

ACRP Regulatory Affairs Committee Review of FDA Draft Guidance Document

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

What is the guidance?

In this guidance, the FDA clarifies what factors the Agency uses in assessing risks and benefits for approving IDE studies and explains in more detail the background information and various factors taken into consideration when making an approval decision. The guidance focuses primarily on significant risk devices. Included as appendices are outlines of frameworks for Sponsors to prepare a benefit-risk assessment as well as hypothetical examples.

Who does it impact & how?

This guidance applies to Sponsors and Sponsor-Investigators of diagnostic and therapeutic devices to strengthen their IDE submissions and better understand the FDA's considerations in reviewing submissions when evaluating benefits vs risks.

What did ACRP RAC have to say about it?

The RAC supports this draft guidance document, it is perceived as a valuable guidance document to be used in conjunction with the March 2012 Guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Pre-Market Approval and De Novo Classifications". Comments provided to the Agency for consideration include but are not limited to the below points:

- Suggested title change to clarify that this guidance document is intended for Significant Risk devices only.
- Request for guidance on how industry should address improbable but serious or severe risks.
- Request for guidance on how to effectively implement the Agency's statement that risks and benefits should be made based on commonly used therapies and treatments and not necessarily on the most technologically advanced alternative.
- Request that the Agency clarify whether they feel that the ancillary benefits a subject may gain from the medical tests and procedures associated with the clinical study may be defined as a potential benefit of research participation.

When were the RAC's comments sent to the agency?

September 9, 2015

Where can I access this document?

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm451440.pdf>



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September 9, 2015

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In reference to docket number: **FDA-2015-D-1777**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions as this issue has a significant impact on our membership. We welcome this Guidance Document and find that it is well thought-out and useful. While it draws a lot from the ISO Standards (purchased standards), most of the important detail is fully described in the Guidance. We find that the Appendix B scenarios are an excellent teaching/interpretation tool. We are pleased that the Agency cited the March 28 2012 Guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Pre-market Approval and De Novo Classifications". That is another valuable guidance document that has addressed many of the same issues, and we don't see conflicts between them. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

A handwritten signature in black ink, appearing to read "Thinkley", written in a cursive style.

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

FDA-2015-D-1777 :Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions			
Page Number	Text Line	Reference (if applicable)	Comments
1	Title	SR vs NSR	Since this guidance addresses Significant Risk devices only, we recommend this be added to the title so as not to confuse IRBs and Sponsor-Investigators dealing with NSR devices.
12	339-341	NA	While focusing on the most probable risks is an important consideration, it is not the only consideration. How industry is expected to address improbable but serious or severe risks should be included in this section.
15	447	NA	Space needed after the word health and before parentheses....."health (e.g., obesity devices)"...
16	500-501	NA	In regard to the statement "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", how will the submitter and the Agency come to agreement on what those therapies are? Is there guidance in this area? If so, please reference the relevant guidance document.
23	772-773		
19	629	Investigational Review Board	We believe the correct terminology here is Institutional Review Board, not Investigational.
20	661-662	NA	From what sources does the Agency accept data to support "Consideration of subject perspective on assuming risk relative to anticipated benefit?"
21	681-693	Benefits	The types of benefit listed are attributable directly to the device or diagnostic being studied. There seems to be a wide spread belief in the industry that the ancillary benefits a subject may gain from the medical tests and procedures associated with the clinical study may be defined as a potential benefit. It would be helpful for FDA to clearly state this here.
23	752-754	NA	From what sources does the Agency accept data to support "When available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context during this assessment."
24	818-831	Least Burdensome	"While FDA does not consider cost 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." This statement is ambiguous and we request additional clarification as to what the Agency will consider in this area.

1 **Factors to Consider When Making**
2 **Benefit-Risk Determinations for**
3 **Medical Device Investigational Device**
4 **Exemptions (IDEs)**

7 **Draft Guidance for IDE Sponsors,**
8 **Sponsor-Investigators and**
9 **Food and Drug Administration Staff**

11 ***DRAFT GUIDANCE***

12 **This guidance document is being distributed for comment purposes only.**

13 **Document issued on June 18, 2015.**

15
16 You should submit comments and suggestions regarding this draft document within 90 days of
17 publication in the *Federal Register* of the notice announcing the availability of the draft
18 guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments
19 to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630
20 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number
21 listed in the notice of availability that publishes in the *Federal Register*.

22
23 For questions about this document regarding CDRH-regulated devices, contact the Office of
24 Device Evaluation, Office of the Director, Investigational Device Exemptions (IDE) Staff at 301-
25 796-5640. For questions about this document for CBER-regulated devices, contact the Office of
26 Communication, Outreach and Development at 1-800-335-4709 or 240-402-7800.



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

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

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Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1783 to identify the guidance you are requesting.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER) by written request from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., WO71, Room 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-7800, by email, ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

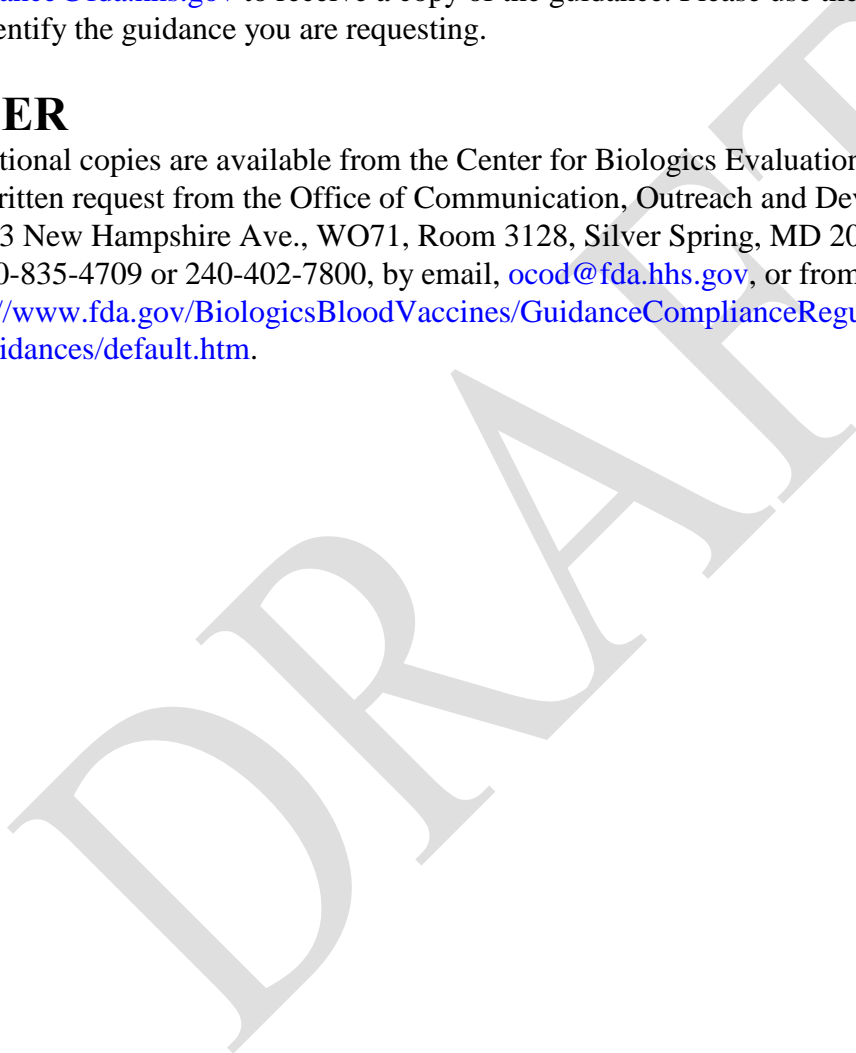


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73 **Factors to Consider When Making**
74 **Benefit-Risk Determinations for**
75 **Medical Device Investigational Device**
76 **Exemptions (IDEs)**
77

