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

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

Contains Nonbinding Recommendations

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

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Guidance for Industry and Food and Drug Administration Staff

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This document supersedes "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" issued August 24, 2016.

For questions about this document concerning devices regulated by CDRH, contact the Office of Policy at 301-796-5441. For questions about this document concerning CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

Identify all comments with the docket number FDA-2011-D-0577. Comments may not be acted upon by the Agency until the document is next revised or updated.

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

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Guidance for Industry and Food and Drug Administration Staff

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

I. Introduction

FDA 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.

II. 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 requests. 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-Submission, and Investigational Device Exemption (IDE) phases as well as in assembling and assessing PMA applications or De Novo requests. 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.

III. Background

A. 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 sponsors 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 indications for use, and if the data analysis demonstrates that the probable[3] benefits of the

[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.

[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.

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 or if a person believes their device is appropriate for classification into Class I or Class II and determines, based on currently available information, there is no legally marketed predicate device, may be eligible to submit a De Novo request 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 requests 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 requests 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.

B. 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 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.

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[4] Equally important is FDA's determination of effectiveness. See footnote 1.
[5] See 21 CFR Part 820.
[6] See FDA guidance "De Novo Classification Process (Evaluation of Automatic Class III Designation)" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-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.

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]

C. 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 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 in 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

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

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

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.

IV. 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.

A. Assessment of the Benefits of Devices

Extent of the probable benefit(s): FDA assesses information provided in a PMA application or De Novo request 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.

- 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 participants' 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 participants. 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 participants may raise different considerations than does a small benefit experienced by a large proportion of participants. 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 participants.

- 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.

B. 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]**

    - **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

[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, 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.

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

C. 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.[15] 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 masking investigators and participants. Furthermore, the

[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.

[15] See FDA guidance "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de.

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.

Patient-centric assessments and patient-reported outcomes (PROs) – We recognize that patient-centric metrics such as validated health-related quality of life measures and other Patient-Reported Outcomes (PROs) (e.g., scales or scores indicating patient's experience of pain or function) can be helpful for patients and health care practitioners when discussing treatment options and decisions, 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.

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 perspectives – 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 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 perspectives on benefits and risks 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. Rather than one-sided evaluations, patient preference assessments should take into account both the patient's willingness and unwillingness to use a device or tolerate risk in exchange for probable benefit, and/or evaluate how patients view trade-offs between benefits and risks of various treatment options.

Patient preference studies can provide insight on how patients value benefits in comparison to risk. Patient preference information is defined as "the qualitative or quantitative assessment of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions."[16] FDA may also consider the preferences of care-partners (e.g., parents) and healthcare professionals to the extent they are relevant in the benefit-risk assessments for a particular device subject to review in a PMA, HDE application, or De Novo request.

[16] Adapted from: *Medical Device Innovation Consortium*. A framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology. 2015. (http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Proof5_Web.pdf).

For more information regarding patient preference studies, consult FDA Guidance: Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.[17]

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 considering developing such data to have early interaction with the appropriate FDA review division.[18]

When assessing such data in a PMA application or De Novo request, 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.[19]

Patient preference information may demonstrate that most, if not all, of the patient population with a specific disease or condition consider the benefit-risk tradeoffs acceptable. Different factors can influence patient perspective on benefits and risks, 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.

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

[17] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.
[18] See FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[19] For the purposes of this guidance "unreasonable risk" refers to 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.[20] 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.[21]

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

[20] 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.

[21] See FDA Guidance "The Least Burdensome Provisions: Concept and Principles: Guidance for Industry and FDA Staff" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

meaningful benefit than existing therapy, posing less risk than existing therapy, or providing a treatment or means of diagnosis where no alternative is available.

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 sponsor 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.

V. 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.

A. 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 participants 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 Perspectives: The sponsor provided data showing that most 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 as a trade-off for 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 novel 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 serious adverse events 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 Perspectives: 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, as well as the progressive nature of Alzheimer's, some patients with these conditions, and their care-partners, often have a very high tolerance for risk, even a risk of serious adverse events, in exchange for a probable improvement of the disease symptoms, and for alleviating the burden that they anticipate they will place on family members during the later stages of the disease. Other patients, such as those at older ages, may be less willing to tolerate such risks.

Patients who are at more advanced stages of their illness and experiencing more severe symptoms are less likely to benefit from the device. Furthermore, 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 some patients because of the probable benefits they offer, and the progressive nature of the untreated condition. Furthermore, the risks are known and quantifiable. Therefore, this device, although it poses substantial risk, may be approvable based on all of these considerations taken in sum. The decision as to whether or not to implant the device in a particular patient is a matter of patient preference (perhaps with the involvement of a legally authorized representative) and medical judgment. 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% serious adverse event rate and would provide through conditions of approval that only 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 Perspectives: 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 failure of the support system are not high because even if the support system fails, it 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 Perspectives: 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 stated they would accept the probable benefits of the device given the probable 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; limiting 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 request to classify this device into Class II.

B. 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 participants 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 standard of care. 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.[22] 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.[23] 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.[24] 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.

[22] ANSI/AAMI/ISO 14971:2007 *Medical devices – Application of risk management to medical devices*, p xi.
[23] Design controls are described in 21 CFR 820.30.
[24] Additionally, the manufacturer can engage FDA during the pre-submission stage regarding their proposed risk management decisions related to clinical study design, biocompatibility testing, non-clinical 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 Assessment

Instructions for FDA Staff: You should make your recommendation regarding the benefit-risk assessment based on the totality of the evidence. The benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the benefits outweigh the risks does not mean that the application satisfies other applicable requirements for a PMA application or a De Novo request.

The following questions are intended as a sequential method to help weigh various factors as part of the benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a benefit-risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant. This checklist should be used when non-clinical and/or clinical evidence has been submitted in the form of valid scientific evidence.

Consider questions 1-8 for the proposed Indications for Use, until you reach a recommendation either that the benefits outweigh the risks or to move to question 9, which prompts you to consider a modified Indications for Use. When considering an acceptable, modified Indications for Use, interact with the sponsor to reach agreement on a modified Indications for Use. However, as reflected under question 1, if the evidence does not support a finding of benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of benefit for the proposed Indications for Use and agreement on a modified Indications for Use is not achievable or applicable, the application would not be approvable or grantable.

Assessment of Benefit

1. **Is there any evidence of clinical benefit?**

   Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
   ☐ A favorable change in at least 1 clinical assessment that meets a predetermined performance goal
   ☐ A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference
   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition
   ☐ A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life
   ☐ A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
   ☐ A favorable clinical performance characteristic (e.g., sensitivity/PPA,[25] specificity/NPA[26], etc.) for screening, diagnosis, prognosis, monitoring or treatment selection
   ☐ Acceptable performance characteristics for analytical validation of the device
   ☐ Other(s):
   ☐ None

Q1: Is there any evidence of clinical benefit?

☐ YES → Continue to Question 2
☐ NO → Move to Question 9

[25] PPA: Positive Percent Agreement
[26] NPA: Negative Percent Agreement

2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility, as applicable). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- ☐ Inconsistent or conflicting results between studies
- ☐ Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s))
- ☐ A significantly underpowered study with statistical insignificance in outcome measure(s)
- ☐ High subject or specimen loss-to-follow-up at critical assessment point(s)
- ☐ Large amount of missing data at critical assessment time(s) +/- imputation
- ☐ Significant number of major protocol deviations
- ☐ Impact of confounding interventions or physiological factors
- ☐ Inconsistent user experience or user experience not representative of likely real-world user
- ☐ Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- ☐ Surrogate endpoint has not been demonstrated to correlate with a clinical outcome
- ☐ Real-World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- ☐ Inspectional findings
- ☐ Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- ☐ Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- ☐ Imperfect comparator method used to calculate performance characteristics
- ☐ Other(s):
- ☐ None

Q2: What is the extent of uncertainty for the benefits?

