Appendix C

Worksheets for Hypothetical Examples

Worksheet for Hypothetical Example 1

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

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

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

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

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

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

Worksheet for Hypothetical Example 2

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

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

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

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

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

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

Worksheet for Hypothetical Example 3

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

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

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

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

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

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

Worksheet for Hypothetical Example 4

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

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

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

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

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

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