78 **Draft Guidance for IDE Sponsors,**
79 **Sponsor-Investigators and**
80 **Food and Drug Administration Staff**
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82

83 *This draft guidance, when finalized, will represent the current thinking of the Food and Drug*
84 *Administration (FDA or Agency) on this topic. It does not establish any rights for any person*
85 *and is not binding on FDA or the public. You can use an alternative approach if it satisfies*
86 *the requirements of the applicable statutes and regulations. To discuss an alternative*
87 *approach, contact the FDA staff responsible for this guidance as listed on the title page.*
88

89 **I. INTRODUCTION**

90 FDA is committed to improving U.S. patient access to new devices by strengthening and
91 streamlining the clinical trial enterprise so that medical device clinical trials are conducted in the
92 U.S. in an efficient and cost-effective manner, while maintaining appropriate patient and research
93 participant protections.
94

95 The purpose of this guidance is to provide greater clarity for FDA staff and investigational device
96 exemption (IDE) sponsors and sponsor-investigators¹ regarding the principal factors that FDA

¹ As defined in 21 CFR 812.3, a sponsor is a person or other entity that initiates but does not actually conduct the investigation. A person other than an individual (e.g., a corporation or an agency) which uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor, not a sponsor-investigator, and the employees are considered to be investigators. A sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual (e.g., a corporation or agency). The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

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97 considers when assessing the benefits and risks of IDE applications for human clinical studies.
98 Consistent with applicable statute and regulations, FDA will generally disapprove an IDE
99 application if, among other reasons, “[t]here is reason to believe that the risks to the subjects are
100 not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to
101 be gained.”² In many cases, the Agency believes that effective risk management, including the
102 application of risk controls and risk mitigation measures, can result in a favorable IDE benefit-
103 risk determination.

104
105 FDA recognizes that in assessing risks and anticipated benefits, the medical device total product
106 lifecycle should be considered, and that earlier stages of device development and investigational
107 clinical study are typically associated with greater *uncertainty* (i.e., a lower level of evidence). A
108 primary goal of this guidance is to clarify the factors that FDA considers when assessing risks
109 and anticipated benefits for approving IDE studies, and how uncertainty may be offset by a
110 variety of *risk mitigation* measures which can assure appropriate patient and research participant
111 protections in investigational research settings. For proposed IDE studies, at earlier stages of
112 device development, FDA considers appropriate mitigation measures for anticipated possible
113 risks and unanticipated risks, whereas in later stages risk mitigation focuses increasingly on the
114 most probable risks.

115
116 Another important goal of this guidance is to characterize benefits in the context of
117 investigational research, which includes direct benefits to the subject and benefits to others (to
118 the extent they are indirect benefits to subjects or reflect the importance of knowledge to be
119 gained from the study).

120
121 As with the benefit-risk framework for evaluating marketing applications,³ FDA assessment of
122 benefits and risks for an IDE application takes into account the contextual setting in which the
123 study is being proposed, including but not limited to characterization of the disease or condition
124 being treated or diagnosed, the availability of and risks associated with alternative treatments or
125 diagnostics. When available, information characterizing subject tolerance for risk and
126 perspective on benefit may provide useful context during this assessment.

127
128 FDA believes use of this benefit-risk framework will facilitate the incorporation of evidence and
129 knowledge from different domains—clinical, nonclinical, and patient—to support a
130 comprehensive, balanced decision-making approach. FDA envisions this will facilitate a
131 common understanding between FDA and sponsors/sponsor-investigators by highlighting which
132 factors are critical in the benefit-risk assessment for a specific application, and clearly explaining
133 how these factors influence FDA’s decisions. FDA also believes implementation of this
134 guidance document will improve the predictability, consistency, and transparency of the review
135 process for IDE applications.

136

² 21 CFR 812.30(b)(4).

³ See e.g., FDA Guidance, [Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications](#) (March 28, 2012).

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm>.

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137 FDA’s guidance documents, including this one, do not establish legally enforceable
138 responsibilities. Instead, guidance documents describe the Agency’s current thinking on a topic
139 and should be viewed only as recommendations, unless specific regulatory or statutory
140 requirements are cited. The use of the word *should* in Agency guidance documents means that
141 something is suggested or recommended, but not required.
142

143 **II. SCOPE**

144
145 This guidance document explains the principal factors that FDA considers when assessing
146 benefits and risks of applications for IDEs for human clinical investigations of certain medical
147 devices to determine safety and effectiveness. The approach discussed in this guidance is
148 applicable to studies subject to the IDE requirements in 21 CFR part 812, including postmarket
149 studies.⁴ This guidance applies to both diagnostic and therapeutic devices.
150

151 **III. INFORMED CONSENT AND IDE DECISIONS**

152
153 The purpose of the IDE regulations, as set forth in 21 CFR part 812, is to encourage, to the extent
154 consistent with the protection of public health and safety and with ethical standards, the
155 discovery and development of useful devices intended for human use, and to maintain optimum
156 freedom for scientific investigators in their pursuit of this purpose.⁵ 21 CFR part 812 applies to
157 all clinical investigations of devices to determine safety and effectiveness with some exceptions.⁶

4 In general, IDE applications are required for clinical investigations of significant risk devices to determine safety and effectiveness. 21 CFR 812.2.

⁵ 21 CFR 812.1.

⁶ See 21 CFR 812.2(c), 21 CFR part 812, with the exception of 21 CFR 812.119, does not apply to investigations of the following categories of devices:

- (1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- (2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- (3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:
 - (i) Is noninvasive,
 - (ii) Does not require an invasive sampling procedure that presents significant risk,
 - (iii) Does not by design or intention introduce energy into a subject, and
 - (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- (4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- (5) A device intended solely for veterinary use.
- (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
- (7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

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158 FDA approval of an IDE application prior to study initiation is typically⁷ required for a clinical
159 investigation conducted in the U.S. of a significant risk device⁸ that is not approved or cleared
160 for the indication being studied.⁹ An approved IDE application exempts the study sponsor from
161 certain provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (such as certain
162 requirements for a marketing application, good manufacturing practice). However, IDE studies
163 must comply with the applicable requirements set forth in 21 CFR part 812, including
164 requirements for informed consent under 21 CFR part 50, labeling of devices for investigational
165 use only, study monitoring, records and reporting, and approval by an Institutional Review Board
166 (IRB) in accordance with 21 CFR part 56.¹⁰
167

168 **A. *Informed Consent***

169
170 A key tenet of FDA's IDE benefit-risk framework is appropriate protection of human subjects
171 and a key principle of human subject protection in clinical investigations is the informed consent
172 process¹¹. This process goes beyond obtaining a signature on an informed consent form. The
173 informed consent process provides the prospective subject or his or her legally authorized
174 representative with adequate information about the study, including pertinent information about
175 the investigational device, its risk and benefits, alternatives, and what is expected of the subject
176 in order to participate in the study (e.g., study visits, procedures, maintaining subject diaries).¹²
177 The subject or his or her legally authorized representative must be given sufficient opportunity to
178 consider whether or not to participate in the clinical study under circumstances that minimize the
179 possibility of coercion or undue influence.¹³
180

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

⁷ See 21 CFR 812.2(b) for conditions under which an IDE application is required prior to study initiation.

⁸ 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.

⁹ See section 520(g) of the Federal Food, Drug and Cosmetic Act (FD&C Act) and 21 CFR part 812.

¹⁰ Section 520(g)(3) of the FD&C Act.

¹¹ See generally, 21 CFR part 50.

¹² See 21 CFR 50.25.

¹³ See 21 CFR 50.20.

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185 reasonably expected benefits and the alternatives to the study.

