Guidance for Industry and Food and Drug Administration Staff

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

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Department of Health and Human Services
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Preface

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

1. Introduction

FDA has developed this guidance document to provide greater clarity for FDA reviewers and industry regarding the principal factors FDA considers when making benefit-risk determinations during the premarket review process for certain medical devices. FDA believes that the uniform application of the factors listed in this guidance document will improve the predictability, consistency, and transparency of the premarket review process.

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

2. Scope

This guidance document explains the principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain medical devices. The processes discussed in this guidance are applicable to devices subject to premarket

approval (PMA) applications or *de novo* classification petitions. This guidance applies to both diagnostic and therapeutic devices. The concepts discussed in this guidance are applicable to the medical device development process from design to market. As such, the benefit-risk factors set out herein should be considered during the design, non-clinical testing, pre-Investigational Device Exemption (IDE), and IDE phases as well as in assembling and assessing PMA applications or *de novo* petitions. Although guidance is not binding, the concepts and factors described herein generally explain how benefit-risk determinations are made by FDA during the premarket review process. The intersection of this Guidance with ISO 14971 is discussed in Appendix A.

3. Background

3.1 The Statutory Standard for Safety and Effectiveness

Under section 513(a) of the Federal Food, Drug & Cosmetic Act (the "FD&C Act"), FDA determines whether PMA applications provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.[1] To aid in this process, PMA applicants submit valid scientific evidence, including one or more clinical investigations where appropriate, which FDA reviews to determine whether "the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device."[2] FDA staff review the data submitted as part of the PMA application and determine – based on a number of factors – if the data support the claims made by the sponsor concerning clinically significant results from the device, i.e., intended use and

[1] In addition to section 513(a), the criteria for establishing safety and effectiveness of a device are set forth in 21 CFR 860.7. Subsection (b)(1) notes, "In determining the safety and effectiveness of a device … the Commissioner and the classification panels will consider the following, among other relevant factors …The probable benefit to health from the use of the device weighed against any probable injury or illness from such use." (21 CFR 860.7(b)).
To make this determination, "the agency relies upon only valid scientific evidence." (21 CFR 860.7(c)(1)). Valid scientific evidence is defined as "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." (21 CFR 860.7(c)(2)).
A reasonable assurance of safety occurs when "it can be determined, based upon valid scientific evidence, that the probable benefits … outweigh any probable risks," and can be demonstrated by establishing "the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use." (21 CFR 860.7(d)(1)).
Similarly, a reasonable assurance of effectiveness occurs when "it can be determined, based upon valid scientific evidence … the use of the device for its intended uses … will provide clinically significant results." (21 CFR 860.7(e)(1)). The evidence of which is demonstrated principally through "well-controlled investigations" (see 21 CFR 860.7(e)(2)), as defined in 21 CFR 860.7(f).

[2] Section 513(a)(3)(A) of the FD&C Act.

indications for use, and if the data analysis demonstrates that the probable[3] benefits of the device outweigh its probable risks. A balanced consideration of probable benefits and probable risks is an essential part of FDA's determination that there are reasonable assurances of safety and effectiveness.[4] Other considerations include that the device is being manufactured in accordance with FDA's quality system requirements.[5]

Similarly, in accordance with section 513(f)(2) of the FD&C Act, sponsors of devices that have been determined to be not substantially equivalent (NSE) through the 510(k) program may be eligible to submit a *de novo* petition requesting FDA to make a risk-based classification determination for the device under section 513(a)(1) of the FD&C Act.[6] Because devices classified under this pathway (*de novo* devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients[7] in order to have a favorable benefit-risk profile. Devices granted marketing authority under *de novo* petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness. Further, devices classified under *de novo* petitions may serve as predicates for future devices which can be appropriately regulated through the 510(k) program; therefore, FDA carefully considers the benefit-risk profile of these devices in the determination that there is reasonable assurance of safety and effectiveness.

3.2 Types of Scientific Evidence

Medical devices can be evaluated using clinical and non-clinical testing methods. Clinical testing methods for medical devices can include, when appropriate, randomized clinical trials in the appropriate target population, well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, reports of significant human experience, and testing on clinically derived human specimens (DNA, tissue, organ and cadaver studies).[8] Non-clinical testing methods can encompass an array of methods including performance testing for product safety/reliability/characterization, human factors and usability engineering testing under simulated conditions of use, animal and

[3] In general, "probable" and "probability" in this guidance have the same connotation as in 21 CFR 860.7(b)(3), i.e. they refer to the likelihood of the patient experiencing a benefit or risk. Hypothesis testing, formal concepts of probability and predictive probability, likelihood, etc., typically are critical elements in the assessment of "probable" benefit and risk. FDA does not intend for the use of the term "probable benefit" in this guidance to refer to the regulatory context for Humanitarian Device Exemptions (HDE) under section 520(m) of the FD&C Act, and FDA's implementing HDE regulations.

[4] Equally important is FDA's determination of effectiveness. See footnote 1.

[5] See 21 CFR Part 820.

[6] See Draft Guidance for Industry and Food and Drug Administration Staff - De Novo Classification Process (Evaluation of Automatic Class III Designation).

[7] In general, for the purposes of this guidance, the use of the term "patient" refers to an individual who is under medical care or treatment and is not a subject, and the use of the term "subject" refers to an individual who participates in a clinical investigation.

[8] See 21 CFR 860.7.

cell-based studies, and computer simulations. These tests characterize mechanical, electrical and chemical properties of the devices including but not limited to wear, tensile strength, compression, flow rate, burst pressure, biocompatibility, toxicity, electromagnetic compatibility (EMC), sterility, stability/shelf life data, software validation, and testing of synthetic samples, including cell lines. The information obtained from any clinical and/or non-clinical testing is taken into account during the premarket review process and FDA's benefit-risk determination.

Although a great deal of emphasis is placed on the importance of clinical data in demonstrating the safety and effectiveness of a medical device, non-clinical data also can be critical to understanding a device's safety and effectiveness. Medical devices often have attributes that cannot be tested using clinical methods alone and that play a major role in the safety or effectiveness of the device.

