under which an IDE application is required prior to study initiation.

An approved IDE application exempts the study sponsor from certain provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (such as certain requirements for a marketing submission and good manufacturing practice). However, IDE studies must comply with the applicable requirements set forth in 21 CFR part 812, including requirements for informed consent under 21 CFR part 50, labeling of devices for investigational use only, study monitoring, records and reporting, and approval by an Institutional Review Board (IRB) in accordance with 21 CFR part 56.[6]

A. Informed Consent

A key tenet of FDA's IDE benefit-risk framework is appropriate protection of human subjects and a key principle of human subject protection in clinical investigations is the informed consent process.[7] This process goes beyond obtaining a signature on an informed consent form. The informed consent process provides the prospective subject or his or her legally authorized representative with adequate information about the study, including pertinent information about the investigational device, its risks and benefits, alternatives, and what is expected of the subject in order to participate in the study (e.g., study visits, procedures, maintaining subject diaries).[8] The subject or his or her legally authorized representative must be given sufficient opportunity to consider whether or not to participate in the clinical study under circumstances that minimize the possibility of coercion or undue influence.[9]

An informed consent process should allow an individual to decide to accept potential risks associated with a study in exchange for the potential for anticipated benefits to the subjects and the importance of the knowledge to be gained. The informed consent process allows individuals to exercise their personal tolerance of risks as weighed against other factors, including the reasonably expected benefits and the alternatives to the study.

The informed consent process ensures that each individual makes a determination about study participation after being informed of the study, including the risks and benefits of study participation, and, if applicable, the possibility of receiving no direct benefit. The informed consent regulations in 21 CFR part 50 describe the informed consent aspects of human subject protection in clinical investigations subject to FDA regulations. For example 21 CFR 50.20, states the following:

> *"Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."*

[6] Section 520(g)(3) of the FD&C Act.
[7] See generally, 21 CFR part 50.
[8] See 21 CFR 50.25.
[9] See 21 CFR 50.20.

In addition, 21 CFR 50.25(a)(2) states that the informed consent must include "a description of any reasonably foreseeable risks or discomforts to the subject."

B. Regulatory Standard for IDE Decisions

Under section 520(g)(4)(B) of the FD&C Act, an IDE application may only be disapproved if FDA finds that the investigation does not conform to the procedures and conditions prescribed under regulations. The purpose of the IDE process is "to encourage, to the extent consistent with the protection of the public health and safety and with ethical standards, the discovery and development of useful devices intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose."[10]

FDA's decision-making process for IDE applications was modified with the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 (Pub. L. No. 112-144). Section 601 of FDASIA amended Section 520(g) of the FD&C Act to specify certain situations in which FDA cannot disapprove an IDE application. Section 520(g)(4)(C) of the FD&C Act states that, consistent with section 520(g)(1), FDA shall not disapprove an IDE application because:

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

Considering the above criteria, when the objective of a proposed study is to support a marketing submission, the sponsor may benefit from learning whether there are protocol modifications that FDA believes are needed for the study to adequately support product approval or clearance. FDA intends to convey such considerations to the sponsor to provide greater clarity and predictability. For more information, see the FDA Guidance, FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations, (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf), issued August 19, 2014 (hereinafter, FDA Decisions for IDE Guidance).

In accordance with 21 CFR 812.30(b), FDA may disapprove or withdraw approval of an IDE application for any of the following reasons:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.
(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

[10] Section 520(g)(1) of the FD&C Act.

(3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.
(4) 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*** *[emphasis added], or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.*
(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:
(i) The report of prior investigations or the investigational plan;
(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or
(iii) Monitoring and review of the investigation.

Consistent with this regulation, FDA will generally disapprove an IDE application if potential risks of the proposed study are not justified, or if data provided are insufficient to adequately characterize the safety profile of the device such that, based on the data contained in the IDE application, human clinical investigation is not considered reasonable.

This guidance document provides greater clarity regarding regulatory assessment of:

- risks and benefits associated with clinical investigational device use proposed in IDE applications;[11] and
- inadequacy or uncertainty regarding the clinical or nonclinical data from prior investigations, the proposed study, the manufacturing, transport and storage of a device, or monitoring oversight of the proposed study.[12]

C. Types of IDE Decisions

FDA regulations[13] provide for three major categories of decision on an IDE application – approval, approval with conditions, and disapproval.

If FDA approves an IDE application the sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA's decision letter, including the maximum numbers of U.S. subjects and investigational sites. See FDA Decisions for IDE Guidance, page 6.

If FDA approves an IDE application with conditions, the sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA's decision letter, including the maximum numbers of U.S. subjects and investigational sites, and FDA

[11] 21 CFR 812.30(b)(4).
[12] 21 CFR 812.30(b)(5).
[13] 21 CFR 812.30(a).

expects that the sponsor will submit information addressing the issues identified as conditions of approval in FDA's letter within 45 days. See FDA Decisions for IDE Guidance, page 7.

If an IDE application is disapproved, the sponsor may not initiate enrollment in the clinical investigation until the sponsor submits an amendment to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions. See FDA Decisions for IDE Guidance, page 10.

Where appropriate, FDA may allow additional flexibility in how outstanding issues can be addressed (i.e., future considerations, study design considerations, contingent approval, staged approval), to allow clinical investigations to commence without unnecessary delay, while ensuring that human subjects are adequately protected.[14] For discussion of contingent approval, see FDA Guidance, Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf), issued October 1, 2013 (hereinafter, FDA Early Feasibility Guidance).

In some cases, FDA may grant staged approval or staged approval with conditions for a portion of the planned study cohort or grant a limited number of subjects enrolled while outstanding questions that may affect the benefit-risk profile for the proposed IDE study are addressed. See FDA Decisions for IDE Guidance for more information on staged approvals, page 8.[15] Staged approval permits the clinical investigation to begin in a timely manner while maintaining appropriate subject protections. Without this mitigation measure, the benefit-risk profile of the proposed investigation may not support study initiation.

FDA may grant *approval with conditions* when there are outstanding issues that do not raise concerns that preclude initiation of the proposed clinical investigation, provided that the sponsor addresses the recommended modifications to the study. Resolution of these issues is not required prior to initiation of study subject enrollment, with exception of issues related to the informed consent document, which must be addressed before enrollment begins, in accordance with 21 CFR part 50 - Protection of Human Subjects.