186

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

193

194 *“Except as provided in 50.23 and 50.24, no investigator may involve a human being as a*
195 *subject in research unless the investigator has obtained the legally effective informed*
196 *consent of the subject or the subject’s legally authorized representative.”*

197

198

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

201

202 FDA recognizes the public health benefit of permitting well-designed clinical investigations of
203 medical devices to proceed in a timely and efficient manner while ensuring proper subject
204 protections including an appropriate informed consent process. When determining whether to
205 approve an IDE application, FDA considers a variety of factors. FDA seeks to offer flexibility to
206 allow clinical investigations to commence without unnecessary delay, while ensuring that human
207 subjects are adequately protected. (See Section III.C. for a more detailed discussion of human
208 subject protection).

209

210 ***B. Regulatory Standard for IDE Decisions***

211

212 Under section 520(g)(4)(B) of the FD&C Act, an IDE application may only be disapproved if
213 FDA finds that the investigation does not conform to the procedures and conditions prescribed
214 under regulations. The purpose of the IDE process is “to encourage, to the extent consistent with
215 the protection of the public health and safety and with ethical standards, the discovery and
216 development of useful devices intended for human use and to that end to maintain optimum
217 freedom for scientific investigators in their pursuit of that purpose.”¹⁴

218

219

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

¹⁴ Section 520(g)(1) of the FD&C Act.

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- (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.*¹⁵

In accordance with 21 CFR 812.30(b), FDA may disapprove 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.*
- (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;¹⁶ and

¹⁵ When the objective of a proposed study is to support a marketing application, the sponsor and other stakeholders may benefit from awareness of protocol modifications that FDA believes are needed to achieve this. FDA will convey such considerations to the sponsor to provide greater clarity and predictability. In addition, FDA will convey certain considerations that FDA believes will be important for future submissions related to the proposed investigation. For more information, see Section IV.A of this document and the [FDA Guidance, FDA Decisions for Investigational Device Exemption \(IDE\) Clinical Investigations](#) (Hereinafter, FDA Decisions for IDE Guidance) (August 19, 2014).

¹⁶ 21 CFR 812.30(b)(4).

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- 263 • inadequacy or uncertainty regarding the clinical or nonclinical data from prior
264 investigations, the proposed study, the manufacturing, transport and storage of a device,
265 or monitoring oversight of the proposed study.¹⁷
266

267 **C. *Types of IDE Decisions***

268
269 FDA regulations¹⁸ provide for three major categories of decision on an IDE application –
270 approval,¹⁹ approval with conditions,²⁰ and disapproval.²¹ Where appropriate, FDA may allow
271 additional flexibility in how outstanding issues can be addressed (i.e., future concerns, study
272 design considerations, contingent approval,²² staged approval), to allow clinical investigations to
273 commence without unnecessary delay, while ensuring that human subjects are adequately
274 protected.²³
275

276 In some cases, FDA may grant *staged approval*,²⁴ a mechanism that limits the number of human
277 subjects that may be enrolled in the clinical study, of an IDE application. This decision may be
278 used to permit the clinical investigation to begin in a timely manner while maintaining
279 appropriate subject protections. Staged approval may be used when there is significant
280 uncertainty (outstanding questions) regarding benefit-risk profile for the proposed IDE study,
281 which FDA and the sponsor believe can be addressed with data gathered in parallel with
282 enrollment of some limited portion of study subjects. Without this mitigation measure, the
283 benefit-risk profile of the proposed investigation may not support study initiation.
284

285 FDA may grant *approval with conditions* when there are outstanding issues that do not raise
286 concerns that preclude initiation of the proposed clinical investigation, provided that the sponsor
287 addresses the recommended modifications to the study. Resolution of these issues is not required

¹⁷ 21 CFR 812.30(b)(5).

¹⁸ 21 CFR 812.30(a). ¹⁹ 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.

¹⁹ 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.

²⁰ If FDA approves an IDE application with conditions, the sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA’s decision letter, including the maximum numbers of U.S. subjects and investigational sites, and must submit information addressing the issues identified as conditions of approval in FDA’s letter within 45 days. See FDA Decisions for IDE Guidance, page 7.

²¹ 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.

²² See FDA Guidance, [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies](#) (Hereinafter, FDA Early Feasibility Guidance) (October 1, 2013), for discussion of contingent approval.

²³ The FDA Guidance, FDA Decisions for IDE Guidance provides more information. ²⁴ See FDA Decisions for IDE Guidance for more information on staged approvals.

²⁴ See FDA Decisions for IDE Guidance for more information on staged approvals.

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288 prior to initiation of study subject enrollment, with exception of issues related to the informed
289 consent document which must be addressed before enrollment begins, in accordance with 21
290 CFR part 50 - Protection of Human Subjects.

291
292 Initial IDE application approval decisions reflect the benefit-risk profile of the proposed
293 investigation at the time of FDA’s assessment. Changes in approval status (e.g., from
294 disapproval to approval) may be appropriate as new information becomes available which:

- 295
- 296 • changes the understanding of risks and benefits or their associated level of uncertainty;
 - 297 • changes confidence in risk control or mitigation measures; or
 - 298 • changes the disease or clinical diagnostic/treatment landscape in a manner which alters
299 the benefit-risk profile of the IDE device relative to alternatives.

300
301 If necessary, FDA may take appropriate regulatory actions to protect study subjects, including
302 placing a clinical hold²⁵ on the study. If the study is placed on hold, no additional subjects may
303 be enrolled.

304
305

306 ***D. Study Design Considerations***

307
308 Study design has a direct bearing on the knowledge than can be gained from that study. A poorly
309 designed study may produce evidence which leads to false conclusions and have significant
310 negative public health implications. A poorly designed study could produce data which are
311 inconclusive or difficult to interpret and thereby expose subjects to unnecessary or preventable
312 risk.

313
314 In contrast, well-designed studies are more likely to produce important knowledge about a device
315 or disease. FDA believes it is most efficient, and consistent with least-burdensome principles, to
316 encourage the conduct of studies which are designed to meet stated objectives. FDA may inform
317 the sponsor of recommended modifications to the study design – *Study Design Considerations*
318 (*SDCs*)²⁶ – that FDA believes will improve the quality of the information and knowledge
319 generated by the study.²⁷

320
321

²⁵ Under section 520(g)(8) of the FD&C Act, FDA can place a study on “clinical hold” when, among other reasons, the device involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation.

²⁶ The FDA Guidance, FDA Decisions for IDE Guidance provides more information on the topic of SDCs.

²⁷ Consistent with section 520(g) of the FD&C Act, FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing application.

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

324 **A. *Stages of Device Development***

325
326 When making IDE benefit-risk assessments, FDA considers: 1) the stage of development of the
327 device, 2) the maturity of the proposed technology, and 3) the availability of non-clinical testing
328 to complement or replace the need for clinical testing.

329
330 FDA guidance defines the following device study types: first in human (FIH),²⁸ early
331 feasibility,²⁹ traditional feasibility,³⁰ and pivotal.³¹ In some cases, IDE studies may also be
332 designed for postmarket investigation of marketed products.

333
334 The approach to benefit-risk assessment in IDE applications should be tailored to the stage of
335 device development, because device investigations during different stages of development are
336 generally associated with different types of risk, and different levels of uncertainty. Specifically,
337 a greater degree of uncertainty is expected for novel technologies, and at earlier stages of device
338 development, such as first in human or early feasibility trials, while relatively more certainty is
339 expected in traditional feasibility and pivotal trials. At earlier stages, the focus is on appropriate
340 risk mitigation measures for anticipated possible risks and unanticipated risks, whereas in later
341 stages focus shifts increasingly to mitigating the most probable risks. Additionally, early
342 development clinical studies are typically designed to assess initial safety and proof of concept
343 about the proposed device use. Later stage studies, particularly those intended to support future
344 regulatory applications, are typically designed to assess safety and effectiveness outcomes in an
345 intended patient population, with sufficient information to quantify uncertainty in each. IDE
346 benefit-risk assessments should focus on whether a proposed study is well-designed to meet its
347 stated objectives as appropriate to the stage of development for the investigated device.