☐ Low → Continue to Question 3
☐ Med → Continue to Question 3
☐ High → Continue to Question 3

Summary of the Assessment of Benefit

For the Proposed Indications for Use:

Considering responses to Q1 and Q2, enter summary of the Assessment of Benefit for the proposed Indications for Use. Include a description of your assessment of the extent of benefit, considering the type, magnitude, and probability of benefit(s); and the duration of effects. Include a description of the impact of uncertainty on your Assessment of Benefit. If no benefit is identified, briefly explain why.

Assessment of Risk

3. **Are known/probable risks more than minimal?**
   Select any of the following elements that demonstrate sources of known/probable risks that are more than minimal, then answer the question in the box below.

   ☐ Adverse events (AEs) or outcomes related to the device itself
   ☐ AEs or outcomes related to the use of the device or procedure to use the device
   ☐ AEs or outcomes related to anesthesia or sedation to use the device
   ☐ AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
   ☐ AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
   ☐ False positive/false negative/failed to provide a result for diagnostics
   ☐ Treatment or diagnostic intended to be used as a standalone rather than an adjunctive use
   ☐ Other(s):
   ☐ None

   Q3: Are known/probable risks more than minimal?

   ☐ YES → Continue to Question 4
   ☐ NO → Continue to Question 4

4. **What is the extent of uncertainty for the risks?**
   Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks. Select any of the following that demonstrate sources of uncertainty for the risks, and then answer the question in the box below.

   ☐ Insufficient patient numbers to detect serious events or false positives/false negatives
   ☐ Insufficient duration of follow-up to detect delayed/late events
   ☐ Lack of data on repeated exposure to the device/use
   ☐ Inconsistent or conflicting results between studies
   ☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
   ☐ Poor or inconsistent adverse event definitions and documentation
   ☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities

☐ High subject loss-to-follow-up at critical assessment point(s)
☐ Large amount of missing data at critical assessment time(s) +/- imputation
☐ Significant number of major protocol deviations
☐ Inconsistent user experience or user experience not representative of likely real-world user
☐ Concerns related to performance characteristics (e.g., sensitivity/PPA, specificity/NPA)
☐ Imperfect comparator method used to calculate performance characteristics
☐ Other(s):
☐ None

Q4: What is the extent of uncertainty for the risks?

☐ Low → Continue to Question 5
☐ Med → Continue to Question 5
☐ High → Continue to Question 5

Summary of the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use:
Enter summary of the Assessment of Risk for the proposed Indications for Use. Include a description of your assessment of the extent of risk, considering the severity, types, number and rates of harmful events associated with use of the device; probability of a harmful event; duration of harmful events; and risk from false-positive or false-negative results for diagnostics. Include a description of the impact of uncertainty on your Assessment of Risk.

Assessment of Benefit-Risk

Instructions for FDA staff: Provide a recommendation based on the totality of the evidence. As noted above, the benefit-risk assessment is part of the decision regarding whether to approve a PMA application or grant a De Novo request but is not an assessment of all applicable requirements.

To approve a PMA application or grant a De Novo request, FDA must find, among other things, that there is a reasonable assurance of safety and effectiveness for the device. FDA determines whether there is a reasonable assurance of safety and effectiveness by weighing any benefit to health from the use of the device against any risk of injury or illness for such use, among other relevant factors. To grant a De Novo request, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

If you answer "yes" for any Q5-8, explain your rationale for how the benefits outweigh the risks. You should also consider and recommend actions that would enhance the benefit-risk profile of the device, such as modifications to the proposed labeling, which may include additional appropriate warnings and precautions, instructions for use, or presentation of data, to help ensure the product labeling is transparent with respect to the benefits and risks.

If you answer "unable to conclude" for Q5-8, please provide the information that you believe would be needed to support a determination that the benefits outweigh the risks for the Indications for Use under consideration in the summary text boxes and also proceed to Q9.

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use:
Summarize the clinical benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risk(s). Include a description of how uncertainty regarding Benefit(s) and Risk(s) affects your assessment.

6. **Do the Benefits outweigh the Risks, when taking into account the following additional considerations?** *Select relevant considerations, and then answer the question in the box below.*

☐ Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks
☐ Available patient preference information (PPI) showing patient willingness or unwillingness to

accept the risks in exchange for the benefits. In circumstances where it is not feasible to obtain PPI (e.g., some pediatric or impaired patient population), care-partner perspectives may be considered.

☐ Understanding of care-partner perspectives on the benefits and risks for a device intended to provide benefit to the care-partner (e.g., ease of care)

☐ Understanding of healthcare professional perspectives on the benefits and risks for a device intended to provide benefit to the healthcare professional (e.g., reduction of radiation exposure)

☐ Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions

☐ Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions

☐ Understanding that the device represents novel technology for which the current device technology is different

☐ Ability to manage or diagnose the condition and consideration of natural history of disease progression in the absence of the intervention or diagnostic information with the device under review

☐ No legally marketed alternative medical product or medical intervention exists, or the device offers advantages over existing alternatives

☐ The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions

☐ The device avoids serious harms associated with currently available therapies for the disease or condition

☐ The adverse events associated with use of the device are reversible

☐ Type of intervention required to address the harmful event (e.g., medication, surgery)

☐ The study is a first of a kind (robustness of the analysis)

☐ Tipping point and/or worst-case sensitivity analysis continuing to show clinical benefit

☐ Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)

☐ Other(s):

☐ None

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination

☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of risk mitigation measures is appropriate – Continue to Q7

Summary of the Assessment of Benefit-Risk, taking into account additional relevant considerations

For the Proposed Indications for Use:

Summarize the clinical benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risk(s). Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding Benefit(s) and Risk(s) affects your assessment. Include a description of how patient

perspectives affected your assessment.

7. **Can the risks be mitigated, so that Benefits outweigh the Risks? Consider if the Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the benefit-risk profile of the device.** *Select relevant considerations, and then answer the question in the box below.*

☐ Additional descriptions of known and probable benefits and risks in physician and patient labeling including appropriate Contraindications, Warnings, and Precautions and description of the clinical events
☐ Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐ Labeling the device "Prescription Only"
Training:
☐ Limitation to caregivers with certain qualifications or clinical training
☐ Limit to users with a minimum set of qualifications and/or training
☐ Physician/user training program
Other:
☐ Device tracking
☐ Other(s):
☐ None

Q7: Can the risks be mitigated, so that Benefits outweigh the Risks?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of postmarket actions is appropriate – Continue to Q8

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use:
Summarize the clinical benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

8. **Do the Benefits outweigh the Risks considering the use of postmarket actions?** *Select appropriate postmarket action(s), and then answer the question in the box below.*

☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket space (e.g., post-approval study, postmarket surveillance)
☐ Collection of additional and/or confirmatory clinical data in the postmarket space (e.g., post-approval study, postmarket surveillance)

If either non-clinical or clinical performance data collections in the postmarket space are checked, consider:

☐ The feasibility of postmarket data collection and likelihood that postmarket data collection will be completed within a reasonable timeframe

☐ Whether it would be appropriate for labeling to include description of postmarket data collection and its purpose

☐ Other(s):

☐ None

Q8: Do the Benefits outweigh the Risks considering the use of postmarket actions?

☐ Yes – The benefits outweigh the risks

☐ Unable to conclude that benefits outweigh the risks – Continue to Q9

Summary of the Assessment of Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use:

Summarize the benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding benefit(s) and risks affects your assessment. Include a description of how patient perspectives affected your assessment.

Q9: Is there any evidence of clinical benefit for a modified Indications for Use?