Both clinical and non-clinical testing methods may be used to assess the probability or severity of a given risk, and/or the success of risk mitigation. For example, in the case of some implants, the most robust long-term evidence comes from engineering tests that are able to challenge the device under worst-case conditions, test the device to failure, and simulate many years of use. In contrast, clinical studies are usually limited in duration of follow-up, and, as a result, may be less informative with respect to the long-term performance of the device. In this case, the results of engineering testing may significantly influence FDA's benefit-risk determination independent of the clinical findings.

Both clinical and non-clinical data can play a role in FDA's benefit-risk determinations, and the factors discussed in this guidance are informed by both types of data.

FDA relies on valid scientific evidence in making risk and benefit determinations, including the critical issue of identifying 'probable risks' and 'probable benefits' in the first place. In general, a 'probable risk' and a 'probable benefit' do not include theoretical risks and benefits, and instead are ones whose existence and characteristics are supported by valid scientific evidence. Generally, isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. However, such information may be considered in identifying a device that has questionable safety and effectiveness.[9]

3.3 Benefit-Risk Determinations

The factors FDA considers as part of the benefit-risk determination are explained in detail below. We also give examples of how the factors interrelate and how they may affect FDA's decisions. By providing greater clarity about FDA's decision-making process, we

[9] 21 CFR 860.7(c)(2).

hope to improve the predictability, consistency, and transparency of the review process for applicable devices.

We have also included a worksheet that reviewers will use in making benefit-risk determinations as part of the premarket review process. The worksheet is attached as Appendix B to this guidance, and examples of how reviewers might use the worksheet are attached as Appendix C. By documenting reviewers' thought processes as part of the administrative record and, in certain cases, the publicly available summary of our decision,[10] sponsors will have a better idea of the basis for FDA's favorable decisions and gain a greater understanding of what factors were considered as part of an approval or a down-classification decision through the *de novo* process. However, because the weighting of the factors for a type of device may change over time – such as a device no longer being a first-of-a-kind or the only available treatment as new therapies are approved – the benefit-risk determination for a specific device at one point in time may no longer represent the proper weighting of the factors for the same or similar type of device in the future.

4. Factors FDA Considers in Making Benefit-Risk Determinations

The factors described below are considered within the intended use of the device, including the target population. These sections are not intended to provide device-specific data requirements for the assessment of the factors or methods by which inferences will be drawn from the data.

4.1 Assessment of the Benefits of Devices

Extent of the probable benefit(s): FDA assesses information provided in a PMA application or *de novo* petition concerning the extent of the probable benefit(s) by taking into account the following factors individually and in the aggregate:

- The **type of benefit(s)** – examples include but are not limited to the device's impact on clinical management, patient health, and patient satisfaction in the target population, such as significantly improving patient management and quality of life, reducing the probability of death, aiding improvement of patient function, reducing the probability of loss of function, and providing relief from symptoms. These endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of validated surrogate endpoints. For diagnostics, a benefit may be assessed according to the public health impact of a particular device, due to its ability to identify a specific disease and therefore prevent its spread, predict future disease onset, provide earlier diagnosis of diseases, or identify patients more likely to respond to a given therapy.

[10] See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma/cfm.

- The **magnitude of the benefit(s)** – we often assess benefit along a scale or according to specific endpoints or criteria (types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in subjects' condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, is what allows us to determine the magnitude of the benefit in subjects. Variation in the magnitude of the benefit across a population may also be considered.

- The **probability of the patient experiencing one or more benefit(s)** – based on the data provided, it is sometimes possible to predict which patients may experience a benefit, whereas other times this cannot be well predicted. The data may show that a benefit may be experienced only by a small portion of patients in the target population, or, on the other hand, that a benefit may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit. If the subgroups can be identified, the device may be indicated for those subgroups. In some cases, however, the subgroups may not be identifiable. In addition, we consider magnitude and probability together when weighing benefits against risks. That is, a large benefit experienced by a small proportion of subjects may raise different considerations than does a small benefit experienced by a large proportion of subjects. For example, a large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of subjects.

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

4.2 Assessment of the Risks of Devices

Extent of the probable risk(s)/harm(s): FDA assesses the extent of the probable risk(s)/harm(s) by taking into account the following factors individually and in the aggregate:

- **Severity, types, number and rates[11] of harmful events associated with the use of the device:[12]**

[11] For purposes of this guidance, "rates" means the number of harmful events per patient or number of harmful events per unit of time.

[12] We have listed each type of harm individually for the purpose of clarifying which of the more commonly recognized harms FDA would consider in benefit-risk assessments. In making benefit-risk assessments,

- **Device-related serious adverse events** – those events that may have been or were attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.[13]

- **Device-related non-serious adverse events** – those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse event.

- **Procedure-related complications** – harms to the patient that would not be included under serious or non-serious adverse events, and that do not directly result from use of the device. For example, anesthetic-related complications associated with the implantation of a device. Similarly, FDA would factor risks associated with the collection of human biological materials into the benefit-risk determination.[14]

- **Probability of a harmful event** – the proportion of the intended population that would be expected to experience a harmful event. FDA would factor whether an event occurs once or repeatedly into the measurement of probability.

- **Duration of harmful events** (i.e., how long the adverse consequences last) – some devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent, debilitating injury. FDA would consider the severity of the harm along with its duration.

- **Risk from false-positive or false-negative results for diagnostics** – if a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. If a diagnostic device gives a false-negative result, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition. The risks associated with false-positives and false-negatives can be multifold, but are considered by FDA in light of probable risks.

We also consider the number of different types of harmful events that can potentially result from using the device and the severity of their aggregate effect. When multiple harmful events occur at once, they have a greater aggregate effect. For example, there may be a harmful event that is considered minor when it occurs on its own, but, when it

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FDA does not consider each type of harm individually, but rather looks at the totality of the harmful events associated with the device.

[13] See 21 CFR 803.3.

[14] These considerations affect the risk profile of in vitro diagnostic devices when the biological material is collected via an invasive procedure for the purpose of performing the diagnostic test.

occurs along with other harmful events, the aggregate effect on the patient can be substantial.