348
349 For IDE benefit-risk determinations throughout all stages of device development, it is also
350 important to recognize that non-clinical data plays a critical role. Medical devices often have
351 attributes that cannot be tested by clinical methods alone and that play a major role in the
352 performance, safety or effectiveness of the device. In some cases, non-clinical testing (e.g., in
353 vitro tests, animal studies, and computer modeling and simulation) can obviate or reduce the
354 need for additional clinical testing to evaluate certain aspects of device design or performance.

²⁸ 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. See FDA Early Feasibility Guidance, page 6.

²⁹ 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). See FDA Early Feasibility Guidance, page 6.

³⁰ 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. See FDA Early Feasibility Guidance, page 6.

³¹ 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. See FDA Early Feasibility Guidance, page 6.

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355 Both clinical and non-clinical testing methods may be used to assess the likelihood/probability or
356 severity of a given risk, and/or the success of risk mitigation measures.

357

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

360

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

362

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

369

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

376

377 Given the more limited level of evidence typically associated with IDE applications compared to
378 marketing applications – especially for earlier stages of investigation – decisions about IDE
379 applications are made in settings involving relatively greater uncertainty and a lower level of
380 evidence. The inherent uncertainty present in clinical investigations can often be offset by
381 appropriately tailored risk control / risk mitigation measures which can assure appropriate patient
382 and research participant protections in investigational research settings (some forms of risk
383 controls that may be applied to IDE studies are listed in Section V.A.4.). In considering benefits
384 of investigational research, FDA considers direct benefits to the subject and benefits to others (to
385 the extent they are indirect benefits to subjects or reflect the importance of knowledge to be
386 gained).

387

388 As with the benefit-risk framework for marketing applications,³² FDA assessment of benefits and
389 risks for an IDE application takes into account the contextual setting, including characterization
390 of the disease or condition being treated or diagnosed; and the availability of alternative
391 therapies, including their associated benefits and risks. When available, information
392 characterizing subject tolerance for risk and perspective on benefit may provide useful context
393 during this assessment.

394

³² See FDA Guidance, [Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm) (March 28, 2012).

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm>

395 **V. ASSESSING BENEFITS AND RISKS FOR IDE APPLICATIONS**

396
397 The approach outlined in this section describes FDA’s key considerations when assessing
398 benefits and risks of IDE studies. FDA recommends using a benefit-risk framework to facilitate
399 the incorporation of evidence and knowledge from different domains—clinical, nonclinical, and
400 patient—to support a comprehensive, balanced decision-making approach. The framework
401 should focus on relevant facts, uncertainties, and key areas of judgment to add clarity and
402 predictability to the regulatory process. FDA envisions that these factors will facilitate common
403 understanding between sponsors and FDA by highlighting which factors are critical in the
404 benefit-risk assessment for a specific application, and clearly explaining how these factors should
405 influence FDA’s decision.

406
407 FDA recommends IDE sponsors provide as part of the IDE application a section that summarizes
408 the key considerations for the IDE benefit-risk assessment. For an outline of the general
409 framework for IDE benefit-risk assessment, please refer to Appendix A. Appendix B contains
410 generic examples of IDE benefit-risk determinations for illustrative purposes.

411
412 This guidance is not intended to provide recommendations regarding device-specific data or
413 study requirements.

414
415 Patient Preferences

416
417 When applying a benefit-risk framework to decisions on IDE applications, FDA’s assessment
418 depends on the value assigned to various risks and anticipated benefits to the patients. In the
419 context of a clinical study, anticipated benefits include not only direct benefits to the patient but
420 also societal benefits in terms of knowledge to be gained from the study.

421
422 It is important to acknowledge that individual patient preferences vary, and that a patient may not
423 assign the same values to various risks and anticipated benefits as their physician, family
424 member, or other individual. Furthermore, patient preferences vary, both in preferred modality
425 of treatment/diagnostic procedure (often devices are one option to be considered in a treatment
426 care path which may include surgery or medication), as well as in risk tolerance. Some patients
427 are willing to take on higher risks to potentially achieve a small benefit, whereas others are more
428 risk averse. In certain circumstances, some patients may be willing to participate in clinical
429 studies that offer no or limited direct benefit to subjects, but have anticipated societal benefits in
430 advancing medical science.

431
432 It may be appropriate to approve an IDE application where only a subset of the eligible study
433 subject population would accept the risks as weighed against the benefits, provided there is
434 enough information and an adequate informed consent process in place for study patients to make
435 informed decisions. However, if, for a certain IDE application, the risks outweigh the anticipated
436 benefits for all subjects, FDA would disapprove the IDE application in accordance with 21 CFR
437 812.30(b).

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439 Patient preference information, as it relates to the participants in the study, may be particularly
440 informative in helping to assess the trade-offs between risks and benefits in certain challenging
441 device areas. For example:

442

- 443 • life-saving but high-risk devices (e.g., ventricular assist devices (VADs) for end-stage
444 heart failure);
- 445 • devices intended to yield improvements in health-related quality of life (e.g., for seizure
446 prevention, sleep apnea);
- 447 • devices intended to yield benefits in terms of health(e.g., obesity devices);
- 448 • aesthetic devices (e.g., breast implants, wrinkle fillers);
- 449 • devices for use in conditions where alternatives include non-device options such as
450 surgical procedures or medical therapy (e.g., minimally invasive alternatives to open
451 surgery).

452

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

456

Investigational Device Description

458

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

462

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

466

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

471

Assessment of Risks Associated with Investigational Device Use

473

474 The investigational plan shall include a risk analysis which describes and analyzes all *increased*
475 *risks* to which subjects will be exposed by the investigation, the manner in which these risks will
476 be minimized, a justification for the investigation, and a description of the patient population
477 including number, age, sex, and condition.³³

478

³³ 21 CFR 812.25.

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479 FDA recommends that IDE sponsors use an accepted method of risk assessment, where
480 appropriate. For example, this guidance incorporates principles from ANSI/AAMI/ISO 14971,³⁴
481 an FDA-recognized standard which provides a framework for systematically managing risks of
482 medical devices throughout the total product life cycle.

483

484 In addition, there are several key concepts which are commonly not well described in IDE
485 applications received by FDA:

486

487 • Harms. Specifying how a hazard could lead to clinical sequelae or other harmful event is
488 important because it allows more precise estimation of risk severity and likelihood.

489

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

492

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

497

498 FDA may disapprove an IDE application if there is reason to believe that the risks to the subjects
499 outweigh the anticipated benefits to the subjects and the importance of the knowledge to be
500 gained.³⁵ Assessment of benefits and risks should not necessarily be made in comparison to the
501 most technologically advanced alternative but rather to commonly used therapies and treatments.

502

503 **A. *Assessment of Risks to Study Subjects***

504

505 In general, the assessment of risks to IDE subjects focuses on risks whose existence and
506 characteristics are supported by objective scientific evidence. The assessment of risks must
507 include a description and analysis of all incremental risks to which subjects will be exposed by
508 the investigation, and the manner in which these risks will be minimized.³⁶ While it is not
509 necessary to include specific mitigations for hypothetical risks that are not supported by scientific
510 evidence or risks that are determined to be negligible due to a low probability of occurrence and
511 low severity of harm, it is helpful to identify all possible risks in the risk assessment and include
512 information on how the level of risk was determined.

513

514 Relationship between Hazards and Harm³⁷

515

516 Risk assessment involves describing the relationships between a hazard (a potential source of
517 harm) and the ultimate consequences in terms of physical injury or damage. As part of FDA's

³⁴ "Medical Devices—Application of risk management to medical devices" ANSI/AAMI/ISO 14971:2007/(R)2010.