☐ Yes → Return to Q1 and proceed with modified Indications for Use

☐ No → Do not approve/grant

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: PMA/De Novo Number: ☐ Interim ☐ Final	**Proposed Indications for Use**
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☐ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the Benefits?	☐ High ☐ Med ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	☐ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the risks?	☐ High ☐ Med ☐Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☐ NO → Do not approve/grant

Appendix C

Worksheets for Hypothetical Examples

Worksheet for Hypothetical Example 1

Instructions for FDA staff: You should make your recommendation regarding the benefit-risk assessment based on the totality of the evidence. The benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the benefits outweigh the probable risks does not mean that the application satisfies other applicable requirements for a PMA application or a De Novo request.

The following questions are intended as a sequential method to help weigh various factors as part of the benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a benefit-risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant. This checklist should be used when non-clinical and/or clinical evidence has been submitted in the form of valid scientific evidence.

Consider questions 1-8 for the proposed Indications for Use, until you reach a recommendation either that the benefits outweigh the risks or to move to question 9, which prompts you to consider a modified Indications for Use. When considering an acceptable, modified Indications for Use, interact with the sponsor to reach agreement on a modified Indications for Use. However, as reflected under question 1, if the evidence does not support a finding of benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of benefit for the proposed Indications for Use and agreement on a modified Indications for Use is not achievable or applicable, the application would not be approvable or grantable.

Assessment of Benefit

1. Is there any evidence of clinical benefit?

Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

- ☒ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
- ☐ A favorable change in at least 1 clinical assessment that meets a predetermined performance goal
- ☐ A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference
- ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition
- ☒ A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life

Other:

- ☐ A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
- ☐ A favorable clinical performance characteristic (e.g., sensitivity/PPA,[27] specificity/NPA[28], etc.) for screening, diagnosis, prognosis, monitoring or treatment selection
- ☐ Acceptable performance characteristics for analytical validation of the device
- ☒ Other(s): Improved mobility. Longer life expectancy.
- ☐ None

Q1: Is there any evidence of clinical benefit?

☒ YES → Continue to Question 2
☐ NO → Move to Question 9

[27] PPA: Positive Percent Agreement
[28] NPA: Negative Percent Agreement

2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility, as applicable). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- ☐ Inconsistent or conflicting results between studies
- ☐ Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s))
- ☐ A significantly underpowered study with statistical insignificance in outcome measure(s)
- ☐ High subject or specimen loss-to-follow-up at critical assessment point(s)
- ☒ Large amount of missing data at critical assessment time(s) +/- imputation
- ☐ Significant number of major protocol deviations
- ☐ Impact of confounding interventions or physiological factors
- ☐ Inconsistent user experience or user experience not representative of likely real-world user
- ☐ Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- ☐ Surrogate endpoint has not yet been demonstrated to correlate with a clinical outcome
- ☐ Real-World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- ☐ Inspectional findings
- ☐ Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- ☐ Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- ☐ Imperfect comparator method used to calculate performance characteristics
- ☒ Other(s): The duration of benefit is unclear.
- ☐ None

Q2: What is the extent of uncertainty for the benefits?

- ☐ Low → Continue to Question 3
- ☒ Med → Continue to Question 3
- ☐ High → Continue to Question 3

Summary of the Assessment of Benefit

For the Proposed Indications for Use:

The probability that a patient will experience a substantial benefit in terms of reduction in symptoms when the device is implanted is 75%. The data also support improved mobility, which is anticipated to

lead to longer life expectancy. The patients who experience the benefit value it substantially. Patients also value the opportunity to achieve the benefit. The study was well designed and conducted. Follow-up was only 1 year and there was missing data, but sensitivity analyses were conducted, and the results are relatively robust.

Assessment of Risk

3. Are known/probable risks more than minimal?

Select any of the following elements that demonstrate sources of known/probable risks that are more than minimal, then answer the question in the box below.

☒ Adverse events (AEs) or outcomes related to the device itself
☐ AEs or outcomes related to the use of the device or procedure to use the device
☐ AEs or outcomes related to anesthesia or sedation to use the device
☐ AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
☐ AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
☐ False positive/false negative/failed to provide a result for diagnostics
☐ Treatment or diagnostic intended to be used as a standalone rather than an adjunctive use
☐ Other(s):
☐ None

Q3: Are known/probable risks more than minimal?

☒ YES → Continue to Question 4
☐ NO → Continue to Question 4

4. What is the extent of uncertainty for the risks?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks. Select any of the following that demonstrate sources of uncertainty for the risks, and then answer the question in the box below.

☐ Insufficient patient numbers to detect serious events or false positives/false negatives
☐ Insufficient duration of follow-up to detect delayed/late events
☐ Lack of data on repeated exposure to the device/use
☐ Inconsistent or conflicting results between studies
☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
☐ Poor or inconsistent adverse event definitions and documentation
☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities
☐ High subject loss-to-follow-up at critical assessment point(s)
☐ Large amount of missing data at critical assessment time(s) +/- imputation

☐ Significant number of major protocol deviations
☐ Inconsistent user experience or user experience not representative of likely real-world user
☐ Concerns related to performance characteristics (e.g., sensitivity/PPA, specificity/NPA)
☐ Imperfect comparator method used to calculate performance characteristics
☒ Other(s): No information is provided regarding removal of the permanent implant. If necessary, removal would be difficult.
☐ None

Q4: What is the extent of uncertainty for the risks?

☐ Low → Continue to Question 5
☒ Med → Continue to Question 5
☐ High → Continue to Question 5

Summary of the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use:
Known risks are those typically associated with permanent, implantable devices and include device fracture, mechanical failure or adverse biological response (less than 3% chance). 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. The device-related adverse events last as long as the device remains implanted but are expected to be reversed by removing the device. However, no information about device removal is provided, and if necessary, removal is expected to be difficult.

Assessment of Benefit-Risk

Instructions for FDA staff: Provide a recommendation based on the totality of the evidence. As noted above, the benefit-risk assessment is part of the decision regarding whether to approve a PMA application or grant a De Novo request but is not an assessment of all applicable requirements.

To approve a PMA application or grant a De Novo request, FDA must find, among other things, that there is a reasonable assurance of safety and effectiveness for the device. FDA determines whether there is a reasonable assurance of safety and effectiveness by weighing any benefit to health from the use of the device against any risk of injury or illness for such use, among other relevant factors. To grant a De Novo request, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

If you answer "yes" for any Q5-8, explain your rationale for how the benefits outweigh the risks. You should also consider and recommend actions that would enhance the benefit-risk profile of the device, such as modifications to the proposed labeling, which may include additional appropriate warnings and precautions, instructions for use, or presentation of data, to help ensure the product labeling is transparent with respect to the benefits and risks.

If you answer "unable to conclude" for Q5-8, please provide the information that you believe would be needed to support a determination that the benefits outweigh the risks for the Indications for Use under consideration in the summary text boxes and also proceed to Q9.

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk

For the Proposed Indications for Use:

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 a fair amount of remaining uncertainty associated with the trial results, especially around the lack of information regarding device removal.