4.3 Additional Factors in the Assessment of the Probable Benefits and Risks of Devices

Uncertainty – there is never 100% certainty when determining reasonable assurance of safety and effectiveness of a device. However, the degree of certainty of the benefits and risks of a device is a factor we consider when making benefit-risk determinations. Factors such as poor design or poor conduct of clinical trials, or inadequate analysis of data, can render the outcomes of the study unreliable. Additionally, for certain device types, it is sometimes difficult to distinguish between a real effect and a placebo effect in the absence of a trial design that is capable of blinding investigators and subjects. Furthermore, the repeatability of the study results, the validation of the analytical approach, and the results of other similar studies and whether the study is the first of its kind or a standalone investigation can all influence the level of certainty. In addition, the generalizability of the trial results to the intended treatment and user population is important. For example, if the device requires in-depth user training or specialization, the results of the clinical study may not be generalizable to a wider physician population. Likewise, if the device is intended to diagnose a disease in a subpopulation, it may not be useful in the general population. In general, it is important to consider the degree to which a clinical trial population is representative of the intended marketing or target population.

Characterization of the disease – the treated or diagnosed condition, its clinical manifestation, how it affects the patients who have it, how and whether a diagnosed condition is treated, and the condition's natural history and progression (i.e., does it get progressively better or worse for the patient and at what expected rate) are all important factors that FDA considers when characterizing disease and determining benefits and risks.

Patient tolerance for risk and perspective on benefit – if the risks are identifiable and definable, risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable[15] in exchange for a probable benefit. When making a benefit-risk determination at the time of approval or *de novo* classification, FDA recognizes that patient tolerance for risk and a patient-centric assessment of risk may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life. How data concerning patient risk tolerance and other patient-centered metrics are developed will vary depending on a number of factors, including the nature of the disease or condition and the availability of existing treatments, as well as the risks and benefits they present. FDA encourages any sponsor that is

[15] 21 CFR 860.7(d)(1) states that "The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

considering developing such data to have early interaction with the appropriate FDA review division.

When assessing such data in a PMA application or *de novo* petition, FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse. Therefore, FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others. It should also be noted that if, for a certain device, the probable risks outweigh the probable benefits for all reasonable patients, FDA would consider use of such a device to be inherently unreasonable.[16]

Different factors can influence patient risk tolerance, including:

- **Severity of disease or condition** – patients suffering from very severe diseases (i.e., those that are life-threatening) may tolerate more risk for devices used in treatment. For diagnostic devices, individuals might be more averse to the risk of a false negative result concerning a severe disease.
- **Disease chronicity** – some patients with chronic diseases who have adapted to their illness and minimized its interference with their daily lives may tolerate less risk and require risky devices to deliver a greater treatment benefit, whereas other patients who have suffered from a debilitating chronic illness over a long period of time may tolerate higher risk to gain less benefit.
- Availability of **alternative treatment/diagnostic options** (also see below) – if there are no other treatment/diagnostic options available, patients may tolerate more risk for even a small amount of benefit.

We recognize that patient-centric metrics such as validated quality of life measures can be helpful for health care practitioners when discussing treatment decisions with their patients, and may be used to demonstrate benefit for purposes of product approval. These types of metrics allow the physician to better quantify the impact of the device on the patient's well-being and help the patient make a more informed decision. Moreover, it may be appropriate to approve a device where only a minority of the intended patient population would accept the risks as weighed against the benefits if the information necessary for patients and health care practitioners to make well-informed decisions is available and can be presented in a manner that can be understood by the practitioners and patients. Patient-centric assessments should take into account both the patient's willingness and unwillingness to use a device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a device.

Availability of alternative treatments or diagnostics – when making benefit-risk determinations, FDA considers whether other treatments or diagnostics, including non-

[16] For the purpose of this guidance the concept of "unreasonable risk" should be construed to mean a risk that no set of reasonable patients would be willing to endure to achieve a probable benefit.

device therapies, have been approved or cleared for the intended condition and patient population. When considering other therapies, FDA takes into account how effective they are; what known risks they pose; how they are used in current medical practice; their benefit-risk profiles; and how well available alternatives address the needs of patients and providers. For a device with a known benefit and a probability of high risk that treats a condition for which no alternative treatments are available, FDA would consider the risk to the patient of having no treatment if a device were not approved. For example, if a new device has a very small significant benefit and there is significant uncertainty about that benefit, we may still approve the product if there are no available alternative treatments and the probable benefits outweigh the probable risks.

Risk mitigation – the use of mitigations, when appropriate, can minimize the probability of a harmful event occurring and improve the benefit-risk profile. The most common form of risk mitigation is to include appropriate information within labeling (e.g., warnings, precautions, etc.), or to restrict the indication to a more limited use. Some harms can be mitigated through other forms of risk communication, including training and patient labeling. For in vitro diagnostics, risks may be mitigated by the use of complementary diagnostic tests.

Postmarket data – the use of devices in a real world setting can provide a greater understanding of their risks and benefits. FDA may consider the collection of postmarket data as a way to clarify the magnitude and effect of mitigations or as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations when making a benefit-risk determination. FDA has the authority to require post-approval studies for PMA devices and postmarket surveillance for PMA and *de novo* devices.[17] In addition, pursuant to section 513(a)(3)(C) of the FD&C Act, in certain cases, such as if a device is likely to be denied approval due to uncertainty about its effectiveness, FDA will consider whether postmarket data collection or other conditions might be structured so as to permit approval subject to those conditions. These types of studies or other data that come to light after the device is used in the real-world setting may alter the benefit-risk profiles of certain devices, especially if new risks are identified, or if the information can be used to confirm that certain risks have been mitigated, to identify which patients are most likely to suffer adverse events, or to identify more specifically how different groups of patients will respond.

Novel technology addressing unmet medical need – in assessing benefit and risk, FDA considers whether a device represents or incorporates breakthrough technologies and addresses an unmet medical need. A device may address unmet medical need by providing a clinically meaningful advantage over existing technologies, providing a greater clinically meaningful benefit than existing therapy, posing less risk than existing therapy, or providing a treatment or means of diagnosis where no alternative is available.

[17] 21 CFR 814.82 states that "FDA may impose postapproval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval." In addition, under section 522 of the FD&C Act, and FDA's implementing regulations at 21 CFR Part 822, FDA may order postmarket surveillance for certain Class II or Class III devices.

It is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit. In addition, the development of innovative technology may provide additional future benefits to patients. With subsequent iterations of the device its benefit-risk profile may change (e.g., the benefits may increase or the risks may be reduced), the expected level of safety and effectiveness may change, and later versions may offer significant advantages over the initial device. In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.