³⁵ 21 CFR 812.30(b)(4).

³⁶ 21 CFR 812.25.

³⁷ See Appendix D for a glossary of risk management terms.

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518 IDE decision-making, this relationship should specifically describe the foreseeable sequences of
519 events, hazardous situations, and associated possible harm. This may include:

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

525

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

528

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

532

- 533 ○ **Basic Safety** – protection against physical hazards, which should be addressed
534 and mitigated with a reasonable level of certainty. For example, an active device
535 should not be unsafe from an electrical safety perspective (e.g., the devices should
536 not deliver an unintended electrical shock and surface temperature increases
537 should not unintentionally burn the patient or operator).
- 538 ○ **Device-related serious adverse events** – events attributable to the investigational
539 use of the device which produce an injury or illness that is life-threatening, results
540 in permanent impairment or damage to the body, or requires medical or surgical
541 intervention to prevent permanent harm to the body.
- 542 ○ **Device-related non-serious adverse events**
- 543 ○ **Procedure-related complications due to the investigation** – This includes not
544 just the device use but risks related to the investigation itself to which the subject
545 would otherwise not be exposed, e.g. risk of anesthesia during procedures
546 involving an investigational device.
- 547 ○ **Risks associated with the study itself** – risks the subject may be exposed to that
548 do not directly result from use of the device and would not be expected as part of
549 usual care outside of the investigational setting. Examples include additional
550 procedures (such as medical imaging) for ascertainment of study endpoints.
- 551 ○ **Risk from false-positive or false-negative results for diagnostics** – if a
552 diagnostic device gives a false-positive result, the subject might be exposed to
553 risks associated with unnecessary additional diagnostic procedures and additional
554 tests, or potential unnecessary treatment, as well as the ramifications of
555 diagnosing a potentially incorrect disease. If a false-negative result is given, the
556 subject might not receive effective treatment (thereby missing benefits that
557 treatment would confer), or might not be diagnosed with the correct disease or
558 condition.

559

560 **A.2 Likelihood or probability of risk(s):**

561 Various approaches are commonly employed to estimate probabilities of risks including
562 but not limited to: use of relevant historical data; prediction of probabilities of risk using

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563 analytical or simulation techniques; use of experimental data from prior investigations;
564 reliability estimates; production data; post-production information; and use of expert
565 judgment. The use of multiple approaches may be considered as this might serve to
566 increase confidence in the results. During earlier development stages, greater uncertainty
567 may exist around these estimates, in which case it may be useful to consider a qualitative
568 approach to risk probability analysis.³⁸

569
570 The likelihood or probability of risk(s) includes the likelihood of the hazard resulting in a
571 harmful event. If known, this includes the number of harmful events per patient or the
572 number of harmful events per unit of time, the proportion of the intended population that
573 would be expected to experience a harmful event, as well as the likelihood of a given
574 subject or study group experiencing a harmful event. FDA considers whether an event
575 occurs once or repeatedly in assessing the probability of risks.

576
577 **A.3 Duration of risk(s):** Some studies expose subjects to temporary, minor harm; some
578 can cause repeated but reversible harm; others can cause permanent, debilitating injury.
579 Duration (i.e., how long the adverse consequence lasts) should be considered along with
580 severity of risk, as described in above in A.1.

581 582 **A.4 Risk Management**³⁹

583
584 Risk Management provides a summary and assessment of any efforts that could help to
585 mitigate the identified safety concerns, or assure that device use is directed to those
586 participants for whom the risk is considered acceptable because it does not outweigh the
587 potential for benefit.

588
589 Risk control measures (including risk mitigation efforts) should be applied, where
590 appropriate, to reduce the likelihood and severity of harm to study subjects and improve
591 the benefit-risk profile of the proposed IDE study. Risk control measures are intended to
592 reduce the risk to an acceptable level. Sponsors should conduct an initial determination
593 regarding which risk controls are appropriate for their proposed IDE study. Benefit-risk
594 assessment for IDE decisions should focus on residual risk, and whether residual risk has
595 been reduced to acceptable levels relative to the anticipated benefits to the subjects. The
596 sponsor must provide in the IDE application a clear justification for the investigation,
597 having considered risks for the intended study population and the manner in which those
598 risks will be minimized.⁴⁰

599
600 Risk mitigation may include device design features/modifications, protective measures
601 (e.g., study design features), and communication of safety information (e.g., training of

³⁸ Such an analysis may include qualitative or semi-quantitative probability levels when the probability has not or cannot be precisely determined, but is known or expected to be within an estimated range. (See ISO 14971, Section D.3 for more information).

³⁹ For additional information on risk management for medical devices, refer to ISO 14971.

⁴⁰ 21 CFR 812.25.

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602 investigational staff). Forms of risk controls that may be applied to IDE studies may
603 include but are not limited to:

604

605 Safety by Design

606

- 607 • Device design features and/or modifications

608

609 Protective Measures

610

- 611 • Physical protective measures (e.g., user & subject radiation shielding)
- 612 • Preparation and readiness of personnel and equipment for anticipated adverse
- 613 events (e.g., crash carts)
- 614 • Study design⁴¹
 - 615 ○ Staged enrollment with limited initial human subject exposure and
 - 616 interim pre-specified subject safety assessment (e.g., IDE staged
 - 617 approval)
 - 618 ○ Staged/graded exposure to device intervention (e.g., low level
 - 619 stimulation before high level stimulation)
 - 620 ○ Pre-specified clinical management of potential adverse events; more
 - 621 frequent reporting
 - 622 ○ Pre-specified monitoring of study conduct, particularly for aspects
 - 623 critical to safety
 - 624 ○ Pre-specified stopping rules or guidelines
- 625 • Performance of study at trained or specialized sites or investigators meeting
- 626 certain criteria (e.g., multidisciplinary heart team).
- 627 • Study oversight
 - 628 ○ Investigational review board/ethics oversight
 - 629 ○ Use of a Clinical Events Committee, Data Monitoring Committee /
 - 630 Data Safety and Monitoring Board, or other Quality by Design features
 - 631 ○ IDE Progress Reports
 - 632 ○ Clinical Hold Authority
- 633 • Adverse Event reporting⁴²
 - 634 ○ More frequent reporting of serious adverse events (e.g., after each
 - 635 occurrence, monthly, quarterly, annually)
 - 636 ○ Accurate reporting of adverse events, including the timing and clinical
 - 637 context and a description of any medical interventions that were
 - 638 provided and the associated outcomes

639

640 Communication of safety information⁴³

⁴¹ In some cases, it may be appropriate to narrow the study population to a subset where the benefit-risk profile is more favorable (e.g., limit high risk novel therapy to treatment-refractory patients). See Section A.5 – Residual risk evaluation.

⁴² See 21 CFR 812.150.

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- 641
- 642
- 643
- 644
- 645
- 646
- 647
- 648
- Informing study subjects about reasonably foreseeable risks of study participation
 - Communication among study sites regarding safety information (e.g., investigator and study coordinator calls)
 - Communicating safety information with the IRB overseeing the study to determine whether any additional human subject protection measures are needed.

649

650 Note that the preferred hierarchy of risk mitigation is to first attempt to eliminate the risk,

651 then if this is not possible, to design and implement protective measures, and

652 communicate the residual risk to patients and operators such as by labeling.