6. **Do the Benefits outweigh the Risks, when taking into account the following additional considerations?** *Select relevant considerations, and then answer the question in the box below.*

☒ Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks
☐ Available patient preference information (PPI) showing patient willingness or unwillingness to accept the risks in exchange for the benefits. In circumstances where it is not feasible to obtain PPI (e.g., some pediatric or impaired patient populations), care-partner perspectives may be considered.
☐ Understanding of care-partner perspectives on the benefits and risks for a device intended to provide benefit to the care-partner (e.g., ease of care)
☐ Understanding of healthcare professional perspectives on the benefits and risks for a device intended to provide benefit to the healthcare professional (e.g., reduction of radiation exposure)
☐ Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions
☐ Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions
☐ Understanding that the device represents novel technology for which the current device technology is different
☐ Ability to manage or diagnose the condition and consideration of natural history of disease progression in the absence of the intervention or diagnostic information with the device under review
☒ No legally marketed alternative medical product or medical intervention exists, or the device offers advantages over existing alternatives
☒ The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions
☐ The device avoids serious harm associated with available therapies for the disease or condition
☐ The adverse events associated with use of the device are reversible
☐ Type of intervention required to address the harmful event (e.g., medication, surgery)
☐ The study is a first of a kind (robustness of the analysis)
☐ Tipping point and/or worst-case sensitivity analysis continuing to show clinical benefit
☐ Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)
☐ Other(s):
☐ None

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☒ Unable to conclude that benefits outweigh the risks – further discussion and consideration of risk mitigation measures is appropriate – Continue to Q7

Summary of the Assessment of Benefit-Risk, taking into account additional relevant considerations

For the Proposed Indications for Use:

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 as a trade-off for obtaining such benefits. Further, the device treats a severe and chronic disease for which alternative treatments have been exhausted. However, it remains unclear which patients will benefit and further mitigation of the risks of the device are needed in order to achieve a favorable benefit-risk assessment.

7. **Can the risks be mitigated, so that Benefits outweigh the Risks? Consider if the Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the benefit-risk profile of the device.** *Select relevant considerations, and then answer the question in the box below.*

☐ Additional descriptions of known and probable benefits and risks in physician and patient labeling including appropriate Contraindications, Warnings, and Precautions and description of the clinical events
☐ Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐ Labeling the device "Prescription Only"
Training:
☒ Limitation to caregivers with certain qualifications or clinical training
☐ Limit to users with a minimum set of qualifications and/or training
☐ Physician/user training program
Other:
☐ Device tracking
☐ Other(s):
☐ None

Q7: Can the risks be mitigated, so that Benefits outweigh the Risks?

☒ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of postmarket actions is appropriate – Continue to Q8

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use:
The risks, although substantial, could be further mitigated through limiting the device use to clinicians with specialized training. With that additional risk mitigation, the benefits provided by the device outweigh the risks.

8. **Do the Benefits outweigh the Risks considering the use of postmarket actions?** *Select appropriate postmarket action(s), and then answer the question in the box below.*

☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket space
☐ Collection of additional and/or confirmatory clinical data in the postmarket space (e.g., post-approval study, postmarket surveillance)

If either non-clinical or clinical performance data collections in the postmarket space are checked, consider:

☐ The feasibility of postmarket data collection and likelihood that postmarket data collection will be completed within a reasonable timeframe

☐ Whether it would be appropriate for labeling to include description of postmarket data collection and its purpose

☐ Other(s):

☐ None

Q8: Do the Benefits outweigh the Risks considering the use of postmarket actions?

☐ Yes – The benefits outweigh the risks

☐ Unable to conclude that benefits outweigh the risks – Continue to Q9

Summary of the Assessment of Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use:

Summarize the benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding benefit(s) and risks.

Q9: Is there any evidence of clinical benefit for a modified Indications for Use?

☐ Yes → Return to Q1 and proceed with modified Indications for Use

☐ No → Do not approve/grant

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: Hypothetical Example 1 PMA/De Novo Number: ☐ Interim ☒ Final	**Proposed Indications for Use** To reduce symptoms for patients with condition X in patients who have failed all other treatment options
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☒ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the Benefits?	☐ High ☒ Med ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	☒ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the Risks?	☐ High ☒ Med ☐Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☒ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☐ NO → Do not approve/grant

Worksheet for Hypothetical Example 2

Instructions for FDA staff: You should make your recommendation regarding the benefit-risk assessment based on the totality of the evidence. The benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the benefits outweigh the risks does not mean that the application satisfies other applicable requirements for a PMA application or a De Novo request.

The following questions are intended as a sequential method to help weigh various factors as part of the benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a benefit-risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant. This checklist should be used when non-clinical and/or clinical evidence has been submitted in the form of valid scientific evidence.

Consider questions 1-8 for the proposed Indications for Use, until you reach a recommendation either that the benefits outweigh the risks or to move to question 9, which prompts you to consider a modified Indications for Use. When considering an acceptable, modified Indications for Use, interact with the sponsor to reach agreement on a modified Indications for Use. However, as reflected under question 1, if the evidence does not support a finding of benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of benefit for the proposed Indications for Use and agreement on a modified Indications for Use is not achievable or applicable, the application would not be approvable or grantable.

Assessment of Benefit

1. **Is there any evidence of clinical benefit?**

   Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
   ☐ A favorable change in at least 1 clinical assessment that meets a predetermined performance goal
   ☐ A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference
   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition
   ☒ A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life

   Other:

☐ A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
☐ A favorable clinical performance characteristic (e.g., sensitivity/PPA,[29] specificity/NPA[30], etc.) for screening, diagnosis, prognosis, monitoring or treatment selection
☐ Acceptable performance characteristics for analytical validation of the device
☐ Other(s):
☐ None

Q1: Is there any evidence of clinical benefit?

☒ YES → Continue to Question 2
☐ NO → Move to Question 9

[29] PPA: Positive Percent Agreement
[30] NPA: Negative Percent Agreement

2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility, as applicable). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- ☐ Inconsistent or conflicting results between studies
- ☐ Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s)
- ☐ A significantly underpowered study with statistical insignificance in outcome measure(s)
- ☐ High subject or specimen loss-to-follow-up at critical assessment point(s)
- ☐ Large amount of missing data at critical assessment time(s) +/- imputation
- ☐ Significant number of major protocol deviations
- ☐ Impact of confounding interventions or physiological factors
- ☐ Inconsistent user experience or user experience not representative of likely real-world user
- ☐ Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- ☐ Surrogate endpoint has not yet been demonstrated to correlate with a clinical outcome
- ☐ Real World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- ☐ Inspectional findings
- ☐ Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- ☐ Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- ☐ Imperfect comparator method used to calculate performance characteristics
- ☒ Other(s): small sample size
- ☐ None

Q2: What is the degree of uncertainty for the benefits?

- ☐ Low → Continue to Question 3
- ☒ Med → Continue to Question 3
- ☐ High → Continue to Question 3

Summary of the Assessment of Benefit

For the Proposed Indications for Use:

Patients place an enormous value on the benefit, which include memory preservation and improvement of quality of life. The magnitude of benefit is large for patients in early stages of the disease; smaller for

patients in later stages of the disease.
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. While the number of subjects eligible and willing to enroll in the trial was small, the data were robust, and the trial was well-designed and conducted. The results of the trial are generalizable.

Assessment of Risk

3. **Are known/probable risks more than minimal?**
   Select any of the following elements that demonstrate sources of known/probable risks that are more than minimal, then answer the question in the box below.

   ☒ Adverse events (AEs) or outcomes related to the device itself
   ☒ AEs or outcomes related to the use of the device or procedure to use the device
   ☒ AEs or outcomes related to anesthesia or sedation to use the device
   ☐ AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
   ☒ AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
   ☐ False positive/false negative/failed to provide a result for diagnostics
   ☐ Treatment or diagnostic intended to be used as a standalone rather than an adjunctive use
   ☐ Other(s):
   ☐ None

   Q3: Are known/probable risks more than minimal?

   ☒ YES → Continue to Question 4
   ☐ NO → Continue to Question 4

4. **What is the extent of uncertainty for the risks?**
   Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks. Select any of the following that demonstrate sources of uncertainty for the risks, and then answer the question in the box below.