5. Examples of Benefit-Risk Determinations

The examples below are hypothetical or simplified and are only offered for illustrative purposes. The decisions described in these examples are not predictive of future FDA decisions, rather they are hypothetical outcomes and are only intended to demonstrate how FDA considers the factors described in this guidance when making benefit-risk determinations. Similar scenarios or devices may result in different approval outcomes depending on the individual performance characteristics of a particular device and the population for which it is indicated.

A description of how FDA would consider these examples in the context of the reviewer worksheet is included in Appendix C.

5.1 Hypothetical Examples

Example 1

An implantable device is developed to treat a severe, chronic condition for patients who have failed all other treatment options.

The device is studied in a pivotal clinical trial with a design where all subjects are implanted with the device, but the device is only turned on in half of them. After completion of the trial, inactive devices can be turned on. The primary endpoint for the trial is the magnitude of the benefit, i.e., the trial is designed to measure how well the device reduces the subject's symptoms as compared to the current standard of care.

The results of the pivotal clinical trial revealed the following:

Benefits: Based on the clinical study, it is inferred that the probability that a patient will experience a substantial benefit when the device is implanted is 75%. The trial was considered to have met its primary endpoint. As a general matter, patients with this disease who are able to maintain good mobility tend to have a longer life expectancy.

However, the duration of the benefit cannot be determined because the subjects in the study were only followed for one year.

Risks: The study showed that there is a very low probability of occurrence (less than 3%) of harmful events after device implantation. However, all implanted devices that require a surgical procedure carry with them their own set of risks. In this case it is known from the literature that the implantation of this device is not routine and there is a 1% chance of death from surgery. In addition, permanent implants pose additional risks, namely, they typically remain with the patient for life and may be difficult to remove. Even in cases where the device is deactivated, it remains implanted and a risk of device fracture, mechanical failure, or an adverse biological response to the device remains (the probability is less than 3%).

Additional Factors

Uncertainty: It is difficult to discern the mechanism of action by which subjects' symptoms improved and whether the surgery may have contributed to such improvement. Because the trial ended after one year, it is difficult to determine the duration of the benefit beyond one year. There is only a 75% chance that a patient will experience total success when implanted with the device.

Patient Tolerance for Risk and Perspective on Benefit: The sponsor provided data showing that patients are willing to take the risk of having the device implanted even for a 75% probability of benefit because the alternative treatment options do not work for them and their symptoms are severe.

Risk Mitigation: The surgery to implant and explant (if necessary) the device is risky, but the risks can be mitigated by requiring the device to be implanted by a specially trained surgeon.

Approval/Non-Approval Considerations: The probability that a patient will experience a benefit is relatively high (approximately 75%, if the clinical trial results hold for the intended use population). In this particular case, FDA does not have the option to limit the use of the device to only those patients who are most likely to experience a benefit because the covariates that determine the subgroup of patients who would definitely experience the benefit are unknown. In addition, this type of permanently implantable device poses significant risks and there is some remaining uncertainty associated with the trial results. However, for those patients in the target population who will experience a benefit, symptom relief and improvement in quality of life is impressive and some patients have expressed a willingness to tolerate the risks for the potential of obtaining such benefits. In addition, the risks, although substantial, could be somewhat mitigated through limiting the device use to clinicians with specialized training. Finally, the device treats a severe and chronic disease for which there are few, if any, alternative treatments. Therefore, FDA is likely to approve the device.

Example 2

A revolutionary device that replaces a patient's memory is developed to treat Alzheimer's disease, dementia, and other memory disorders. The device is designed to be permanently implanted and the patient must undergo a brain resection for the device to work properly. The device functions by downloading all of a patient's memories onto a computer chip. Once the device is implanted, any residual memory the patient retained is no longer accessible to the patient.

Benefits: A clinical trial of the device showed significant improvement in subjects who were in the early stages of dementia and minimal improvement in subjects who were in more advanced stages. Subjects who received implanted devices when the majority of their memory was intact experienced the greatest benefit and their overall quality of life was enhanced. Since the trial design accounted for two subgroups, subjects at the early stage of the disease and subjects at advanced stages of the disease, it can be inferred that, if the device is marketed, the patient population in early stages of the disease is likely to experience significant improvement, whereas the patient population in advanced stages is likely to experience only minimal improvement.

Risks: The surgery to implant the device is highly risky and is usually only performed by specially trained neurosurgeons. Even with these procedural restrictions, it is known from previous studies and literature that there is an 8% risk of mortality from the surgery alone. In addition, the clinical study showed that adverse events include partial paralysis, loss of vision, loss of motor skills, vertigo, and insomnia (predictive probability of 1%). Non-serious adverse events include temporary personality shifts, mood swings, and slurred speech (predictive probability shown in the study was 5%).

Additional Factors

Uncertainty: The number of subjects eligible and willing to enroll in the trial was small, but the data were robust and the trial was well-designed and conducted. The results of the trial are generalizable. The study showed that the subjects likely to experience the best results are the ones at early stages of memory loss.

Patient Tolerance for Risk and Perspective on Benefit: Because of the serious effect on patients' quality of life from diseases like Alzheimer's, other forms of dementia, and other conditions that are associated with severe memory loss, patients suffering from these diseases often have a very high tolerance for risk in exchange for a potential improvement of the disease symptoms, and for potentially alleviating the burden that they anticipate they will place on family members during the later stages of the disease. Patients who are at more advanced stages of their illness and experiencing more severe symptoms are less likely to benefit from the device. However, their tolerance for risk is difficult to assess due to their advanced disease.

Availability of Alternative Treatments or Diagnostics: There are currently no alternative treatments available.

Risk Mitigation: The risks associated with this device are great. The risks associated with implantation and explantation (if necessary) can be somewhat mitigated by limiting use to surgeons who have undergone special training, but the risks associated with personality changes cannot be mitigated or predicted. The risks can also be mitigated by indicating the device for patients at earlier stages of the disease who are more likely to benefit, and explaining in the labeling using data from the clinical trial that individuals experiencing more severe symptoms are less likely to benefit from the device.

Novel Technology Addressing Unmet Medical Need: There is no other similar technology available. It is possible that future improvements of the device may allow treatment of many other conditions that affect cognitive function. Moreover, there are no other treatments that provide the level of benefit that this device confers on the target population.