653

654 **A.5 Residual risk evaluation**

655 After risk control measures are applied, the following measures may be considered when

656 evaluating any residual risk, particularly in cases where there are substantial risks

657 associated with the study:

658

- 659
- 660
- 661
- 662
- 663
- 664
- 665
- 666
- Risk communication and disclosure of residual risk during the informed consent process
 - Consideration of subject perspective on assuming risk relative to anticipated benefit
 - Performance of initial limited study in subjects most likely to experience benefits
 - Select a participant subset where the benefit-risk profile is more favorable (e.g., treatment-refractory patients)

667 **B. *Assessment of Other Risks Considerations⁴⁴ of Investigational Study***

668

669 **B.1 Risks related to study data and benefit of knowledge to be gained —**

- 670
- 671
- 672
- Risk of drawing a false conclusion based on clinical data obtained
 - Risk of data which are inconclusive or difficult to interpret⁴⁵

673 **B.2 Risks to others** – Certain investigations may involve risks to others, in which case

674 these risks should be considered. For example:

- 675
- 676
- Risk of radiation exposure of health care practitioner
 - If treated subjects become drowsy while operating a vehicle

⁴³ All research includes some risk. After taking appropriate steps to mitigate risk through device design features/modifications and protective measures, it is important to communicate relevant safety information about residual risks.

⁴⁴Consistent with section 520(g)(4)(B) of the FD&C Act, FDA may consider these risks in protection of the public health and safety. FDA review of these risk considerations will focus on appropriate mitigation measures to control these risks.

⁴⁵ Refer to Section III.D. for further discussion on this point.

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677 **C. Assessment of Direct Benefits to the Study Subject**

678

679 In general, the assessment of anticipated benefits to IDE subjects does not include purely
680 hypothetical benefits, and instead focuses on those direct benefits whose existence and
681 characteristics are supported by objective scientific evidence. FDA’s assessment of anticipated
682 benefits of study participation includes the direct benefits to the subject — benefits that may be
683 realized by the subjects participating in the research, including:

684

685 **C.1 Type of benefit(s)** – examples include but are not limited to the device’s anticipated
686 impact on clinical management, subject health, and subject satisfaction in the target
687 population, such as improving clinical management and quality of life, reducing the
688 probability of death, aiding improvement of subject function, reducing the probability of
689 loss of function, and providing relief from symptoms. For diagnostics, an anticipated
690 benefit may be due to its ability to identify a specific disease and therefore prevent its
691 spread, predict future disease onset, provide earlier diagnosis of diseases, or identify
692 participants more likely to respond to a given therapy.

693

694 **C.2 Magnitude of the benefit(s)** – determined by the anticipated change in subjects’
695 condition or clinical management, or as determined by an improvement or worsening of
696 the endpoint. Variation in the magnitude of the benefit across a population may also be
697 considered.

698

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

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

711

712 **D. Assessment of Benefits to Others**

713

714 In addition to assessing the anticipated direct benefits to IDE subjects, an IDE benefit-risk
715 assessment also includes a consideration of the anticipated benefits to others (to the extent they
716 are indirect benefits to subjects or reflect the importance of the knowledge to be gained).

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718 A required element of the informed consent is a description of any benefits to the subject *or to*
719 *others* [emphasis added] which may reasonably be expected from the research.⁴⁶ Benefits to
720 others that may also indirectly benefit the subjects include benefits to caregivers or family
721 members.

722
723 A benefit to others of an investigational study is the “importance of the knowledge to be
724 gained.”⁴⁷ This is not a direct benefit to the subject, but rather is considered a societal benefit in
725 terms of increasing the understanding of a disease condition and potential treatment or diagnostic
726 applications. This benefit is unique to research and does not apply to marketing applications. A
727 greater degree of uncertainty about the benefits and risks of study participation typically exists in
728 IDE submissions, and one should consider the possibility that study subjects will receive no
729 direct benefit from study participation. However, subjects may still be willing to participate
730 because of the indirect benefits, such as the importance of the knowledge to be gained. Studies
731 which are well-designed may be considered to have greater benefits in this regard, because it
732 generates knowledge that can inform safe use and may lead to earlier patient access to high
733 quality, safe and effective devices.⁴⁸

734
735 In assessing an IDE study for the importance of the knowledge to be gained, a key consideration
736 is the likelihood that the study will yield generalizable knowledge about the disorder or condition
737 being studied. There are additional safeguards for the inclusion of children in clinical
738 investigations that are likely to yield generalizable knowledge about the subjects’ disorder or
739 condition, but that involve greater than minimal risk with no prospect of direct benefit to
740 individual subjects.⁴⁹

741
742 Finally, studies which are well-designed may be considered to make greater contributions to the
743 knowledge to be gained, as they are more likely to yield useful information and meaningfully
744 increase patient access to reasonably safe and effective devices.

745
746

⁴⁶ 21 CFR 50.25(a)(3).

⁴⁷ 21 CFR 812.30(b)(4).

⁴⁸ Consistent with section 520(g) of the FD&C Act, FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing application.

⁴⁹ In accordance with 21 CFR 50.53, any clinical investigation within the scope described in 21 CFR 50.1 and 21 CFR 56.101 in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

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

748
749 The assessment of benefits and risks for an IDE study takes into account the uncertainty
750 surrounding the knowledge and available evidence, the contextual setting in which the study is
751 being proposed, including characterization of the disease or condition being treated or diagnosed,
752 and availability of alternatives and risks associated with them. When available, information
753 characterizing subject tolerance for risk and perspective on benefit may provide useful context
754 during this assessment.

755
756 **E.1 Characterization of the disease:** The treated or diagnosed condition, its clinical
757 manifestation and severity (e.g., temporary or permanent loss of function), how it affects
758 the subjects who have it, how and whether a diagnosed condition is treated, and the
759 condition's natural history and progression (i.e., does it get progressively better or worse
760 for the subject and at what expected rate) are all important factors that FDA considers
761 when characterizing a disease and assessing benefits and risks. For instance, conditions
762 with more severe symptoms and natural course, relatively fewer and less effective
763 treatment options, and less chance of responding to current treatment options, may
764 warrant tolerating greater risk in a study.

765
766 **E.2 Availability of alternatives:** When characterizing the availability of alternatives,
767 important factors that FDA considers are treatment (or diagnostic) options, treatment
768 strategy (if applicable, such as for chronic diseases) and the safety and effectiveness of
769 alternatives including the potential for adverse events. If alternative therapies (or
770 diagnostic options) exist, are effective for the subject population, and are associated with
771 relatively fewer adverse events, then subjects may not tolerate a higher degree of risk of
772 study participation. Assessment should not necessarily be made in comparison to the
773 most technologically advanced alternative but rather to commonly used therapies and
774 treatments.

775
776 **E.3 Subject tolerance for risk and perspective on benefit:** Risk tolerance varies among
777 subjects, and this will affect individual subject decisions to participate in a study. When
778 evaluating benefits and risks, FDA recognizes that tolerance for risk and a subject-centric
779 assessment of risk may reveal reasonable individuals who are willing to tolerate a high
780 level of risk to achieve an anticipated benefit, especially if that benefit results in an
781 improvement in quality of life or achieves societal benefit from knowledge gained. In
782 addition, a thorough informed consent process serves to assure that prospective subjects
783 are informed of, among other information, the risks and benefits of study participation,
784 and agree to the risks of study participation given other factors, including the potential
785 benefits.

786
787 **E.4 Uncertainty:** There is always some uncertainty when weighing benefits and risks
788 prior to clinical study conduct. However, the degree of certainty is a factor we consider
789 when assessing benefit-risk for IDE applications.