Initial IDE application approval decisions reflect the benefit-risk profile of the proposed investigation at the time of FDA's assessment. Changes in approval status (e.g., from disapproval to approval) may be appropriate as new information becomes available which:

- changes the understanding of risks and benefits or their associated level of uncertainty;
- changes confidence in risk control or mitigation measures (refer to Appendix D); or

[14] See FDA Decisions for IDE Guidance (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf) for more information.

[15] See FDA Decisions for IDE Guidance (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf) for more information on staged approvals, page 8.

- changes the disease or clinical diagnostic/treatment landscape in a manner which alters the benefit-risk profile of the IDE device relative to alternatives.

If necessary, FDA may take appropriate regulatory actions to protect study subjects, including placing a clinical hold on the study. FDA can place a study on "clinical hold" when, taking into consideration the factors in section 520(g)(8) of the FD&C Act, the device involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation. If the study is placed on hold, no additional subjects may be enrolled.

D. Study Design Considerations

Although FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing submission in accordance with section 520(g)(4)(C) of the FD&C Act, study design has a direct bearing on the knowledge that can be gained from that study. A poorly designed study may produce evidence which leads to false conclusions that have significant negative public health implications. A poorly designed study could produce data, which are inconclusive or difficult to interpret and thereby limit the degree to which useful knowledge is generated from the study.

In contrast, well-designed studies are more likely to produce important knowledge about a device or disease. FDA believes it is most efficient, and consistent with least-burdensome principles, to encourage the conduct of studies which are designed to meet stated objectives. FDA may inform the sponsor of recommended modifications to the study design – *Study Design Considerations (SDCs)*[16]– that FDA believes will improve the quality of the information and knowledge generated by the study which the sponsor is encouraged but not required to address.

IV. IDE APPLICATION ASSESSMENT IN THE CONTEXT OF A DEVICE DEVELOPMENT PATHWAY

A. Stages of Device Development

When making IDE benefit-risk assessments, FDA considers: 1) the stage of development of the device, 2) the maturity of the proposed technology, and 3) the availability of non-clinical testing to complement or replace the need for clinical testing.

FDA's Early Feasibility Guidance (page 6) defines the following device study types:

[16]See FDA Decisions for IDE Guidance (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf) for more information on the topic of SDCs.

First in Human (FIH): A first in human study is a type of study in which a device for a specific indication is evaluated for the first time in human subjects.

Early Feasibility: 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).

Traditional Feasibility: 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.

Pivotal 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.

In some cases, IDE studies may also be designed for investigation of marketed products. For example, an IDE study may be conducted to expand the indications for use or update the device labeling.

The approach to benefit-risk assessment in IDE applications should be tailored to the stage of device development, because device investigations during different stages of development are generally associated with different types of risk, and different levels of uncertainty. Specifically, a greater degree of uncertainty is expected for novel technologies, and at earlier stages of device development, such as first in human or early feasibility trials, while relatively more certainty is expected in traditional feasibility and pivotal trials. At earlier stages, the focus is on whether the proposed investigation has appropriate risk control measures for anticipated possible risks and unanticipated risks, whereas in later stages focus shifts increasingly to mitigating the most probable risks. Additionally, early development clinical studies are typically designed to assess initial safety and proof of concept about the proposed device use. Later stage studies, particularly those intended to support future regulatory applications, are typically designed to assess safety and effectiveness outcomes in an intended patient population, with additional information to quantify uncertainty in each of these outcomes. IDE benefit-risk assessments should take into consideration whether the level of uncertainty is appropriate to the stage of development for the investigational device. It should be noted that regardless of the stage of development, risk mitigation measures may be needed for certain serious events that have a low rate of occurrence in order to support a favorable benefit-risk assessment.

For IDE benefit-risk determinations throughout all stages of device development, it is also important to recognize that non-clinical and prior clinical data play a critical role. Medical devices often have attributes that cannot be tested by clinical methods alone and that play a major role in the performance, safety or effectiveness of the device. In some cases, non-clinical testing (e.g., in vitro tests, animal studies, and computer modeling and simulation) can obviate or reduce the need for additional clinical testing to evaluate certain aspects of device design or performance. Both clinical and non-clinical testing methods may be used to assess the likelihood/probability or severity of a given risk, and/or the success of risk control measures,

including risk mitigation measures. Data from early clinical studies and/or studies conducted outside the U.S. may inform the benefit/risk assessment and the appropriate risk mitigation and control measures for future IDE studies.

For a reference guide to the information FDA considers when assessing benefit-risk in the context of a device development pathway, refer to Appendix A.

B. Applying Benefit-Risk Framework to IDE Decision-Making

A benefit-risk framework is used both for supporting IDE decision-making, as well as decisions related to marketing submissions (e.g., PMA, de novo, and for certain aspects of 510(k) substantial equivalence determinations). Importantly, however, benefit-risk decision-making is fundamentally different for IDE applications because clinical investigations, by their very definition, are research studies with inherent uncertainty regarding the relative benefits and risks of a given device, technology, or treatment.

Therefore, FDA intends to permit appropriate latitude for the conduct of IDE studies within the boundaries of applicable laws and regulations. In considering whether risks outweigh the potential benefits to the subjects and the importance of the knowledge to be gained, absence of definitive evidence of benefit or the presence of purely hypothetical risks are not sufficient justification, in and of themselves, to disapprove an IDE application (see Section III.B. of this guidance).

Given the more limited level of evidence typically associated with IDE applications compared to marketing applications – especially for earlier stages of investigation – decisions about IDE applications are made in settings involving relatively greater uncertainty and a lower level of evidence. The inherent uncertainty present in clinical investigations can often be offset by appropriately tailored risk control / risk mitigation measures which can help ensure appropriate patient and research participant protections in investigational research settings (some forms of risk controls that may be applied to IDE studies are listed in Section III.A.4.). In considering benefits of investigational research, FDA considers direct benefits to the subject and benefits to others (to the extent there are indirect benefits to subjects such as knowledge to be gained from the study or information that may contribute to developing a treatment).

As with the benefit-risk framework for marketing applications,[17] FDA assessment of benefits and risks for an IDE application takes into account the contextual setting, including characterization of the disease or condition being treated or diagnosed; and the availability of alternative therapies, including their associated benefits and risks. When available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context during this assessment.