   ☐ Insufficient patient numbers to detect serious events or false positives/false negatives
   ☐ Insufficient duration of follow-up to detect delayed/late events
   ☐ Lack of data on repeated exposure to the device/use
   ☐ Inconsistent or conflicting results between studies
   ☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
   ☐ Poor or inconsistent adverse event definitions and documentation
   ☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities

☐ High subject loss-to-follow-up at critical assessment point(s)
☐ Large amount of missing data at critical assessment time(s) +/- imputation
☐ Significant number of major protocol deviations
☐ Inconsistent user experience or user experience not representative of likely real-world user
☐ Concerns related to performance characteristics (e.g., sensitivity/PPA, specificity/NPA)
☐ Imperfect comparator method used to calculate performance characteristics
☒ Other(s): small sample size
☐ None

Q4: What is the extent of uncertainty for the risks?

☐ Low → Continue to Question 5
☒ Med → Continue to Question 5
☐ High → Continue to Question 5

Summary of the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use:
The risks associated with this device are great. The surgery to implant the device is highly risky. Serious adverse events include partial paralysis, loss of vision, loss of motor skills, vertigo, and insomnia. Non-serious adverse events include temporary personality shifts, mood swings, and slurred speech. It is known from previous studies and literature that there is an 8% risk of serious adverse events from the surgery alone. 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 exposure to the device.

Assessment of Benefit-Risk

Instructions for FDA staff: Provide a recommendation based on the totality of the evidence. As noted above, the benefit-risk assessment is part of the decision regarding whether to approve a PMA application or grant a De Novo request but is not an assessment of all applicable requirements.

To approve a PMA application or grant a De Novo request, FDA must find, among other things, that there is a reasonable assurance of safety and effectiveness for the device. FDA determines whether there is a reasonable assurance of safety and effectiveness by weighing any benefit to health from the use of the device against any risk of injury or illness for such use, among other relevant factors. To grant a De Novo request, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

If you answer "yes" for any Q5-8, explain your rationale for how the benefits outweigh the risks. You should also consider and recommend actions that would enhance the benefit-risk profile of the device, such as modifications to the proposed labeling, which may include additional appropriate warnings and precautions, instructions for use, or presentation of data, to help ensure the product labeling is transparent with respect to the benefits and risks.

If you answer "unable to conclude" for Q5-8, please provide the information that you believe would be needed to support a determination that the benefits outweigh the risks for the Indications for Use under consideration in the summary text boxes and also proceed to Q9.

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk

For the Proposed Indications for Use:

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 reasonably narrow. The uncertainty about results is based on the small sample size and 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. Based solely on the benefits, risks and degree of uncertainty, it cannot be concluded that the benefits outweigh the risks.

6. **Do the Benefits outweigh the Risks, when taking into account the following additional considerations?** *Select relevant considerations, and then answer the question in the box below.*

☒ Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks
☐ Available patient preference information (PPI) showing patient willingness or unwillingness to accept the risks in exchange for the benefits. In circumstances where it is not feasible to obtain PPI (e.g., some pediatric or impaired patient populations), care-partner perspectives may be considered.
☒ Understanding of care-partner perspectives on the benefits and risks for a device intended to provide benefit to the care-partner (e.g., ease of care)
☐ Understanding of healthcare professional perspectives on the benefits and risks for a device intended to provide benefit to the healthcare professional (e.g., reduction of radiation exposure)
☐ Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions
☐ Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions
☒ Understanding that the device represents novel technology for which the current device technology is different
☒ Ability to manage or diagnose the condition and consideration of natural history of disease progression in the absence of the intervention or diagnostic information with the device under review
☒ No legally marketed alternative medical product or medical intervention exists, or the device offers advantages over existing alternatives
☒ The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions
☐ The device avoids serious harm associated with available therapies for the disease or condition
☐ The adverse events associated with use of the device are reversible
☐ Type of intervention required to address the harmful event (e.g., medication, surgery)
☐ The study is a first of a kind (robustness of the analysis)
☐ Tipping point and/or worst-case sensitivity analysis continuing to show clinical benefit
☐ Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)
☐ Other(s):
☐ None

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☒ Unable to conclude that benefits outweigh the risks – further discussion and consideration of risk mitigation measures is appropriate – Continue to Q7

Summary of the Assessment of Benefit-Risk, taking into account additional relevant considerations

For the Proposed Indications for Use:

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 some patients because of the probable benefits the device offers, and the progressive nature of the untreated condition. However, given the small sample size and the high-risk nature of the device, including the fact that this is a permanent implant, the benefits do not outweigh the risks without additional labeling limitations and postmarket data collection.

7. **Can the risks be mitigated, so that Benefits outweigh the Risks? Consider if the Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the benefit-risk profile of the device.** *Select relevant considerations, and then answer the question in the box below.*

☐ Additional descriptions of known and probable benefits and risks in physician and patient labeling including appropriate Contraindications, Warnings, and Precautions and description of the clinical events
☐ Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐ Labeling the device "Prescription Only"
Training:
☒ Limitation to caregivers with certain qualifications or clinical training
☐ Limit to users with a minimum set of qualifications and/or training
☒ Physician/user training program
Other:
☐ Device tracking
☒ Other(s): requiring the labeling to prominently address the 8% serious adverse event rate
☐ None

Q7: Can the risks be mitigated, so that Benefits outweigh the Risks?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☒ Unable to conclude that benefits outweigh the risks – further discussion and consideration of postmarket actions is appropriate – Continue to Q8

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use:
While the risks associated with the device are great, they can be partially mitigated by prominently explaining the 8% serious adverse event rate in the labeling, limiting device to use to physicians with appropriate expertise and by training the physicians who implant/explant (if necessary) the device. However, without postmarket data collection, the probable benefits do not outweigh the probable risks.

8. **Do the Benefits outweigh the Risks considering the use of postmarket actions?** *Select appropriate postmarket action(s), and then answer the question in the box below.*

☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket

space

☒ Collection of additional and/or confirmatory clinical data in the postmarket space (e.g., post-approval study, postmarket surveillance)

If either non-clinical or clinical performance data collections in the postmarket space are checked, consider:

☒ The feasibility of postmarket data collection and likelihood that postmarket data collection will be completed within a reasonable timeframe☐ Whether it would be appropriate for labeling to include description of postmarket data collection and its purpose

☐ Other(s):

☐ None

Q8: Do the Benefits outweigh the Risks considering the use of postmarket actions?

☒ Yes – The benefits outweigh the risks

☐ Unable to conclude that benefits outweigh the risks – Continue to Q9

Summary of the Assessment of Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use:

After full consideration of the probable benefits and risks provided by the device, 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 and training requirements described above are addressed and post-approval study is conducted to evaluate longer term performance, including maintenance of effectiveness, long term adverse events, and device duration.

Q9: Is there any evidence of clinical benefit for a modified Indications for Use?

☐ Yes → Return to Q1 and proceed with modified Indications for Use

☐ No → Do not approve/grant

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: Hypothetical Example 2 PMA/De Novo Number: ☐ Interim ☒ Final	**Proposed Indications for Use** The device is indicated as a memory replacement device for patients with Alzheimer's disease, dementia, and other memory disorders
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☒ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the benefits?	☐ High ☒ Med ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
3. Are known/probable risks more than minimal?	☒ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the Risks?	☐ High ☒ Med ☐Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☒ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☐ NO → Do not approve/grant

Worksheet for Hypothetical Example 3

Instructions for FDA staff: You should make your recommendation regarding the benefit-risk assessment based on the totality of the evidence. The benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the benefits outweigh the risks does not mean that the application satisfies other applicable requirements for a PMA application or a De Novo request.

The following questions are intended as a sequential method to help weigh various factors as part of the benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a benefit-risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant. This checklist should be used when non-clinical and/or clinical evidence has been submitted in the form of valid scientific evidence.

Consider questions 1-8 for the proposed Indications for Use, until you reach a recommendation either that the benefits outweigh the risks or to move to question 9, which prompts you to consider a modified Indications for Use. When considering an acceptable, modified Indications for Use, interact with the sponsor to reach agreement on a modified Indications for Use. However, as reflected under question 1, if the evidence does not support a finding of benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of benefit for the proposed Indications for Use and agreement on a modified Indications for Use is not achievable or applicable, the application would not be approvable or grantable.