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- 791 • **Quality of prior nonclinical and clinical investigations:** Well-conducted non-
792 clinical and clinical prior investigations can help reduce uncertainty, particularly
793 related to identified potential hazards. However, poor study design or conduct, or
794 inadequate analysis of prior study data, can produce data which are inconclusive
795 or difficult to interpret.
796
- 797 • **Predictive capability of evidence from prior investigations:** The ability of the
798 nonclinical testing and prior clinical experience to predict clinical performance in
799 the proposed study is an important consideration, as is the generalizability of early
800 results to the intended study and user population. For example, if the device
801 requires in-depth user training or specialization, the clinical study should be
802 designed to address this issue to assure appropriate risk mitigation. It is important
803 to distinguish between purely hypothetical risks, actual hazards, and the likelihood
804 of subject harm.
805
- 806 • **Different uncertainty considerations at different stages of development:**
807 Different questions of uncertainty may arise at different stages of study. A higher
808 level of uncertainty is expected and may be acceptable in the early stages of
809 device development. Generally, while the types of uncertainty (and questions to
810 be answered) varies across stage of investigation and development, the overall
811 degree of uncertainty of risks and benefits should decline as more data are
812 collected throughout device development and exploration. Refer to Section IV.A.
813 for more information.
814

815 **E.5 Least burdensome study design:** When considering elements of study design,
816 incorporating additional elements often involves trade-offs in terms of time, cost and
817 practicality of study conduct, which may affect other aspects of clinical trial start-up, such
818 as IRB approval and feasibility of subject enrollment. While FDA does not consider cost
819 when deciding to approve an IDE application, the potential impact of study design
820 elements on trial start-up, IRB approvability, and feasibility of subject enrollment should
821 be considered.
822

823 **F. Overall IDE Benefit Risk Determination**

824
825 Consistent with applicable statute and regulations, FDA may disapprove an IDE application if,
826 among other reasons, there is reason to believe that the risks to the subjects outweigh the
827 anticipated benefits to the subjects and the importance of the knowledge to be gained. In many
828 cases, the Agency believes that effective risk management, including the application of risk
829 controls and risk mitigation measures, can reduce the residual risk and result in a favorable IDE
830 benefit-risk determination.

831
832 FDA believes that the use of a common framework and structured approach to assessing IDE
833 benefits and risks will facilitate the submission not only of relevant evidence and knowledge but
834 also a clear rationale for why the submitted information is sufficient to justify the initiation of the

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835 proposed study. Application of the factors listed in this guidance document can ultimately
836 improve the predictability, consistency, and transparency of FDA's IDE decision-making,
837 resulting in the strengthening and streamlining of the clinical trial enterprise in the U.S. so that
838 medical device clinical trials are conducted in an efficient and cost-effective manner, while
839 maintaining appropriate patient and research participant protections.

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841 **APPENDIX A – RECOMMENDED GENERAL FRAMEWORK FOR BENEFIT-RISK**
842 **ASSESSMENT**

843
844 *FDA recommends IDE sponsors provide as part of the IDE application a section that*
845 *summarizes the key considerations in the IDE benefit-risk assessment. The benefit-risk summary*
846 *should provide a concise synopsis and may reference relevant sections in the IDE application*
847 *where supporting information and evidence can be found. The intent of this summary is not to*
848 *provide an all-encompassing summary of the benefit-risk assessment, but rather to focus on*
849 *those items which are likely to significantly affect FDA’s decision or recommendation.*

850
851 *FDA recommends that the benefit-risk summary address the following key elements:*
852

853 **1. CONTEXT OF THE PROPOSED INVESTIGATION**

854
855 Provide a summary of the disease or condition to be treated or diagnosed, a description of
856 the device in the context of currently available treatment or diagnostic options, and a brief
857 description of the investigation (its objective and design).
858

859 **2. ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION**

860
861 A summary of the key risk elements identified in Section 5 of the guidance including risk
862 characterization, risk control measures, and residual risk.
863

864 **3. ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION**

865
866 A summary of the key benefits of the proposed investigation as identified in Section 5 of
867 the guidance including direct benefits to study subjects of the proposed investigation and
868 benefits to others (to the extent they are indirect benefits to subjects or reflect the
869 importance of the knowledge to be gained).
870

871 **4. CONSIDERATION OF PATIENT PREFERENCE INFORMATION**

872
873 A summary of available patient preference information, if any. If none, state that none
874 was provided.
875

876 **5. ASSESSMENT OF UNCERTAINTY**

877
878 Summarize key sources of uncertainty in the available evidence and proposed
879 investigation as identified in Section 5 of the guidance, and provide a rationale for why
880 the level of uncertainty is acceptable for the proposed investigation.
881

882 **6. CONCLUSIONS**

883
884 Summarize how the consideration of the factors discussed in this summary justify the
885 decision to proceed with human clinical investigation.

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886 **APPENDIX B – HYPOTHETICAL EXAMPLES OF SUMMARY BENEFIT-RISK**
887 **ASSESSMENTS**

888
889 *FDA recommends IDE sponsors provide as part of the IDE application a section that*
890 *summarizes the key considerations in the IDE benefit-risk assessment. The benefit-risk summary*
891 *should provide a concise synopsis and may reference relevant sections in the IDE application*
892 *where supporting information and evidence can be found (see Appendix A for details).*

893
894 *The examples below are simplified and offered for illustrative purposes only. The decisions*
895 *described in these examples are intended to demonstrate how to present the factors described in*
896 *this guidance when making benefit-risk assessments and how FDA may analyze these factors.*

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

899 CONTEXT OF THE PROPOSED INVESTIGATION

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

906 ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

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

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

916 ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

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

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924 CONSIDERATION OF PATIENT PREFERENCE INFORMATION

925

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

929 ASSESSMENT OF UNCERTAINTY

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

935 CONCLUSIONS

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

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

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946 **Example 2 – Feasibility study proposal for a device to treat a life-limiting condition with**
947 **reasonable alternative treatments**

948 CONTEXT OF THE PROPOSED INVESTIGATION

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

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

955 ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

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

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

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

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

972 ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

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

975 CONSIDERATION OF PATIENT PREFERENCE INFORMATION

976 The sponsor has provided a small survey regarding patient preference. The survey indicates that
977 some patients are satisfied with the currently available devices. However, there is a modest level

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978 of interest in novel technologies that could reduce the potential need for future surgery for device
979 removal or replacement.

980 ASSESSMENT OF UNCERTAINTY

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

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

984 CONCLUSIONS

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

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995
996 **Example 3 – Early feasibility study proposal for a device to treat a life-threatening**
997 **condition without an alternative treatment option**

998 CONTEXT OF THE PROPOSED INVESTIGATION

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

1000 No effective treatment alternative exists for patients with the advanced form of the disease.
1001 Treatments that are successful for patients with less severe forms of the disease have failed in
1002 patients with advanced disease.

1003 The sponsor proposes an early feasibility study to provide proof of principle and initial clinical
1004 safety data for the use of a device to treat the condition.

1005 ASSESSMENT OF RISKS OF THE PROPOSED INVESTIGATION

1006 This intervention has risks associated with both the procedure as well as the potential for long-
1007 term adverse effects. The procedural risks have been evaluated in an animal study. In addition,
1008 information can be leveraged from the clinical experience with a similar device for a different
1009 intended use. With available leveraged information and an understanding of the device design
1010 concept, the types of risks are known, but the frequency and severity are unknown. In cases
1011 where patient characteristics (e.g., age, gender, or other key variables) are not comparable for the
1012 new intended use, the extent to which this previous clinical experience can be leveraged may be
1013 more limited.