V. ASSESSING BENEFITS AND RISKS FOR IDE APPLICATIONS

The approach outlined in this section describes FDA's key considerations when assessing benefits and risks of IDE studies. FDA recommends using a benefit-risk framework to facilitate the incorporation of evidence and knowledge from different domains—clinical, nonclinical, and patient—to support a comprehensive, balanced decision-making approach. The framework should focus on relevant facts, uncertainties, and key areas of judgment to add clarity and predictability to the regulatory process. FDA envisions that these factors will facilitate common understanding between sponsors and FDA by highlighting which factors are critical in the benefit-risk assessment for a specific application, and clearly explaining how these factors should influence FDA's decision.

FDA recommends IDE sponsors provide as part of the IDE application a section that summarizes the key considerations for the IDE benefit-risk assessment For an outline of the general framework for IDE benefit-risk assessment, please refer to Appendix A. Appendix B contains generic examples of IDE benefit-risk determinations for illustrative purposes.

Patient Preferences

When applying a benefit-risk framework to decisions on IDE applications, FDA's assessment depends on the value assigned to various risks and anticipated benefits to the patients. In the context of a clinical study, anticipated benefits include not only direct benefits to the patient but also societal benefits in terms of knowledge to be gained from the study.

It is important to acknowledge that individual patient preferences vary, and that a patient may not assign the same values to various risks and anticipated benefits as their physician, family member, or other individual. Furthermore, patient preferences vary, both in preferred modality of treatment/diagnostic procedure (often devices are one option to be considered in a treatment care path which may include surgery or medication), as well as in risk tolerance. Some patients are willing to take on higher risks to potentially achieve a small benefit, whereas others are more risk averse. In certain circumstances, some patients may be willing to participate in clinical studies that offer no or limited direct benefit to subjects, but have anticipated societal benefits in advancing medical science. Please see FDA Guidance, Patient Preference Information--

[17] See FDA Guidance, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf).

Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf).

It may be appropriate to approve an IDE application where only a subset of the eligible study subject population would accept the potential risks as weighed against the potential benefits, including the benefit of the importance of the knowledge to be gained provided there is enough information on those potential risks and benefits and an adequate informed consent process in place for study participants to make informed decisions. However, if, for a certain IDE application, the potential risks outweigh the anticipated benefits for all subjects, FDA would disapprove the IDE application in accordance with 21 CFR 812.30(b).

Patient preference information, as it relates to the participants in the study, may be particularly informative in helping to weigh the risks and benefits in certain challenging device areas. For example:

- life-saving but high-risk devices (e.g., ventricular assist devices (VADs) for end-stage heart failure);
- devices intended to directly affect health-related quality of life (e.g., for seizure prevention, sleep apnea);
- devices intended to yield significant health benefits (e.g., obesity devices);
- devices intended to yield significant appearance benefits (e.g., breast implants, wrinkle fillers);
- devices for use in conditions where alternatives include non-device options such as surgical procedures or medical therapy (e.g., minimally invasive alternatives to open surgery).

When available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context for assessing the benefits and risks of a proposed clinical investigation.

Investigational Device Description

Fundamental to an assessment of benefits and risks associated with investigational device use is an understanding of the investigational device itself. Title 21 CFR 812.25(d) requires that the investigational plan include a:

> *description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation).*

Deficiencies related to an incomplete or inadequate investigational device description are the single most common type of non-protocol related deficiency in IDE applications that fail to attain full approval. Appendix C lists the device attributes that FDA recommends be included in the IDE application device description section.

Assessment of Risks Associated with Investigational Device Use

The investigational plan must include a risk analysis, which describes and analyzes all *increased risks* to which subjects will be exposed by the investigation.[18] FDA compares the risks associated with the investigation with not participating in the study. FDA also considers the manner in which these risks will be minimized, a justification for the investigation, and a description of the patient population including number, age, sex, and condition. The investigational-use risk analysis should align with the device-specific risk analysis (e.g., Failure Modes and Effects Analysis (FMEA)) as part of the overall device history file and risk management process.

FDA recommends that IDE sponsors use an accepted method of risk assessment, where appropriate. For example, this guidance incorporates principles from ANSI/AAMI/ISO 14971: *Medical Devices – Application of risk management to medical devices*, an FDA-recognized standard, which provides a framework for systematically managing risks of medical devices throughout the total product life cycle.

In addition, there are several key concepts, which are not commonly well described in IDE applications received by FDA and should be included in the application when assessing risks during the investigation:

- Harms. Specifying how a hazard could lead to clinical sequelae including length of time experienced and residual affect (if any) or other harmful event is important because it allows more precise estimation of risk severity and likelihood.

- Likelihood. Focusing on severity of a risk along with likelihood is important for a complete estimation of that risk.

- Residual risk and completeness of risk control. Many identified risks are reduced to an acceptable level through effective risk controls. FDA's benefit-risk assessment of IDE applications focuses on completeness of risk control measures and whether residual risk outweighs anticipated benefits to the subjects.

FDA may disapprove an IDE application if there is reason to believe that the risks to the subjects outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained.[19] Assessment of benefits and risks should not necessarily be made in comparison to the most technologically advanced alternative but rather to commonly used therapies and treatments for a specific disease or condition.

A. Assessment of Risks to Study Subjects

[18] 21 CFR 812.25(c).
[19] 21 CFR 812.30(b)(4).

In general, the sponsor's assessment of risks to IDE subjects focuses on risks whose existence and characteristics are supported by objective scientific evidence and are reasonably foreseeable. The assessment of risks must include a description and analysis of all incremental risks to which subjects will be exposed by the investigation, and the manner in which these risks will be minimized.[20] While it is not necessary to include specific mitigations for hypothetical risks that are not supported by scientific evidence or risks that are determined to be negligible due to a low probability of occurrence and low severity of harm, it is recommended to identify all possible risks in the risk assessment and include information on how the level of risk was determined.

Relationship between Hazards and Harm[21]

Risk assessment involves describing the relationships between a hazard (a potential source of harm) and the ultimate harm in terms of injury or damage. As part of FDA's IDE decision-making, this relationship should specifically describe the foreseeable sequences of events, hazardous situations, and associated possible harm. This should include (as applicable):

- the initiating hazard, failure mode, or circumstance;
- the sequence of events that could lead to a hazardous situation occurring;
- the likelihood of such a situation arising;
- the likelihood that the hazardous situation leads to harm;
- the nature of the harm that could result.