Approval/Non-Approval Considerations: The device will confer a substantial benefit for a defined and predictable subgroup of patients and a minimal benefit for another defined and predictable subgroup. Even though the clinical trial was small, the quality of the data was good and the resulting confidence intervals are narrow. The uncertainty about results is the usual uncertainty resulting from drawing inferences from a sample in the study to the population in the market. The risks associated with the device are great and can be partially mitigated by training the physicians who implant/explant (if necessary) the device. And, because patients experience the greatest benefit when the device is implanted earlier, they must expose themselves to the risks for a longer period of time in order to reap the greatest benefit; therefore, the patients who stand to benefit most also take on the greatest amount of risk. The sponsor provided data showing that many patients who suffer from memory disorders are willing to try novel approaches that have significant risk, in order to preserve their memories and quality of life. The fact that there are no alternative treatments for this condition is another important consideration. Even though the device-related risks are high, they are tolerable to the patients because of the benefits they reap. Furthermore, the risks are known and quantifiable. Therefore, this device, although risky, may be approvable based on all of these considerations. The decision as to whether or not to implant the device is a matter of patient preference (perhaps with the involvement of a legally authorized representative) and medical opinion. After full consideration of the likelihood of, and timeframe for, progression of disease and the predictability of future impairment without intervention, FDA is likely to approve the device as long as the labeling prominently addresses the 8% mortality rate and would provide through conditions of approval that only a very small group of highly trained physicians will be able to implant the device.

Example 3

A sponsor claims that its new in vitro diagnostic device (IVD), a serum-based test, can differentiate patients with BI-RADS 4 mammography results into two groups, namely patients with a low probability of having cancer for whom the physician may recommend

waiting a few months for additional testing, thus avoiding the morbidity associated with a biopsy, and all other BI-RADS 4 patients for whom a biopsy would be recommended as currently occurs under standard of care. The proposed intended use is:

> The in vitro diagnostic test measures 10 peptide analytes and yields a single qualitative result. The test is intended for females 40 years or older following mammography of a breast lesion with a BI-RADS of 4 result to aid physicians in the decision to recommend a breast biopsy.
>
> Negative test result (Low Risk): immediate biopsy is not recommended, wait a few months for further tests.
>
> Positive test result (High Risk): immediate biopsy is recommended.

Results from a clinical study in the intended use population (with biopsy results for all subjects) are:

		Biopsy		
		Malignancy	Benign	
Test	Positive	97	75	172
	Negative	3	225	228
		100	300	400

Sensitivity=97% (97/100) with 95% two-sided CI: 91.5% to 99.0%
Specificity=75% (225/300) with 95% two-sided CI: 69.8% to 79.6%
Prevalence=25% (100/400)
NPV=98.7% (225/228)
PPV=56.4% (97/172)

Benefits: The main benefit from use of the device is avoiding morbidity associated with an immediate biopsy for the 57% (228/400) of subjects whose test results indicate a low probability of having breast cancer.

Risks: Among test-negative subjects, the observed (from immediate biopsy) prevalence of cancer is 1.3% (3/228 = 1-NPV). The main risk from use of the device is in failing to biopsy some BI-RADS 4 patients who have biopsy-detectible breast cancer, thus delaying their diagnosis and treatment. Concerning this risk, the sponsor asserts that a clinically acceptable prevalence for cancer among non-biopsied BI-RADS 4 subjects is 2% or lower, because: a) BI-RADS 3 patients are usually counseled not to have an immediate biopsy (waiting a few months, instead, for further evaluation), and b) the expected prevalence of breast cancer among BI-RADS 3 patients is 2%. The benefit-risk odds measurable from the clinical study is 75 (225/3), and the observed risk for non-biopsied BI-RADS 4 subjects is lower than the expected risk in BI-RADS 3 patients.

Additional factors:

Uncertainty: There are the usual uncertainties tied to statistical confidence intervals surrounding observed study results.

The benefit-risk odds are not weighted for the clinical impact of avoiding biopsy morbidity compared to the clinical impact of missing a biopsy-detectible cancer. That is, the type of benefit is not necessarily commensurate with the type of risk.

There is no assurance that the clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results is equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results. Hence, there is uncertainty about the extent of the probable risk(s)/harm(s).

Test-negative BI-RADS 4 patients, who do not undergo biopsy, will receive no histopathological assessment of benign disease that is present.

Patient Tolerance for Risk and Perspective on Benefit: Patients' tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.

Availability of alternative treatments or diagnostics: There are no other in vitro diagnostic devices cleared or approved for the new test's intended use.

Risk mitigation: All women with negative test results will have follow-up visits for further evaluation and testing.

Approval/Non-Approval Considerations: The kinds and probabilities of benefits and risks are reasonably defined. A clinical practice reference for acceptable risk is put forth, to which the test's performance characteristics are aligned. Weighting of the different kinds of benefits versus risks is not directly addressed, and additional information is needed to establish whether the trade-offs are acceptable. Given that the benefits are uncertain and the risk (for a very small number of patients) could be substantial, FDA might determine that this device is not approvable, but would likely take it to an advisory panel prior to making a decision.

Example 4 – *De Novo*

A new standalone therapeutic device is developed to provide enhanced stability for more invasive, higher-risk implanted devices, which could otherwise affix themselves without support. The device can be used to support a primary device at the time of implantation, or can be added to an already-implanted device that is malfunctioning.

The device is studied in a prospective, multi-center, single-arm clinical study of over 200 subjects. The primary endpoint for the trial is the magnitude of the benefit, i.e., the trial is designed to measure how well the device prevents movement and malfunction of the

primary device as compared to when it is implanted without the benefit of enhanced stability.

The results of the pivotal clinical trial revealed the following:

Benefits: Through one year of follow-up, no subject experienced device movement and only two subjects experienced complications related to the device malfunctioning. This is a significant improvement over primary device performance when implanted alone and gives a very high predictive probability that a patient receiving the device will not experience device movement.

Risks: Through one year of follow-up, there were no fractures of any primary device and only a handful of malfunctions of the support system, none of which lead to serious adverse events. The risks of the support system are not high because its potential failure is unlikely to lead to an overall failure of the primary device.

Even though all implanted devices that require a surgical procedure carry with them their own set of risks (e.g., 1% chance of death from surgery), this device is implanted along with the primary device and consequently does not require an additional surgery to implant. Or, if it is placed to enhance the performance of a malfunctioning primary device, it is put in during a surgery that would have otherwise been performed to fix the malfunctioning primary device. Therefore, the data suggest that adding the support device during surgery does not appear to increase the risk to the patient.