Assessment of Benefit

1. **Is there any evidence of clinical benefit?**

   Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
   ☐ A favorable change in at least 1 clinical assessment that meets a predetermined performance goal
   ☐ A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference
   ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition
   ☒ A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life

   Other:

☐ A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
☒ A favorable clinical performance characteristic (e.g., sensitivity/PPA,[31] specificity/NPA[32], etc.) for screening, diagnosis, prognosis, monitoring or treatment selection
☐ Acceptable performance characteristics for analytical validation of the device
☐ Other(s):
☐ None

Q1: Is there any evidence of clinical benefit?

☒ YES → Continue to Question 2
☐ NO → Move to Question 9

[31] PPA: Positive Percent Agreement
[32] NPA: Negative Percent Agreement

2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- ☐ Inconsistent or conflicting results between studies
- ☐ Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s))
- ☐ A significantly underpowered study with statistical insignificance in outcome measure(s)
- ☐ High subject or specimen loss-to-follow-up at critical assessment point(s)
- ☐ Large amount of missing data at critical assessment time(s) +/- imputation
- ☐ Significant number of major protocol deviations
- ☐ Impact of confounding interventions or physiological factors
- ☐ Inconsistent user experience or user experience not representative of likely real-world user
- ☐ Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- ☒ Surrogate endpoint has not yet been demonstrated to correlate with a clinical outcome
- ☐ Real World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- ☐ Inspectional findings
- ☐ Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- ☐ Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- ☐ Imperfect comparator method used to calculate performance characteristics
- ☒ Other(s): Clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results may not be equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results
- ☐ None

Q2: What is the degree of uncertainty for the benefits?

- ☐ Low → Continue to Question 3
- ☐ Med → Continue to Question 3
- ☒ High → Continue to Question 3

Summary of the Assessment of Benefit

For the Proposed Indications for Use:

The main benefit from use of the device is avoiding morbidity associated with an immediate biopsy for

the 57% of the 400 subjects in the clinical trial whose test results indicate a low probability of having breast cancer. This is demonstrated based on sensitivity and specificity values of 97% and 75%, respectively, and PPV and NPVs of 56.4% and 98.7%, respectively.

Assessment of Risk

3. **Are known/probable risks more than minimal?**
   Select any of the following elements that demonstrate sources of known/probable risks that are more than minimal, then answer the question in the box below.

☐ Adverse events (AEs) or outcomes related to the device itself
☐ AEs or outcomes related to the use of the device or procedure to use the device
☐ AEs or outcomes related to anesthesia or sedation to use the device
☐ AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
☐ AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
☒ False positive/false negative/failed to provide a result for diagnostics
☒ Treatment or diagnostic intended to be used as a standalone rather than an adjunctive use
☐ Other(s):
☐ None

Q3: Are known/probable risks more than minimal?

☒ YES → Continue to Question 4
☐ NO → Continue to Question 4

4. **What is the extent of uncertainty for the risks?**
   Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks. Select any of the following that demonstrate sources of uncertainty for the risks, and then answer the question in the box below.

☐ Insufficient patient numbers to detect serious events or false positives/false negatives
☐ Insufficient duration of follow-up to detect delayed/late events
☐ Lack of data on repeated exposure to the device/use
☐ Inconsistent or conflicting results between studies
☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
☐ Poor or inconsistent adverse event definitions and documentation
☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities
☐ High subject loss-to-follow-up at critical assessment point(s)
☐ Large amount of missing data at critical assessment time(s) +/- imputation
☐ Significant number of major protocol deviations

☐ Inconsistent user experience or user experience not representative of likely real-world user
☒ Concerns related to performance characteristics (e.g., sensitivity/PPA, specificity/NPA)
☐ Imperfect comparator method used to calculate performance characteristics
☒ Other(s): Prolonged natural history of breast cancer increases uncertainty with respect to the ultimate results of clinical follow-up
☐ None

Q4: What is the extent of uncertainty for the risks?

☐ Low → Continue to Question 5
☐ Med → Continue to Question 5
☒ High → Continue to Question 5

Summary of the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use:
The main risk from use of the device is in failing to biopsy some BI-RADS 4 patients who have biopsy-detectable breast cancer, thus delaying their diagnosis and treatment. Concerning this risk, the sponsor asserts that a clinically acceptable negative predictive value for cancer among non-biopsied BI-RADS 4 subjects is 98% or higher. This cut-off was based on the clinical acceptability of a 2% prevalence for cancer in BI-RADS 3 patients who are usually counseled not to have an immediate biopsy (waiting a few months, instead, for further evaluation, such as follow-up diagnostic imaging in 6 months). 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 high uncertainty about the extent of the probable risk(s)/harm(s).

Assessment of Benefit-Risk

Instructions for FDA staff: Provide a recommendation based on the totality of the evidence. As noted above, the benefit-risk assessment is part of the decision regarding whether to approve a PMA application or grant a De Novo request but is not an assessment of all applicable requirements.

To approve a PMA application or grant a De Novo request, FDA must find, among other things, that there is a reasonable assurance of safety and effectiveness for the device. FDA determines whether there is a reasonable assurance of safety and effectiveness by weighing any benefit to health from the use of the device against any risk of injury or illness for such use, among other relevant factors. To grant a De Novo request, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

If you answer "yes" for any Q5-8, explain your rationale for how the benefits outweigh the risks. You should also consider and recommend actions that would enhance the benefit-risk profile of the device, such as modifications to the proposed labeling, which may include additional appropriate warnings and precautions, instructions for use, or presentation of data, to help ensure the product labeling is transparent with respect to the benefits and risks.

If you answer "unable to conclude" for Q5-8, please provide the information that you believe would be needed to support a determination that the benefits outweigh the risks for the Indications for Use under consideration in the summary text boxes and also proceed to Q9.

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk

For the Proposed Indications for Use:

Based solely on the benefits and risks as demonstrated by the performance data and its associated uncertainties, the benefits associated with avoiding a biopsy-related morbidity do not outweigh the risks associated with missing a biopsy detectable cancer. Based on the available information, FDA cannot establish that there is a reasonable assurance of safety and effectiveness for the proposed benefit to health and additional information is needed to establish that the overall benefits outweigh the risks.

6. **Do the Benefits outweigh the Risks, when taking into account the following additional considerations?** *Select relevant considerations, and then answer the question in the box below.*

   ☒ Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks

☒ Available patient preference information (PPI) showing patient willingness or unwillingness to accept the risks in exchange for the benefits. In circumstances where it is not feasible to obtain PPI (e.g., some pediatric or impaired patient population), care-partner perspectives may be considered.
☐ Understanding of care-partner perspectives on the benefits and risks for a device intended to provide benefit to the care-partner (e.g., ease of care)
☐ Understanding of healthcare professional perspectives on the benefits and risks for a device intended to provide benefit to the healthcare professional (e.g., reduction of radiation exposure)
☐ Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions
☐ Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions
☐ Understanding that the device represents novel technology for which the current device technology is different
☒ Ability to manage or diagnose the condition and consideration of natural history of disease progression in the absence of the intervention or diagnostic information with the device under review
☒ No legally marketed alternative medical product or medical intervention exists, or the device offers advantages over existing alternatives
☐ The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions
☐ The device avoids serious harm associated with available therapies for the disease or condition
☐ The adverse events associated with use of the device are reversible
☒ Type of intervention required to address the harmful event (e.g., medication, surgery)
☐ The study is a first of a kind (robustness of the analysis)
☐ Tipping point and/or worst-case sensitivity analysis continuing to show clinical benefit
☐ Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)
☐ Other(s):
☐ None

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☒ Unable to conclude that benefits outweigh the risks – further discussion and consideration of risk mitigation measures is appropriate – Continue to Q7

Summary of the Assessment of Benefit-Risk, taking into account additional relevant considerations

For the Proposed Indications for Use:

Detailed patient preference information (PPI) showing patient willingness to accept the probable risks in exchange for the proposed benefits was not obtained for this in vitro diagnostic. Care-partner and/or healthcare professional perspectives were also not obtained. However, 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. Delayed diagnosis of breast cancer may result in a more advanced stage of cancer requiring serious medical intervention, such as aggressive chemotherapy, surgery or radiation, and may be associated with increased mortality. There are no legally marketed alternative in vitro diagnostics, it is not apparent that the device offers advantages over existing alternatives. It is unknown if patients with missed breast cancer diagnoses and BI-RADS 4 mammography results will have similar clinical outcomes to patients with BI-RADS 3 mammography results. Therefore, the additional relevant considerations do not clearly demonstrate that the benefits outweigh the risks for the proposed assay.