The extent of risk(s)/harm(s) associated with an IDE study is assessed by taking into account the following factors, individually and in aggregate:

A.1 Type(s) of risk(s), including severity: The various risks, including the severity of the risk, assumed by the subject from participation in the investigation should be considered. These include:

- **Basic Safety –** protection against physical hazards, which should be addressed and mitigated with a reasonable level of certainty. For example, an active device should not be unsafe from an electrical safety perspective (e.g., the devices should not deliver an unintended electrical shock and surface temperature increases should not unintentionally burn the patient or operator).
- **Device-related serious adverse events –** events attributable to the investigational use of the device which produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
- **Device-related non-serious adverse events –** events attributable to the investigational use of the device which do not produce an injury or illness that is life-threatening, do not result in permanent impairment or damage to the body, or do not require medical or surgical intervention to prevent permanent harm to the body**.**

[20] 21 CFR 812.25(c).
[21] See Appendix D for a glossary of risk management terms.

- **Procedure-related complications due to the investigation – t**his includes not just the device use but risks related to the investigation itself to which the subject would otherwise not be exposed, e.g. risk of anesthesia during procedures involving an investigational device.
- **Risks associated with the study itself –** risks the subject may be exposed to that do not directly result from use of the device and would not be expected as part of usual care outside of the investigational setting. Examples include additional procedures (such as medical imaging) for ascertainment of study endpoints.
- **Risk from false-positive or false-negative results for diagnostics –** if a diagnostic device gives a false-positive result, the subject might be exposed to risks associated with unnecessary additional diagnostic procedures and tests, or potentially unnecessary treatment, as well as the ramifications of falsely diagnosing a disease. If a false-negative result is given, the subject might not receive effective treatment (thereby missing benefits that treatment would confer), or might not be diagnosed with the correct disease or condition. Failure to correctly diagnose a transmissible disease could also result in transmissions to other individuals which would present a broader public health issue.

A.2 Likelihood or probability of risk(s): Various approaches are commonly employed to estimate probabilities of risks including but not limited to: use of relevant historical data; prediction of probabilities of risk using analytical or simulation techniques; use of experimental data from prior investigations; reliability estimates; production data; post-production information; and use of expert judgment. The use of multiple approaches may be considered as this might serve to increase confidence in the results. During earlier development stages, greater uncertainty may exist around these estimates, in which case it may be useful to consider a qualitative approach to risk probability analysis. Such an analysis may include qualitative or semi-quantitative probability levels when the probability cannot be precisely determined, but is known or expected to be within an estimated range.

The likelihood or probability of risk(s) includes the likelihood of the hazard resulting in a harmful event. If known, this includes the number of harmful events per patient or the number of harmful events per unit of time, the proportion of the intended population that would be expected to experience a harmful event, as well as the likelihood of a given subject or study group experiencing a harmful event. FDA considers whether an event occurs once or repeatedly in assessing the probability of risks.

A.3 Duration of risk(s): Some studies expose subjects to temporary, minor harm; some can cause repeated but reversible harm; others can cause permanent, debilitating injury. Duration (i.e., how long the adverse consequence lasts) should be considered along with severity of risk, as described in above in A.1.

A.4 Risk Management:[22] Risk Management provides a summary and assessment of any efforts that could help to mitigate the identified safety concerns, or ensure that device use is directed to those participants for whom the risk is considered acceptable because it does not outweigh the potential for benefit.

Risk control measures (including risk mitigation efforts) should be applied, where appropriate, to reduce the likelihood and severity of harm to study subjects and improve the benefit-risk profile of the proposed IDE study. Risk control measures are intended to reduce the risk to an acceptable level. Sponsors should conduct an initial determination regarding which risk controls are appropriate for their proposed IDE study. Benefit-risk assessment for IDE decisions should focus on residual risk, and whether residual risk has been reduced to acceptable levels relative to the anticipated benefits to the subjects. The sponsor must provide in the IDE application a clear justification for the investigation, having considered risks for the intended study population and the manner in which those risks will be minimized.[23]

Risk control measures may include device design features/modifications and risk mitigation may include protective measures (e.g., study design features), and communication of safety information (e.g., training of investigational staff). Forms of risk controls that may be applied to IDE studies may include but are not limited to:

Safety by Design

- Device design features and/or modifications

Protective Measures

- Physical protective measures (e.g., user & subject radiation shielding)
- Preparation and readiness of personnel and equipment for anticipated adverse events (e.g., crash carts)
- Study design[24]
    - Staged enrollment with limited initial human subject exposure and interim pre-specified subject safety assessment (e.g., IDE staged approval)
    - Staged/graded exposure to device intervention (e.g., low level stimulation before high level stimulation)
    - Pre-specified clinical management of potential adverse events; more frequent reporting
    - Pre-specified monitoring of study conduct, particularly for aspects critical to safety
    - Pre-specified stopping rules or guidelines

[22] For additional information on risk management for medical devices, refer to ANSI/AAMI/ISO 14971 "Medical Devices—Application of risk management to medical devices."
[23] 21 CFR 812.25(c).
[24] See Section A.5 – Residual risk evaluation section of this guidance.

  - If appropriate, a narrow study population that consists of a subset where the benefit-risk profile is more favorable (e.g., limit high risk novel therapy to treatment-refractory patients)
- Performance of study at trained or specialized sites or investigators meeting certain criteria (e.g., multidisciplinary heart team).
- Study oversight
  - Institutional review board/ethics oversight
  - Use of a Clinical Events Committee, Data Monitoring Committee / Data Safety and Monitoring Board[25]or other Quality by Design features
  - IDE Progress Reports
  - Clinical Hold Authority[26]
- Adverse Event reporting[27]
  - More frequent reporting of serious adverse events (e.g., after each occurrence, monthly, quarterly, annually)
  - Accurate reporting of adverse events, including the timing and clinical context and a description of any medical interventions that were provided and the associated outcomes

Communication of Safety Information

All clinical investigations include some risk. After taking appropriate steps to mitigate risk through device design features/modifications and protective measures, sponsors are required to communicate relevant safety information about residual risks in the following ways:[28]

- Informing study subjects about reasonably foreseeable risks of study participation
- Optimizing communication among study sites regarding safety information (e.g., investigator and study coordinator calls concerning safety-related actions (Risk control measures.)
- Communicating safety information with the IRB overseeing the study to determine whether any additional human subject protection measures are needed

Note that the preferred hierarchy of risk management including risk control measures is to first attempt to eliminate the risk, then if this is not possible, to design and implement protective measures (e.g., reduce the probability of occurrence of risk or the extent of potential harm as well as is reasonably possible)) and communicate the residual risk to study subjects and operators (e.g., through informed consent or labeling).