FDA determined that the support device poses low-to-moderate risk, the risks associated with its use are well-defined and understood, and the risks can be mitigated by general and special controls, which would provide reasonable assurance of the safety and effectiveness of the device. As a consequence, the support device is appropriate for the *de novo* pathway.

Additional Factors

Uncertainty: The results of the pivotal clinical trial are limited to one-year of follow-up. For a permanent, implantable device, longer follow-up times can reduce uncertainty regarding the long-term safety and effectiveness of the device.

Patient Tolerance for Risk and Perspective on Benefit: Patients who receive the support device either are already undergoing a surgery and implantation of the primary device or have had complications with an existing device that the support device can be used to correct non-surgically. The results of the pivotal clinical trial indicate that future patients stand to benefit from greater stability of the primary device as a result of the use of the support device; therefore, most patients feel that the benefits of the device greatly outweigh the risks.

Risk Mitigation: For this *de novo*, FDA established special controls to mitigate the risks associated with the device and make it appropriate to be classified under Class II. For

this device, FDA required demonstration of biocompatibility, sterility, safety and effectiveness data (including clinical performance data, durability, compatibility, migration, resistance, corrosion resistance, and delivery and deployment); evaluation of the MR-compatibility of the device; validation of electromagnetic compatibility of device; restriction of the device to prescription use; and clear instructions in the labeling regarding the safe and effective use of the device. Since this device does not require an additional surgery to be implanted, the surgical risk is not an issue.

Novel Technology Addressing Unmet Medical Need: This device is the first system that can access and repair a failed or problematic primary device, providing surgeons with a minimally-invasive option for re-affixing devices that are not properly positioned or that have migrated, or those that are at risk of such complications.

Approval/Non-Approval Considerations: The clinical trial results provide assurance of at least one year of clinical effectiveness of the device. Furthermore, it is important to consider that the device merely supports and supplements the effectiveness of another device and its failure would not significantly affect the performance of the primary device. The device does not pose risks that would rise to the level of a Class III device. Any safety concerns regarding device failure can be readily addressed through special controls related to appropriate testing and labeling. Given the device benefits, the ability to mitigate risks through special controls, and the fact that this device is not life-supporting or life-sustaining, FDA would be likely to grant a *de novo* petition to classify this device into Class II.

5.2 Examples Based on Actual FDA Benefit-Risk Determinations

- A device to treat a very rare cancer was tested in a clinical trial that demonstrated with some uncertainty that the device performed as well as standard treatment, but not better. However, use of the device did not have harmful effects as severe as those associated with the standard anti-cancer treatment, and neither treatment was curative. The cancer was rapidly progressive and terminal, so the subjects had very little time to live after they were diagnosed. FDA approved this device because it gave patients access to a treatment that appeared to be equivalent to the standard of care (with some uncertainty remaining), but that did not cause the same severity of side effects.
- A permanently implanted cardiovascular monitoring device is intended to diagnose heart failure. The device is studied and the study shows that its use reduces the number of days the subject is hospitalized for heart failure by about three. However, the implantation procedure for the device requires that the patient be hospitalized for two days. There are similar devices on the market that provide a similar level of benefit as this device that do not require an implantation procedure. FDA determined that the benefit of saving one day of hospitalization does not outweigh the risk of

complication from the surgery needed to implant the device and found the device to be not approvable.

- A permanent birth control device can be placed in a woman's reproductive system through the vagina using a specialized delivery catheter. This device is a permanent implant and is not intended to be removed. Explantation of the device would require surgery. Clinical data show that the device is effective in preventing pregnancy over a two-year period in women and the safety data show a low incidence of adverse clinical events. However, study results also show that there are several cases where the physician had difficulty correctly placing the device. In addition, the device was noted to be fractured on a follow-up x-ray in a few study subjects. Given the uncertainty of the long-term impact of the device, the possibility of device fracture (which was not predicted in any of the bench and animal testing), and the safety and effectiveness of alternative therapies, FDA deemed the device to be not approvable for the intended patient population.
- An implanted device offers a unique design feature in comparison to the standard of care used to treat similar conditions. While the current standard of care works very well, it has limitations associated with hindering the mobility of the patient; in contrast, the novel implanted device does not affect patient mobility. Based upon the effectiveness data from the clinical study, the device demonstrates that it has significantly improved functional outcomes in comparison to the current standardcare. However, from a safety perspective, the device did present different adverse events that were different from those of the current standard of care. The risks can be appropriately mitigated with training of surgical professionals as well as through proper labeling. In the event the implant was to fail over time, the clinician could also resort to the current standard of care. In this situation, despite the different adverse events, the probable benefits outweighed the risks and FDA approved the device.

Appendix A

Intersection of this Guidance with ISO 14971

ISO 14971 provides medical device manufacturers with a framework to systematically manage the risks to people, property and the environment associated with the use of medical devices. Specifically, the standard describes a process through which the medical device manufacturer can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of those controls throughout the product's lifecycle.[18] Implementing this standard requires the user to make decisions on the acceptability of individual risks, and overall residual risk for a medical device throughout its lifecycle.

ISO 14971 is an FDA-recognized standard, and assuring conformity with this standard may help device manufacturers meet the design validation requirements specified in the Design Controls section of Part 820 of FDA's regulations governing quality systems.[19] Part of the premarket review process is an evaluation (direct and/or indirect) of a medical device manufacturer's risk management decisions as they pertain to the requirements to market a device in the United States.[20] The medical device manufacturer's risk management decisions that are directly and/or indirectly evaluated include those pertaining to risk estimation, risk evaluation, risk acceptability, risk control measures, and overall residual risk. Good documentation of risk management decisions by manufacturers helps to streamline the premarket review process for both FDA and manufacturers. At some point, after the manufacturer has completed its risk management activities associated with the design phase of product development, the premarket submission process with FDA is initiated, and the benefit-risk assessment takes on a different shape, which is the primary focus of this guidance. This guidance discusses the considerations FDA makes when assessing the benefit-risk profile of a device that has been designed to deliver the most benefit for the least amount of risk and to provide a reasonable assurance of safety and effectiveness.

[18] ANSI/AAMI/ISO 14791:2007 *Medical devices – Application of risk management to medical devices*, p xi.