1014 The sponsor has proposed several clinical study mitigation strategies to minimize the frequency
1015 and severity of risks to study subjects including the following:

- 1016 • use of study sites that have sufficient expertise and resources to manage adverse events
1017 and provide appropriate additional therapies if needed;
- 1018 • identification of qualified investigators with adequate training to conduct the early
1019 feasibility study;
- 1020 • implementation of an informed consent process which adequately conveys to potential
1021 subjects the high degree and seriousness of both known and unknown risks and the low
1022 likelihood of direct benefits;
- 1023 • a plan to capture human factors information during the course of the study to modify the
1024 procedures or device as necessary based on the information obtained prior to the
1025 treatment of additional participants;

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- 1026 • limiting the sample size to a reasonable number for an early feasibility study (e.g., 5-10
1027 initial subjects);
- 1028 • frequent follow-up assessments to monitor subject safety and device effectiveness;
- 1029 • timely reporting of serious adverse events (i.e., after each occurrence rather than only in a
1030 periodic progress report);
- 1031 • timely reporting of device performance parameters, which help determine whether the
1032 device functions as intended;
- 1033 • non-sequential enrollment, that is, initial device use in subjects with more favorable
1034 anatomical characteristics as compared to the population otherwise eligible for the early
1035 feasibility study (i.e., selecting subjects that meet study eligibility requirements but do not
1036 have anatomic features that may increase the difficulty of device use); and
- 1037 • a pre-specified plan for periodic participant outcome assessments and reporting prior to
1038 enrollment of additional participants (i.e., after each use of the device).

1039 ASSESSMENT OF BENEFITS OF THE PROPOSED INVESTIGATION

1040 Initial data from the previous nonclinical studies, with the available leveraged information,
1041 suggest the potential for clinically relevant reductions in morbidity and mortality from the
1042 condition, despite the potential for procedure-related and long-term adverse effects.

1043 CONSIDERATION OF PATIENT PREFERENCE INFORMATION

1044 Given the lack of an effective alternative treatment and the morbidity and mortality associated
1045 with the condition, patients are expected to have a high risk tolerance for considering potential
1046 new treatments. However, no definitive data have been provided by the sponsor to support this
1047 expectation.

1048 ASSESSMENT OF UNCERTAINTY

1049 Due to the novelty of the device and procedure and the lack of a nonclinical model to predict the
1050 clinical safety and effectiveness of the device, there is a high degree of uncertainty regarding the
1051 device, including the initial safety, the long-term adverse effects of the treatment, and the
1052 anticipated benefits.

1053 CONCLUSIONS

1054 Potential study subjects have failed conventional treatments that can be beneficial to patients
1055 with less severe cases. The proposed study is characterized by a significant degree of
1056 uncertainty, given the early phase of device development and the novelty of the proposed device

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1057 and procedure. Information available on a similar device from a different intended use and from
1058 an animal study provide some assurance that catastrophic failures would not be anticipated
1059 during the early feasibility study. Conducting additional nonclinical testing is unlikely to provide
1060 information to decrease the level of uncertainty.

1061 Considering that: (1) the proposed device treats a severe disease for which there is no alternative
1062 treatment; (2) information is available from the clinical experience with a similar device for a
1063 different intended use to suggest that catastrophic failures will not occur; (3) there is reason to
1064 believe that patients may benefit from treatment with the device; and (4) additional nonclinical
1065 testing will not provide the information needed to advance the device design, FDA is likely to
1066 approve the early feasibility study IDE.

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1070 **APPENDIX C – REFERENCE GUIDE: DESCRIPTION OF INVESTIGATIONAL**
1071 **DEVICE**

1072

1073 Fundamental to an assessment of benefits and risks associated with investigational device use is
1074 an understanding of the investigational device itself. 21 CFR 812.25(d) requires that the
1075 investigational plan include a:

1076

1077 *description of this device (a description of each important component, ingredient,*
1078 *property, and principle of operation of the device and any anticipated changes in*
1079 *the device during the investigation).*

1080

1081 Deficiencies related to an incomplete or inadequate investigational device description
1082 are the single most common type of non-clinical deficiency in IDE applications that fail
1083 to attain full approval. This Appendix lists the device attributes that CDRH
1084 recommends be included in the IDE device description.

1085

1086 The investigational device description should include an explanation of how the device
1087 functions, the scientific concepts that form the basis for the device, and the significant
1088 physical and performance characteristics of the device, such as device design, material
1089 used, and physical properties. A complete description of the device may be facilitated
1090 by the submission of engineering schematics or other figures. If the device consists of
1091 multiple components, a diagram identifying how the different components of the device
1092 system work together may be beneficial. The device description should also include a
1093 discussion of the physical specifications, dimensions and mechanical tolerances of the
1094 investigational device.

1095

1096 CDRH recognizes that an IDE application may be approvable even if there is
1097 uncertainty regarding some elements of the device description, depending on the
1098 novelty of the device, its stage of development, and its intended use. In addition, in
1099 some cases, such as sponsor-investigator initiated studies, the IDE sponsor may not
1100 have access to all recommended elements.

1101

1102 In general, it is recommended that the investigational device description include the
1103 following details or provide a rationale for why information concerning the specified
1104 element is not needed or does not apply:

1105

- 1106 ○ Device Identification:
 - 1107 ■ List all device components (e.g., catheter, cable wire, leads, sizing tools,
1108 delivery system, etc.)
 - 1109 ■ List all models to be used in the investigation and briefly explain the
1110 differences among models

1111

- 1112 ○ Brief Written Description of the Device:

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- 1113 ▪ Explanation of how the device works/principle of operation
- 1114 ▪ Mechanism of action, if known
- 1115 ▪ Key performance specifications and manufacturing tolerances of the
- 1116 device
- 1117 ▪ Key device features/characteristics (address all that apply)
 - 1118 ▪ Software
 - 1119 ▪ Electrical properties
 - 1120 ▪ Mechanical properties
 - 1121 ▪ Biologics
 - 1122 ▪ Drugs
 - 1123 ▪ Coating(s) and surface modifications (e.g., an abraded material
 - 1124 surface to encourage implant retention)
 - 1125 ▪ Single-use or multi-use
 - 1126 ▪ Single patient or multi-patient
 - 1127 ▪ Sterile or sterilization method [specify]
 - 1128 ▪ Energy source (if applicable)
 - 1129 ▪ This not only includes energy delivery to the device,
 - 1130 including the use of batteries, but also energy delivery that is
 - 1131 part of the functional aspect of the device (e.g., laser,
 - 1132 radiofrequency, ultrasound, etc.).
 - 1133 ▪ Materials of use
 - 1134 ▪ Chemical formulation used in the materials of construction,
 - 1135 especially for those materials that come into contact with the
 - 1136 patient, should be provided.
 - 1137 ▪ Duration and type of contact
 - 1138 ▪ Other critical device features
 - 1139 ▪ These may include, but are not limited to, software/
 - 1140 hardware features, density, porosity, degradation
 - 1141 characteristics, nature of reagents (recombinant, plasma
 - 1142 derived, etc.), principle of the assay method,
 - 1143 manufacturing-related aspects, etc., that are not explicitly
 - 1144 included as part of the materials, design or energy source
 - 1145 characteristics.
 - 1146 ▪ If modifications are made to the device during the course of
 - 1147 a study or between different stages of investigation (e.g.,
 - 1148 early feasibility to pivotal), a detailed comparison of the
 - 1149 original and modified device should be provided.
- 1150

1151 **APPENDIX D – GLOSSARY OF RISK MANAGEMENT TERMS⁵⁰**

1152

1153 Terminology / Definitions – Risk Assessment

1154

1155 For the purposes of this guidance, terms are defined as follows:

1156

1157 • **Harm** – physical injury or damage to the health of people, or damage to property or the
1158 environment.

1159 • **Hazard** – potential source of harm

1160 • **Risk** – a combination of the probability of occurrence of harm and the severity of that
1161 harm. Note that in earlier stages of development a relative sense of likelihood may be
1162 used instead of probability of occurrence, which is difficult or impossible to estimate
1163 when little evidence is available.

1164 • **Risk estimation** – process used to assign values to the probability of occurrence of harm
1165 and the severity of harm

1166 • **Risk analysis** – systematic use of available information to identify hazards and to
1167 estimate the risk

1168 • **Risk control** – process in which decisions are made and measures implemented by which
1169 risks are reduced to, or maintained within, specified levels.

1170 • **Residual risk** – risk remaining after risk control measures have been taken

1171

⁵⁰ Consistent with ISO 14971