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[25] See FDA Guidance, Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006), (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf).
[26] See Section 606 of FDASIA "Clinical Holds on Investigational Device Exemptions."
[27]See 21 CFR 812.150.
[28] 21 CFR 50.25.

A.5 Residual risk evaluation: After risk control measures are applied, the following measures may be considered when evaluating any residual risk, particularly in cases where there are substantial risks associated with the study:

- Risk communication and disclosure of residual risk during the informed consent process, including information as to how subjects can/should act to further control or mitigate risk
- When reliable information is available, consideration of subject perspective and tolerance for assuming risk relative to anticipated benefit
- Performance of initial limited study in subjects most likely to experience benefits or select a participant subset where the benefit-risk profile is more favorable (e.g., treatment-refractory patients)

B. Assessment of Other Risks Considerations of Investigational Study

Consistent with section 520(g)(4)(B) of the FD&C Act, FDA may consider the risks discussed in Section A above these risks to protect the public health and safety. FDA review of risk management measures will focus on appropriate measures to control these risks.

B.1 Risks related to interpretation of the study data and the benefit of knowledge that could be gained:

- Risk of drawing a false conclusion based on clinical data obtained
- Risk of data which are inconclusive or difficult to interpret[29]

B.2 Risks to others: Certain investigations may involve risks to others that should be considered. For example:

- Risk of radiation exposure of health care practitioner
- If treated subjects become drowsy while operating a vehicle

C. Assessment of Direct Benefits to the Study Subject

In general, the assessment of anticipated benefits to IDE subjects does not include purely hypothetical benefits, and instead focuses on those direct benefits whose existence and characteristics are supported by valid scientific evidence commensurate with the stage of development for the device, including diagnostics. FDA's assessment of anticipated benefits of study participation includes the direct benefits to the subject — benefits that may be realized by the subjects participating in the research, including:

[29]Refer to Section III.D. in this guidance for further discussion on this point.

C.1 Type of benefit(s): Examples include but are not limited to the device's anticipated impact on clinical management, subject health, and subject satisfaction in the target population, such as improving clinical management and quality of life, reducing the probability of death, aiding improvement of subject function, reducing the probability of loss of function, and providing relief from symptoms. For diagnostics, an anticipated benefit may be due to its ability to identify a specific disease (thereby enabling measures that prevent its spread or progression), predict future disease onset, provide earlier diagnosis of diseases, reduce the frequency of diagnostic and ancillary testing, or identify participants more likely to respond to a given therapy.

C.2 Magnitude of the benefit(s): Determined by the anticipated change in subjects' condition or clinical management, or as determined by an improvement or worsening of the endpoint. Variation in the magnitude of the benefit across a population may also be considered. Perceived benefit derived from various sources, such as human factors simulation testing, questionnaire analysis and other published data with similar devices may also provide an insight into the subjects' preference or whether their experience is positive or negative.

C.3 Probability of the participant experiencing one or more benefit(s): Based on the evidence provided from prior investigations, it is sometimes possible to predict which subjects may be more or less likely to experience a benefit. In other cases, however, particularly at earlier stages of device development, it may not be possible to assess the probability of a participant experiencing one or more benefits or identifying subgroups most likely to experience a benefit.

C.4 Duration of effect(s): (i.e., how long the benefit can be expected to last for the participant): Some treatments are curative, whereas, some may need to be repeated frequently over the patient's lifetime. To the extent that it is known, the duration of a treatment's effect may directly influence how its anticipated benefit is defined. Treatments that must be repeated over time may introduce greater cumulative risk, or the benefit experienced may diminish each time the treatment is repeated.

D. Assessment of Benefits to Others

In addition to assessing the anticipated direct benefits to IDE subjects, an IDE benefit-risk assessment also includes a consideration of the anticipated benefits to others (to the extent they are indirect benefits to subjects such as knowledge to be gained from the study or information that may contribute to developing a treatment).

A required element of the informed consent is a description of any benefits to the subject *or to others* [emphasis added] which may reasonably be expected from the research.[30] Benefits to

[30] 21 CFR 50.25(a)(3).

others that may also indirectly benefit the subjects include benefits to caregivers or family members and healthcare professionals.

A benefit to others of an investigational study is the "importance of the knowledge to be gained."[31] This is not a direct benefit to the subject, but rather is considered a societal benefit in terms of increasing the understanding of a disease condition and potential treatment or diagnostic applications. This benefit is unique to research and does not apply to marketing applications. A greater degree of uncertainty about the benefits and risks of study participation typically exists in IDE submissions, and one should consider the possibility that study subjects will receive no direct benefit from study participation. However, subjects may still be willing to participate because of the indirect benefits such as knowledge to be gained from the study or information that may contribute to developing a treatment. Studies which are well-designed may be considered to have greater benefits in this regard, because they generate knowledge that can inform safe device use and may lead to earlier patient access to high quality, safe and effective devices.

In assessing an IDE study for the importance of the knowledge to be gained, a key consideration is the likelihood that the study will yield generalizable knowledge about the disorder or condition being studied. Additional safeguards may be necessary for the inclusion of children in clinical investigations that are likely to yield generalizable knowledge about the subjects' disorder or condition, but that involve greater than minimal risk with no prospect of direct benefit to individual subjects, as described in 21 CFR 50.53.

E. Other Factors to Consider When Assessing Benefit-Risk for IDE Applications

The assessment of benefits and risks for an IDE study takes into account the uncertainty surrounding the knowledge and available evidence, the contextual setting in which the study is being proposed, including characterization of the disease or condition being treated or diagnosed, and availability of alternatives and risks associated with them. When available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context during this assessment. Such information could be derived from a variety of sources including literature and/or patient reported outcome tools.

E.1 Characterization of the disease: The treated or diagnosed condition, its clinical manifestation and severity (e.g., temporary or permanent loss of function), how it affects the subjects who have it, how and whether a diagnosed condition is treated, and the condition's natural history and progression (i.e., does it get progressively better or worse for the subject and at what expected rate) are all important factors that FDA considers when characterizing a disease and assessing benefits and risks. For instance, with conditions that have more severe symptoms in the course of the natural disease relatively fewer and less effective treatment options, and less chance of responding to current treatment options, tolerating greater risk in a study (consistent with patient preferences) may be warranted.