[19] Design controls are described in 21 CFR 820.30.

[20] Additionally, the manufacturer can engage FDA during the pre-submission stage regarding their proposed risk management decisions related to clinical study design, biocompatibility testing, preclinical animal testing, bench testing, etc, and receive preliminary feedback on the adequacy of the decisions probability for generating information that will establish whether the device meets the requirements to be marketed in the United States.

Appendix B

Worksheet for Benefit-Risk Determinations

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	
Availability of alternative treatments or diagnostics	- What other therapies are available for this condition? - How effective are the alternative treatments? o How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? o How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments?	
Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**

Conclusions Do the probable benefits outweigh the probable risks?

Appendix C

Worksheets for Hypothetical Examples

Worksheet for Hypothetical Example 1

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Reduction of symptoms. Improved mobility. Longer life expectancy.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Substantial reduction of the patient's symptoms.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	There is 75% probability (predictive probability) that a patient will experience the benefit once the device is on the market. The patients who experience the benefit value it substantially. Patients also value the potential to achieve the benefit.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Follow-up only to one year. Patients with improved mobility tend to have higher life expectancy. Patients value the benefit, even if it were only for one year.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Known risks associated with permanent, implantable devices. Device fracture, mechanical failure or adverse biological response. If necessary, it would be difficult to remove the device.
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	N/A
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	Surgery is non-routine and carries high risks.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	Low. 1% chance of death from surgery Less than 3% chance of occurrence of a harmful event after implantation. Less than 3% chance of device fracture, mechanical failure, and adverse biological response.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	The device-related adverse events last as long as the device remains implanted, but can be reversed by removing the device.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	Clinical study was well designed and conducted, but the follow up was only 1 year.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Questionable – there were missing data.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	There were missing data, but sensitivity analyses were conducted and the results are relatively robust.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The device is more appropriate for use by surgeons with specialized training.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted for a potential benefit because there are no other treatment options and their symptoms are severe.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life and mobility.
• Disease chronicity	- Is the disease chronic? - How long do to patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and incurable.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because they failed all other treatment options and the treatment and potentially improve their overall quality of life.
Availability of alternative treatments or diagnostics	- What other therapies are available for this condition? - How effective are the alternative treatments? o How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? o How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments?	There are alternatives available, but patients receiving this device have already failed alternative treatments.
Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Limit use to surgeons who have completed specialized training.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	There are similar devices in the market for different indications and that enhances the inference about long term adverse event rates, such as device fractures. Longer term device performance, such as duration of the benefit and long term adverse event rates (beyond 1 year) could be evaluated in the postmarket setting. As long as the device is implanted by specially trained surgeons, as required in the labeling, "real world" performance should be similar to premarket performance. Effectiveness of training could be assessed (and improved) as postmarket information becomes available.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	N/A
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
75% chance of improved patient mobility and quality of life.	Permanently implantable device that requires surgery. 25% chance that patient will experience no benefit. Serious adverse events include death, device fracture, mechanical failure or an adverse biological response.	Patients are willing to tolerate the risks because they have a high probability of receiving a substantial benefit. Risks can be mitigated by limiting to surgeons who have received specialized training.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. There are no alternative treatments available for the intended population and the device treats a severe condition. Patients have a 75% chance of experiencing a significant improvement in quality of life. Patients are willing to take the risk even though it is uncertain that they will achieve the benefit, because if they benefit, the benefit is great. These patients have failed alternative treatments, so they are not foregoing an effective treatment for an uncertain benefit. Finally, the risks associated with this device, although serious, are not higher than those for similar treatments.

Worksheet for Hypothetical Example 2

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Memory preservation. Improvement of quality of life. Patients place an enormous value on the benefit.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Large for patients in early stages of the disease; smaller for patients in later stages of the disease.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	The trial was designed to study two subgroups, subjects at early stages of the disease and subjects at late stages of the disease. It can be inferred that benefits will be higher for patients in early stages of the disease and lower for patients in later stages of the disease.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Benefits should last as long as the device remains implanted.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Partial paralysis, loss of vision, loss of motor skills, vertigo, and insomnia
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Personality shifts, mood swings, and slurred speech
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	8% risk of mortality from surgery alone, even when done by highly trained neurosurgeon.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	High – 8% risk of death from surgery; 1% chance of a serious adverse event; and 5% chance of a non-serious adverse event. When considered together, these present a high risk. Patients in the early stages of the disease will have higher risks due to longer permanence of the device. However, those patients experience the higher benefit.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Permanent for death and serious adverse events; possible reversal for non-serious adverse events.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	Good. The study was small, but the confidence intervals for the endpoints were reasonably narrow.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Very good. Almost all subjects retuned for the follow up visits.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	Very robust. Subgroups for which the device worked the best were identifiable from the results. A subgroup analysis was pre-planned during the trial design.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	Generalizable because we know patients at an earlier stage of the disease respond better.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted because there are no other treatment options and their symptoms are extremely severe. Patients with this kind of disease are often willing to risk death in order to improve their prognosis.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life and memories.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and incurable.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because they have no other treatment options and it could substantially improve their quality of life.
Availability of alternative treatments or diagnostics	- What other therapies are available for this condition? - How effective are the alternative treatments? o How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? o How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments?	There are no alternative treatments available.
Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Provide training for surgeons. Note in the labeling that this device is most effective for patients in the early stages of the disease.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	The device is "first-of-a-kind" and there are no similar devices on the market. As a consequence, there is no prior information on other devices that could be used for inferences on the performance of this device. Therefore, longer term performance, including maintenance of effectiveness, long term adverse events, and device duration, should be assessed in the postmarket setting. A postmarket study will probably be recommended.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	Breakthrough technology. It is expected that future improvements will reduce the risks associated with the current version of the device.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
High chance of benefit for patients in the early stages of the disease. Benefits include improved memory and quality of life. Benefits are extremely valued by patients and their families.	Permanently implantable device that requires surgery. 8% risk of death from surgery; 1% risk of serious adverse events; 5% risk of non-serious adverse events. For younger patients, the risk is higher because they will live with the device for a longer period of time.	Patients are willing to tolerate the risks because they receive a substantial benefit if the device works and there are no alternative treatments available. Risks can be mitigated by providing training and limitations in the labeling.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. The benefits outweigh the risks for some patients and FDA would like to provide the opportunity for those patients who would like to take the risk to obtain the benefit. There are no alternative treatments available, the device treats a severe condition, and patients experience a significant improvement in quality of life and memory. Patients are willing to take the risk even though there is a high risk of death because the benefits that they receive are so significant and life-changing. The risks associated with this device are high; however, they can be mitigated through training and limitations in the labeling. Also, this treatment is novel and there are no other similar alternatives on the market. Therefore, even though the risks are high, due to the substantial benefit achieved and the mitigations available, the benefits outweigh the risks in this case. Finally, it is expected that the technology and surgical technique will improve with further iterations and the adverse event rates will decrease.