7. **Can the risks be mitigated, so that Benefits outweigh the Risks? Consider if the Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the benefit-risk profile of the device.** *Select relevant considerations, and then answer the question in the box below.*

☒ Additional descriptions of known and probable benefits and risks in physician and patient labeling including appropriate Contraindications, Warnings, and Precautions and description of the clinical events
☐ Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐ Labeling the device "Prescription Only"
Training:
☐ Limitation to caregivers with certain qualifications or clinical training
☐ Limit to users with a minimum set of qualifications and/or training
☒ Physician/user training program
Other:
☐ Device tracking
☐ Other(s):
☐ None

Q7: Can the risks be mitigated, so that Benefits outweigh the Risks?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☒ Unable to conclude that benefits outweigh the risks – further discussion and consideration of postmarket actions is appropriate – Continue to Q8

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use:
Additional risk mitigation strategies are not sufficient for the proposed assay, due to the underlying uncertainty regarding clinical outcomes in patients with a missed breast cancer diagnosis and a BI-RADS 4 mammography result. Additional descriptions of the benefits and risks cannot be added to the device labeling due to limited knowledge of the clinical outcomes associated with a missed cancer diagnosis. Similarly, there is insufficient information to establish an effective physician/user training program to

mitigate the risks.

8. **Do the Benefits outweigh the Risks considering the use of postmarket actions?** *Select appropriate postmarket action(s), and then answer the question in the box below.*

☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket space
☐ Collection of additional and/or confirmatory clinical data in the postmarket space (e.g., post-approval study, postmarket surveillance)

If either non-clinical or clinical performance data collections in the postmarket space are checked, consider:

☐ The feasibility of postmarket data collection and likelihood that postmarket data collection will be completed within a reasonable timeframe
☐ Whether it would be appropriate for labeling to include description of postmarket data collection and its purpose

☐ Other(s):
☒ None

Q8: Do the Benefits outweigh the Risks considering the use of postmarket actions?

☐ Yes – The benefits outweigh the risks
☒ Unable to conclude that benefits outweigh the risks – Continue to Q9

Summary of the Assessment of Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use:

We are unable to conclude that benefits outweigh risks based on the available data, and due to the high degree of uncertainty and the clinical impact of a missed cancer diagnosis, postmarket actions are not sufficient to address these issues.

Q9: Is there any evidence of clinical benefit for a modified Indications for Use?

☐ Yes → Return to Q1 and proceed with modified Indications for Use
☒ No → Do not approve/grant

At this time, FDA is unable to approve the PMA because we are unable to conclude that the benefits outweigh the risks. Given that the benefits are uncertain and the risk for a small number of patients could be substantial, FDA cannot conclude that there is reasonable assurance of safety and effectiveness to support approval of the premarket application at this time, however an advisory panel may be considered to further evaluate the benefit-risk profile of the assay for the proposed or a modified Indications for Use.

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: Hypothetical Example 3 PMA/De Novo Number: ☒ Interim ☐ Final	**Proposed Indications for Use** 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.
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☒ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the benefits?	☒ High ☐ Med ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	☒ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the Risks?	☒ High ☐ Med ☐Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☒ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☒ NO → Do not approve/grant

Worksheet for Hypothetical Example 4

Instructions for FDA staff: You should make your recommendation regarding the benefit-risk assessment based on the totality of the evidence. The benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the benefits outweigh the risks does not mean that the application satisfies other applicable requirements for a PMA application or a De Novo request.

The following questions are intended as a sequential method to help weigh various factors as part of the benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a benefit-risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant. This checklist should be used when non-clinical and/or clinical evidence has been submitted in the form of valid scientific evidence.

Consider questions 1-8 for the proposed Indications for Use, until you reach a recommendation either that the benefits outweigh the risks or to move to question 9, which prompts you to consider a modified Indications for Use. When considering an acceptable, modified Indications for Use, interact with the sponsor to reach agreement on a modified Indications for Use. However, as reflected under question 1, if the evidence does not support a finding of benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of benefit for the proposed Indications for Use and agreement on a modified Indications for Use is not achievable or applicable, the application would not be approvable or grantable.

Assessment of Benefit

1. Is there any evidence of clinical benefit?

Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

- ☐ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
- ☐ A favorable change in at least 1 clinical assessment that meets a predetermined performance goal
- ☐ A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference
- ☒ A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition
- ☐ A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life

Other:

- ☐ A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
- ☐ A favorable clinical performance characteristic (e.g., sensitivity/PPA,[33] specificity/NPA[34], etc.) for screening, diagnosis, prognosis, monitoring or treatment selection
- ☐ Acceptable performance characteristics for analytical validation of the device
- ☐ Other(s):
- ☐ None

Q1: Is there any evidence of clinical benefit?

☒ YES → Continue to Question 2
☐ NO → Move to Question 9

[33] PPA: Positive Percent Agreement
[34] NPA: Negative Percent Agreement

2. What is the extent of uncertainty for the benefits?

Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data that affect your assessment of the clinical benefit. Consider sources of uncertainty related to clinical and/or analytical performance characteristics (e.g., sensitivity, specificity, accuracy, precision, reproducibility, as applicable). *Select any of the following that demonstrate sources of uncertainty for the benefits, and then answer the question in the box below.*

- ☐ Inconsistent or conflicting results between studies
- ☐ Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s))
- ☐ A significantly underpowered study with statistical insignificance in outcome measure(s)
- ☐ High subject or specimen loss-to-follow-up at critical assessment point(s)
- ☐ Large amount of missing data at critical assessment time(s) +/- imputation
- ☐ Significant number of major protocol deviations
- ☐ Impact of confounding interventions or physiological factors
- ☐ Inconsistent user experience or user experience not representative of likely real-world user
- ☐ Unclear correlation between non-clinical data, pre-selected enriched data, or computer modeling and clinical performance
- ☐ Surrogate endpoint has not yet been demonstrated to correlate with a clinical outcome
- ☐ Real World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
- ☐ Inspectional findings
- ☐ Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.
- ☐ Physiological or clinically meaningful range of the diagnostic output is unknown, or generalizability of proposed clinical cut-off is unknown
- ☐ Imperfect comparator method used to calculate performance characteristics
- ☒ Other(s): limited duration of follow-up
- ☐ None

Q2: What is the degree of uncertainty for the benefits?

- ☒ Low → Continue to Question 3
- ☐ Med → Continue to Question 3
- ☐ High → Continue to Question 3

Summary of the Assessment of Benefit

For the Proposed Indications for Use:

Through one year of follow-up, no subject experienced device movement; therefore, there is a very high probability (almost 100%) of reduction of primary device migration. 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.

While the data only demonstrates benefit for up to one year, the benefit is expected to last for as long as the device remains implanted.