[31] 21 CFR 812.30(b)(4).

E.2 Availability of alternatives: When characterizing the availability of alternatives, important factors that FDA considers are treatment (or diagnostic) options, treatment strategy (if applicable, such as for chronic diseases) and the safety and effectiveness of alternatives including the potential for adverse events. If alternative therapies (or diagnostic options) exist, are effective for the subject population, and are associated with relatively fewer adverse events, then subjects may not tolerate a higher degree of risk of study participation. Assessment should not necessarily be made in comparison to the most technologically advanced alternative but rather to commonly used therapies and treatments for the specific disease or condition.

E.3 Subject tolerance for risk and perspective on benefit: Risk tolerance varies among subjects, and this will affect individual subject decisions to participate in a study. When evaluating benefits and risks, FDA recognizes that tolerance for risk and a subject-centric assessment of risk may reveal reasonable individuals who are willing to tolerate a high level of risk to achieve an anticipated benefit, especially if that benefit results in an improvement in quality of life or achieves societal benefit from knowledge gained. In addition, a thorough informed consent process serves to assure that prospective subjects are informed of, among other information, the risks and benefits of study participation, and agree to the risks of study participation given other factors, including the potential benefits.

E.4 Uncertainty: There is always some uncertainty when weighing benefits and risks prior to clinical study conduct. However, the degree of certainty is a factor FDA considers when assessing benefit-risk for IDE applications.

- **Quality of prior nonclinical and clinical investigations**: Well-conducted non-clinical and clinical prior investigations can help reduce uncertainty, particularly related to identified potential hazards. However, poor study design or conduct, or inadequate analysis of prior study data, can produce data which are inconclusive or difficult to interpret.

- **Predictive capability of evidence from prior investigations:**[32] The ability of the nonclinical testing and prior clinical experience to predict clinical performance in the proposed study is an important consideration, as is the generalizability of early results to the intended study and user population. This should include insights gathered from other studies sponsored and not sponsored by the applicant, including international peer-reviewed investigations, applicable to the current study design. For example, if the device requires in-depth user training or specialization, the clinical study should be designed to address this issue to ensure appropriate risk mitigation. It is important to distinguish between purely hypothetical risks, actual hazards, and the likelihood of subject harm.

[32] 21 CFR 812.27.

- **Different uncertainty considerations at different stages of development**: Different questions of uncertainty may arise at different stages of study. A higher level of uncertainty is expected and may be acceptable in the early stages of device development. Generally, while the types of uncertainty (and questions to be answered) vary across the stage of investigation and development, the overall degree of uncertainty of risks and benefits should decline as more data are collected throughout device development and exploration.

E.5 Least burdensome study design: When considering elements of study design, incorporating additional elements often involves trade-offs in terms of time, cost and practicality of study conduct, which may affect other aspects of clinical trial start-up, such as IRB approval and feasibility of subject enrollment. While FDA does not generally consider cost to the sponsor when deciding to approve an IDE application, the potential impact of study design elements on trial start-up, IRB approvability, and feasibility of subject enrollment should be considered. For example, although it may be desirable to implement an additional diagnostic procedure to screen out potential subjects who may be less likely to benefit from the study, if the diagnostic procedure itself is so time-consuming, costly or burdensome on subjects or investigators that enrollment in the study becomes impractical, FDA will consider these challenges in its decision making.

F. Overall IDE Benefit Risk Determination

Consistent with applicable statute and regulations, FDA may disapprove an IDE application if, among other reasons, there is reason to believe that the risks to the subjects outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. In many cases, the Agency believes that effective risk management, including the application of risk control measures, including risk mitigation measures, can reduce the residual risk and result in a favorable IDE benefit-risk determination.

FDA believes that the use of a common framework and structured approach to assessing IDE benefits and risks will facilitate not only the submission of relevant evidence and knowledge but also a clear rationale for why the submitted information is sufficient to justify the initiation of the proposed study. Application of the factors listed in this guidance document can ultimately improve the predictability, consistency, and transparency of FDA's IDE decision-making, resulting in the strengthening and streamlining of the clinical trial enterprise in the U.S. so that medical device clinical trials are conducted in an efficient and cost-effective manner, while maintaining appropriate patient and research participant protections.

APPENDIX A – RECOMMENDED GENERAL FRAMEWORK FOR BENEFIT-RISK ASSESSMENT

FDA recommends IDE sponsors provide as part of the IDE application a section that summarizes the key considerations in the IDE benefit-risk assessment. The benefit-risk summary should provide a concise synopsis and may reference relevant sections in the IDE application where supporting information and evidence can be found. The intent of this summary is not to provide an all-encompassing summary of the benefit-risk assessment, but rather to focus on those items which are likely to significantly affect FDA's decision or recommendation. Of note, the Device Evaluation Strategy worksheet recommended in FDA's Early Feasibility Guidance provides similar information and can also be used to address the recommendations provided here.

FDA recommends that the benefit-risk summary address the following key elements:

1. CONTEXT OF THE PROPOSED INVESTIGATION

   Provide a summary of the disease or condition to be treated or diagnosed, a description of the device in the context of currently available treatment or diagnostic options, and a brief description of the investigation (its objective and design).

2. ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

   A summary of the key risk elements identified in Section 5 of the guidance including risk characterization, risk control measures, and residual risk.

3. ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

   A summary of the key benefits of the proposed investigation as identified in Section 5 of the guidance including direct benefits to study subjects of the proposed investigation and benefits to others (to the extent they are indirect benefits to subjects such as knowledge to be gained from the study or information that may contribute to developing a treatment).

4. CONSIDERATION OF PATIENT PREFERENCE INFORMATION

   A summary of available patient preference information, if any is available. If none, state that none was available.

5. ASSESSMENT OF UNCERTAINTY

   Summarize key sources of uncertainty in the available evidence and proposed investigation as identified in Section 5 of the guidance, and provide a rationale for why the level of uncertainty is acceptable for the proposed investigation.

6. CONCLUSIONS

Summarize how the consideration of the factors discussed in this summary justify the decision to proceed with human clinical investigation.

APPENDIX B – HYPOTHETICAL EXAMPLES OF SUMMARY BENEFIT-RISK ASSESSMENTS

FDA recommends IDE sponsors provide as part of the IDE application a section that summarizes the key considerations in the IDE benefit-risk assessment. The benefit-risk summary should provide a concise synopsis and may reference relevant sections in the IDE application where supporting information and evidence can be found (see Appendix A for details).