Worksheet for Hypothetical Example 3

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Avoidance of morbidity from breast biopsy procedures.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Avoiding inconvenience, pain and potential complications associated with breast biopsy procedure.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	Approximately 57% (228/400), for the intended use population.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Variable. Might be long term (no biopsy needed, lifelong), or might last only until follow-up exam prompts a biopsy.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Some patients with biopsy-detectible breast cancer will not have the cancer detected/treated until follow-up exam (assuming that follow-up exam occurs).
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Failure to characterize non-malignant disease that would have been revealed by biopsy.
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	N/A
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	For the most serious harmful events, approximately 1% (3/400) in the intended use population. Slightly more than 1% (3/228) among test-negative subjects.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Potentially lifelong, if treatable/curable breast cancer is not detected.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	See above.

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	There is no assurance that the clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results is equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results. Hence, there is uncertainty about the extent of the probable risk(s)/harm(s).
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Good.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	Reasonably robust.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The relative value that patients place on avoiding biopsy morbidity, compared to the clinical impact of missing a biopsy-detectible cancer, is not known.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients' tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic, potentially incurable and, in some cases, fatal.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	Patients weigh differently the value of the benefits and the risks. Information about patients who elect not to have biopsies after receiving a BI-RADS 3 result might be helpful.
Availability of alternative treatments or diagnostics	- What other therapies are available for this condition? - How effective are the alternative treatments? o How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? o How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments?	None, for the proposed intended use.
Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Follow-up evaluation of patients might limit harms caused by erroneous test results. A plan is needed to handle circumstances with serially "BI-RADS 4" mammograms and negative test results.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	If it is determined that the device is approvable, then additional (postmarket) information that refines the understanding of the uncertainties and patient tolerance for risk and perspective on benefit might be in order.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	The technology is not novel.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
The benefit in this case is to avoid biopsy-related morbidity in a substantial fraction of BI-RADS 4 patients.	Approximately 1% of tested patients (slightly more than 1% of test-negative patients) will have delay in detection/treatment of breast cancer.	In current practice, approximately 2% of patients with abnormal (i.e., BI-RADS 3) mammography results have breast cancer that (because of deferred biopsy) might not be detected until follow-up exam.

Conclusions Do the probable benefits outweigh the probable risks?
The kinds and probabilities of benefit and risk are reasonably defined. A clinical practice reference for acceptable risk is put forth, and the test's performance characteristics are aligned with that clinical practice reference. Weighting of the different kinds of benefit versus risk is not directly addressed. Additional information is needed to establish the overall acceptability of trade-offs between the different kinds of benefit and risk. Given that the benefits are uncertain and the downside risk (for a very small number of patients) could be substantial, this device could be not approvable, but FDA would be likely to take it to panel prior to making a decision.

Worksheet for Hypothetical Example 4

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Support the stability of the primary device (movement prevention) and reduction in primary device complications.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	A very high probability (almost 100%) of reduction of primary device migration and substantial reduction of primary device complications.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	A very high probability (almost 100%) of prevention of migration. A very high probability (almost 100%) of prevention of complications.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Data up to one year of follow-up. However, the benefit is expected to last for as long as the device remains implanted.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	None.
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Complications related to movement.
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	None.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	Very low.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Harmful events are reversible.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	The trial was designed to study an investigational system that included this device. The level of data collected was very good for a Class II device.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Very good.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	The results are robust for up to one year of follow-up. Subjects will receive continual follow-up through five years, but only the one year data were required to evaluate the device.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The device has been evaluated for use with all commercially-available primary devices in the U.S. Use with other devices used only outside the U.S. has not been evaluated.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted because they are already undergoing or have undergone surgery and the device has an excellent record of preventing migration and complications, which can be present without the use of the device.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	In this case, because the device is lower-risk, the disease does not have to be as severe in order to achieve a favorable benefit-risk ratio.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and treatable with either open surgery or minimally-invasive device placement. This device offers an additional method of improved treatment for those who use the minimally-invasive procedure.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because it provides for a minimally-invasive solution to a problem that would otherwise have to be addressed by surgery, and the clinical trial results show that the device works, even if the follow-up is only one year in duration.
Availability of alternative treatments or diagnostics	- What other therapies are available for this condition? - How effective are the alternative treatments? o How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? o How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments?	There are no alternative minimally-invasive treatments available to provide support for a primary device that could migrate or present complications. This device is first-of-a-kind.
Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Special controls, which include demonstration of biocompatibility, sterility, safety and effectiveness (including durability, compatibility, migration, resistance, corrosion resistance, and delivery and deployment); evaluation of the MR-compatibility of the device; validation of electromagnetic compatibility of device; restriction of the device to prescription use; and clear instructions in the labeling regarding the safe and effective use of the device.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	Patients were followed for one year during the clinical trial. Long term performance of the device may be assessed in the postmarket setting.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	This is a first-of-a-kind device.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
Highly probable improvement in treatment of failed or failing underlying device. How treatment will affect patient outcomes is highly variable on other cofactors.	Permanently implantable device that requires minimally-invasive surgery. Serious adverse events include death, device fracture, mechanical failure or an adverse biological response.	Patients are willing to tolerate the risks because they receive a substantial benefit.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. The device provides substantial benefits and low risks. Moreover, given the ability to mitigate risks through special controls and the fact that this device is not life-supporting or life-sustaining, FDA would be likely to grant a *de novo* petition to classify this device into Class II. For lower-risk devices, less evidence may be necessary to tip the benefit-risk balance in favor of approval. In this case, even though the follow-up data are only one year in duration, the moderate-risk nature of the device, its non-invasive application method and the fact that the risks can be mitigated through special controls could lead to a *de novo* classification under Class II.