Assessment of Risk

3. **Are known/probable risks more than minimal?**
   Select any of the following elements that demonstrate sources of known/probable risks that are more than minimal, then answer the question in the box below.

☒ Adverse events (AEs) or outcomes related to the device itself
☐ AEs or outcomes related to the use of the device or procedure to use the device
☐ AEs or outcomes related to anesthesia or sedation to use the device
☐ AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
☐ AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
☐ False positive/false negative/failed to provide a result for diagnostics
☐ Treatment or diagnostic intended to be used as a standalone rather than an adjunctive use
☐ Other(s):
☐ None

Q3: Are known/probable risks more than minimal?

☒ YES → Continue to Question 4
☐ NO → Continue to Question 4

4. **What is the extent of uncertainty for the risks?**
   Recognizing that some extent of uncertainty always exists, select the sources of uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks. Select any of the following that demonstrate sources of uncertainty for the risks, and then answer the question in the box below.

☐ Insufficient patient numbers to detect serious events or false positives/false negatives
☒ Insufficient duration of follow-up to detect delayed/late events
☐ Lack of data on repeated exposure to the device/use
☐ Inconsistent or conflicting results between studies
☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
☐ Poor or inconsistent adverse event definitions and documentation
☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities
☐ High subject loss-to-follow-up at critical assessment point(s)

☐ Large amount of missing data at critical assessment time(s) +/- imputation
☐ Significant number of major protocol deviations
☐ Inconsistent user experience or user experience not representative of likely real-world user
☐ Concerns related to performance characteristics (e.g., sensitivity/PPA, specificity/NPA)
☐ Imperfect comparator method used to calculate performance characteristics
☐ Other(s):
☐ None

Q4: What is the extent of uncertainty for the risks?

☒ Low → Continue to Question 5
☐ Med → Continue to Question 5
☐ High → Continue to Question 5

Summary of the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use:
Through one year of follow-up, there were no device-related serious adverse events (no fractures of any primary device) and only a handful of malfunctions of the support system, none of which lead to serious adverse events. Despite the insufficient duration of follow-up to detect delayed events, the risks of failure of the support system are not high because even if the support system fails, it is unlikely to lead to an overall failure of the primary device. Two subjects experienced complications related to the device malfunctioning (device movement). 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 substantially increase the risk to the patient.

Assessment of Benefit-Risk

Instructions for FDA staff: Provide a recommendation based on the totality of the evidence. As noted above, the benefit-risk assessment is part of the decision regarding whether to approve a PMA application or grant a De Novo request but is not an assessment of all applicable requirements.

To approve a PMA application or grant a De Novo request, FDA must find, among other things, that there is a reasonable assurance of safety and effectiveness for the device. FDA determines whether there is a reasonable assurance of safety and effectiveness by weighing any benefit to health from the use of the device against any risk of injury or illness for such use, among other relevant factors. To grant a De Novo request, FDA must find that general controls or general and special controls provide a reasonable assurance of safety and effectiveness for the device.

If you answer "yes" for any Q5-8, explain your rationale for how the benefits outweigh the risks. You should also consider and recommend actions that would enhance the benefit-risk profile of the device, such as modifications to the proposed labeling, which may include additional appropriate warnings and precautions, instructions for use, or presentation of data, to help ensure the product labeling is transparent with respect to the benefits and risks.

If you answer "unable to conclude" for Q5-8, please provide the information that you believe would be needed to support a determination that the benefits outweigh the risks for the Indications for Use under consideration in the summary text boxes and also proceed to Q9.

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☒ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use:
The clinical trial was well-designed and conducted, and the results are robust. The clinical trial results provide assurance of at least one year of clinical effectiveness of the device, with a high probability of reduction of primary device migration. 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.

6. **Do the Benefits outweigh the Risks, when taking into account the following additional considerations?** *Select relevant considerations, and then answer the question in the box below.*

☐ Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks
☐ Available patient preference information (PPI) showing patient willingness or unwillingness to accept the risks in exchange for the benefits. In circumstances where it is not feasible to obtain PPI (e.g., some pediatric or impaired patient population), care-partner perspectives may be considered.
☐ Understanding of care-partner perspectives on the benefits and risks for a device intended to provide benefit to the care-partner (e.g., ease of care)
☐ Understanding of healthcare professional perspectives on the benefits and risks for a device intended to provide benefit to the healthcare professional (e.g., reduction of radiation exposure)
☐ Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions
☐ Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions
☐ Understanding that the device represents novel technology for which the current device technology is different
☐ Ability to manage or diagnose the condition and consideration of natural history of disease progression in the absence of the intervention or diagnostic information with the device under review
☐ No legally marketed alternative medical product or medical intervention exists, or the device offers advantages over existing alternatives
☐ The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions
☐ The device avoids serious harm associated with available therapies for the disease or condition
☐ The adverse events associated with use of the device are reversible
☐ Type of intervention required to address the harmful event (e.g., medication, surgery)
☐ The study is a first of a kind (robustness of the analysis)
☐ Tipping point and/or worst-case sensitivity analysis continuing to show clinical benefit
☐ Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)
☐ Other(s):
☐ None

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of risk mitigation measures is appropriate – Continue to Q7

<u>Summary of the Assessment of Benefit-Risk, taking into account additional relevant considerations</u>
For the Proposed Indications for Use:
Summarize the clinical benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative

modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

7. **Can the risks be mitigated, so that Benefits outweigh the Risks? Consider if the Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the benefit-risk profile of the device.** *Select relevant considerations, and then answer the question in the box below.*

☐ Additional descriptions of known and probable benefits and risks in physician and patient labeling including appropriate Contraindications, Warnings, and Precautions and description of the clinical events
☐ Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐ Labeling the device "Prescription Only"
Training:
☐ Limitation to caregivers with certain qualifications or clinical training
☐ Limit to users with a minimum set of qualifications and/or training
☐ Physician/user training program
Other:
☐ Device tracking
☐ Other(s):
☐ None

Q7: Can the risks be mitigated, so that Benefits outweigh the Risks?

☐ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of postmarket actions is appropriate – Continue to Q8

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use:
Summarize the clinical benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

8. **Do the Benefits outweigh the Risks considering the use of postmarket actions?** *Select appropriate postmarket action(s), and then answer the question in the box below.*

☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket space
☐ Collection of additional and/or confirmatory clinical data in the postmarket space (e.g., post-

approval study, postmarket surveillance)

If either non-clinical or clinical performance data collections in the postmarket space are checked, consider:

☐ The feasibility of postmarket data collection and likelihood that postmarket data collection will be completed within a reasonable timeframe☐ Whether it would be appropriate for labeling to include description of postmarket data collection and its purpose

☐ Other(s):

☐ None

Q8: Do the Benefits outweigh the Risks considering the use of postmarket actions?

☐ Yes – The benefits outweigh the risks

☐ Unable to conclude that benefits outweigh the risks – Continue to Q9

Summary of the Assessment of Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use:

Summarize the benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their benefits and risks, affect your assessment. Include a description of how uncertainty regarding benefit(s) and risks affects your assessment. Include a description of how patient perspectives affected your assessment.

Q9: Is there any evidence of clinical benefit for a modified Indications for Use?

☐ Yes → Return to Q1 and proceed with modified Indications for Use

☐ No → Do not approve/grant

Benefit-Risk Assessment Summary

Based on the totality of the data Device Name: Hypothetical Example 4 PMA/De Novo Number: ☐ Interim ☒ Final	**Proposed Indications for Use** The device is indicated as an adjunct to provide enhanced stability for other implanted devices, which could otherwise affix themselves without support.
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☒ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the benefits?	☐ High ☐ Med ☒Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	☒ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the Risks?	☐ High ☐ Med ☒Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☒ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☐ NO → Do not approve/grant