The examples below are simplified and offered for illustrative purposes only. The decisions described in these examples are intended to demonstrate how to present the factors described in this guidance when making benefit-risk assessments and how FDA may analyze these factors.

Example 1 – Pivotal study proposal for a device to treat a life-threatening condition with poor alternative treatments

CONTEXT OF THE PROPOSED INVESTIGATION

A company has developed a permanently implantable device to treat a disease that affects adults and is associated with a high risk of mortality. Generally there is progression to advanced disease within 12 months, and 30% of patients die within 24 months. While pharmacological treatments are available, they primarily offer only transient symptomatic relief and are associated with significant complications. The sponsor proposes a prospective randomized study to assess the use of a device to treat the condition compared with a standard pharmacological treatment.

ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

The device has risks associated with both the surgical procedure required for implantation and long-term use. These risks have been evaluated in animal studies and a small short-term clinical feasibility study. The risks are potentially severe and the likelihood of occurrence is only partially understood.

Based on the information gained from the previous non-clinical and clinical studies, the sponsor has proposed minor changes to the implant procedure that may reduce the risk. Additional risk mitigation procedures include: careful subject selection, the use of specialized/experienced study investigators, subject monitoring procedures, and use of an independent Data Safety and Monitoring Board.

ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

Initial data from the previous nonclinical and clinical studies demonstrated the potential for clinically relevant reductions in morbidity and mortality from the condition, although the amount of data available is limited and a control group was not used. In addition, the long-term effectiveness of the device has not yet been explored.

CONSIDERATION OF PATIENT PREFERENCE INFORMATION

Given the lack of effective current treatments and the significant morbidity and mortality associated with the disease, patients are expected to have a high risk tolerance for considering potential new treatments. However, definitive patient preference data are lacking.

ASSESSMENT OF UNCERTAINTY

The greatest degree of uncertainty is regarding the anticipated benefits of the device. While the nonclinical and clinical feasibility study data are encouraging, it is unclear whether clinically relevant benefits will be demonstrated in a controlled study with long-term follow-up. There is also uncertainty regarding the risk profile, and whether the changes in the implant procedure and implementation of the other mitigation strategies will be effective.

CONCLUSIONS

This study is characterized by a significant degree of risk and a high level of uncertainty regarding the anticipated benefits. However, given the lack of effective alternative treatments, the risks associated with those treatments, the consequences of ineffective treatment, and that the benefits and risks of the device have been reasonably characterized in non-clinical and feasibility clinical studies, FDA is likely to approve the pivotal IDE study.

If current treatments were more effective at controlling or curing the disease process, or if the disease process were more benign, the benefit-risk assessment might be unfavorable. If feasibility clinical study data were not available, there would be a significantly higher degree of uncertainty regarding anticipated benefits.

Example 2 – Feasibility study proposal for a device to treat an activity limiting condition with reasonable alternative treatments

CONTEXT OF THE PROPOSED INVESTIGATION

A company has developed an absorbable device to treat a condition associated with modest pain and functional limitations, but not increased mortality. Several reasonably effective permanently implantable device alternatives exist, although they are associated with chronic adverse events that in some patients require surgical revision, device removal, or replacement.

The sponsor proposes a prospective non-randomized feasibility study to provide a preliminary assessment of the safety and potential for benefit of an absorbable device.

ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

Compared to the currently available alternatives there are two primary unaddressed risks associated with this device.

The first risk is that the device is comprised of new materials that have not been fully characterized and may have significant toxicities. While the materials are similar to those used in other devices, the differences in formulation and processing for this device have the potential to lead to an unacceptable safety profile. The biocompatibility of the device can be addressed with additional nonclinical testing that was not provided by the sponsor.

The effectiveness of the device is dependent on the concept that preservation of structural integrity is only needed during the acute healing phase of the condition and that the device degradation profile is consistent with the healing timeline. However, there is a risk that premature device degradation will result in the loss of structural integrity prior to complete healing and subsequent reoccurrence of the condition. Assessment of the chronic performance of the device will likely require clinical evaluation.

The sponsor has not specified any clinical mitigation strategies for the study. To address the biocompatibility concern, the sponsor states that the similarity in materials to other absorbable devices is sufficient mitigation.

ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

There is theoretical support for the concept that an absorbable device could reduce the chronic adverse events associated with the currently available devices while maintaining effectiveness.

CONSIDERATION OF PATIENT PREFERENCE INFORMATION

The sponsor has provided a small survey regarding patient preference. The survey indicates that some patients are satisfied with the currently available devices. However, there is a modest level of interest in novel technologies that could reduce the potential need for future surgery for device removal or replacement.

ASSESSMENT OF UNCERTAINTY

There is considerable uncertainty regarding whether this absorbable device provides sufficient structural integrity over an appropriate timeframe to support chronic healing of the condition.

There is also considerable uncertainty regarding the potential toxicity of degradants.

CONCLUSIONS

This device is intended to treat a condition associated with modest pain and discomfort for which there are reasonable alternatives currently available. The new materials raise biocompatibility concerns which may result in unacceptable risks for subjects which can and should be addressed with nonclinical testing that the sponsor has not provided. There does not appear to be a strong basis for allowing the clinical study to proceed until the biocompatibility data are provided, as FDA does not concur that the claim of similarity in materials is adequate to address this concern. Therefore, FDA would likely not approve this study until these data are provided and found to be supportive of an acceptable biocompatibility profile.

Example 3 – Early feasibility study proposal for a device to treat a life-threatening condition without an alternative treatment option

CONTEXT OF THE PROPOSED INVESTIGATION

The condition affects adults and is associated with a high risk of morbidity and mortality.

No effective treatment alternative exists for patients with the advanced form of the disease. Treatments that are successful for patients with less severe forms of the disease have failed in patients with advanced disease.

The sponsor proposes an early feasibility study to provide proof of principle and initial clinical safety data for the use of a device to treat the condition.

ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

This intervention has risks associated with both the procedure as well as the potential for long-term adverse effects. The procedural risks have been evaluated in an animal study. In addition, information can be leveraged from the clinical experience with a similar device for a different intended use. With available leveraged information and an understanding of the device design concept, the types of risks are known, but the frequency and severity are unknown. In cases where patient characteristics (e.g., age, sex, or other key variables) are not comparable for the new intended use, the extent to which this previous clinical experience can be leveraged may be more limited.

The sponsor has proposed several strategies to minimize the frequency and severity of risks to study subjects including the following:

- use of study sites that have sufficient expertise and resources to manage adverse events and provide appropriate additional therapies if needed;
- identification of qualified investigators with adequate training to conduct the early feasibility study;
- implementation of an informed consent process which adequately conveys to potential subjects the high degree and seriousness of both known and unknown risks and the low likelihood of direct benefits; 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 prior to the treatment of additional participants;
- limiting the sample size to a reasonable number for an early feasibility study (e.g., 5-10 initial subjects);
- frequent follow-up assessments to monitor subject safety and device effectiveness;
- timely reporting of serious adverse events (i.e., 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;
- refine study eligibility criteria to subjects with favorable anatomical characteristics to avoid subjects with anatomic features thought likely to increase difficulty of device use; and
- a pre-specified plan for periodic participant outcome assessments and reporting prior to enrollment of additional participants (i.e., after each use of the device).

ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

Initial data from the previous nonclinical studies, with the available leveraged information, suggest the potential for clinically relevant reductions in morbidity and mortality from the condition, despite the potential for procedure-related and long-term adverse effects.

CONSIDERATION OF PATIENT PREFERENCE INFORMATION

Given the lack of an effective alternative treatment and the morbidity and mortality associated with the condition, patients are expected to have a high risk tolerance for considering potential new treatments. However, no definitive data have been provided by the sponsor to support this expectation.

ASSESSMENT OF UNCERTAINTY

Due to the novelty of the device and procedure and the lack of a nonclinical model to predict the clinical safety and effectiveness of the device, there is a high degree of uncertainty regarding the device, including the initial safety, the long-term adverse effects of the treatment, and the anticipated benefits.

CONCLUSIONS

Potential study subjects have failed conventional treatments that can be beneficial to patients with less severe cases. The proposed study is characterized by a significant degree of uncertainty, given the early phase of device development and the novelty of the proposed device and procedure. Information available on a similar device from a different intended use and from an animal study provide some assurance that catastrophic failures would not be anticipated during the early feasibility study. Conducting additional nonclinical testing is unlikely to provide information to decrease the level of uncertainty.

Considering that: (1) the proposed device treats a severe disease for which there is no alternative treatment; (2) information is available from the clinical experience with a similar device for a different intended use to suggest that catastrophic failures will not occur; (3) there is reason to believe that patients may benefit from treatment with the device; and (4) additional nonclinical testing will not provide the information needed to advance the device design, FDA is likely to approve the early feasibility study IDE.

APPENDIX C – REFERENCE GUIDE: DESCRIPTION OF INVESTIGATIONAL DEVICE

Fundamental to an assessment of benefits and risks associated with investigational device use is an understanding of the investigational device itself. 21 CFR 812.25(d) requires that the investigational plan include a:

> *description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation).*

Deficiencies related to an incomplete or inadequate investigational device description are the single most common type of non-protocol related deficiency in IDE applications that fail to attain full approval. This Appendix lists the device attributes that CDRH recommends be included in the IDE device description.

The investigational device description should include an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties. A complete description of the device may be facilitated by the submission of engineering schematics or other figures. If the device consists of multiple components, a diagram identifying how the different components of the device system work together may be beneficial. The device description should also include a discussion of the physical specifications, dimensions and mechanical tolerances of the investigational device. *Of note, the Device Evaluation Strategy worksheet recommended in FDA's Early Feasibility Guidance provides similar information and can also be used to address the recommendations provided here.*

In general, it is recommended that the investigational device description include the following details or provide a rationale for why information concerning the specified element is not needed or does not apply:

- Device Identification:
  - List all device components (e.g., catheter, cable wire, leads, sizing tools, delivery system, etc.)
  - List all models to be used in the investigation and briefly explain the differences among models

- Brief Written Description of the Device:
  - Explanation of how the device works/principle of operation
  - Mechanism of action, if known
  - Key performance specifications and manufacturing tolerances of the device, if known
  - Key device features/characteristics (address all that apply)
    - Software

- Electrical properties
- Mechanical properties
- Biologics
- Drugs
- Coating(s) and surface modifications (e.g., an abraded material surface to encourage implant retention)
- Single-use or multi-use
- Single patient or multi-patient
- Defined User Type – Patient, Caregiver, Healthcare Professional or combination.
- Sterile or sterilization method [specify]
- Energy source (if applicable)
    - This not only includes energy delivery to the device, including the use of batteries, but also energy delivery that is part of the functional aspect of the device (e.g., laser, radiofrequency, ultrasound, etc.).
- Materials of use
    - Chemical formulation used in the materials of construction, especially for those materials that come into contact with the patient, should be provided if available.
    - Duration and type of contact
- Procedure for use
    - For in vitro diagnostic devices, a step-by-step outline of recommended pre-analytical and analytical procedures from receipt of specimens to obtaining results.
- Other critical device features
    - These may include, but are not limited to, software/ hardware features, density, porosity, degradation characteristics, nature of reagents (recombinant, plasma derived, etc.), principle of the assay method, manufacturing-related aspects, etc., that are not explicitly included as part of the materials, design or energy source characteristics.
    - If modifications are made to the device during the course of a study or between different stages of investigation (e.g., early feasibility to pivotal), a detailed comparison of the original and modified device should be provided.

APPENDIX D – GLOSSARY OF RISK MANAGEMENT TERMS

Terminology/Definitions – Risk Assessment

The following risk management terms are consistent with ISO 14971. For the purposes of this guidance, terms are defined as follows:

- **Harm** – physical injury or damage to the health of people, or damage to property or the environment.
- **Hazard** – potential source of harm
- **Risk** – a combination of the probability of occurrence of harm and the severity of that harm. Note that in earlier stages of development a relative sense of likelihood may be used instead of probability of occurrence, which is difficult or impossible to estimate when little evidence is available.
- **Risk estimation** – process used to assign values to the probability of occurrence of harm and the severity of harm
- **Risk analysis** – systematic use of available information to identify hazards and to estimate the risk
- **Risk control** – process in which decisions are made and measures implemented (e.g..; risk mitigations) by which risks are reduced to, or maintained within, specified levels. [Please note, the term risk mitigation is not used in ISO 14971.]
- **Residual risk** – risk remaining after risk control measures have been taken
- **Risk Assessment** – overall process comprising a risk analysis and a risk evaluation
- **Risk Evaluation –** process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk
- **Risk Management –** systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk