Contains Nonbinding Recommendations

Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)

Guidance for Industry and Food and Drug Administration Staff

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For questions about this document, contact OHT3: Office of Reproductive, Gastro-Renal, Urological, General Hospital Device, & Human Factors/DHT3B: Division of Reproductive and Urology Devices at (301) 796-7030.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Preface

Public Comment

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Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)

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

As men age, the prostate enlarges over time obstructing the prostatic urethra resulting in anatomic and functional changes in the bladder. The resulting condition, known as benign prostatic hyperplasia (BPH), can be associated with decreased peak urinary flow rate (Q_{max}) and increased post void residual urine (PVR). Men with BPH experience bothersome lower urinary tract symptoms (LUTS) that affect their quality of life by disrupting sleep patterns or interfering with daily activities. The development of LUTS is a complex process that involves the interaction of prostatic enlargement and bladder outlet obstruction with age-related effects on the bladder and nervous system.

Although BPH is uncommon in young men, it is remarkably common in older men. Epidemiological studies estimate that 50% of men have histological BPH by age 60. The prevalence increases to 90% in men over 85.[1, 2] Similar to the histological evidence, the prevalence of LUTS and other clinical indicators of BPH increases with age and is similar across

[1] Berry SJ, Coffey DS, Walsh PC, Ewing LL, The development of human benign prostatic hyperplasia by age. *J Urol*, 1984, 132:474-479.

[2] Isaacs, JT, Coffey DS, Etiology and disease process of benign prostatic hyperplasia. *Prostate*, 1989, 2(Suppl):33-50.

various countries and ethnic groups studied.[3, 4, 5, 6, 7] Therefore, BPH is considered a significant medical condition that has, and will continue to have, considerable public health impact.

A well-designed, scientifically sound investigational plan, both non-clinical and clinical, is essential to evaluate the safety and effectiveness of a medical device intended to treat BPH.

Prior to use in humans, it is essential to demonstrate that the device will function as intended in its environment of use. The design of medical devices involves the development and verification of a battery of specifications that define basic safety and performance requirements of the device. Most design specifications are validated in non-clinical testing, which allows assessment of device function and safety under controlled circumstances. Additionally, a comprehensive non-clinical battery of testing provides a foundation for evaluating future changes to the device.

The ultimate goal when conducting a clinical investigation of a device to treat BPH is to design a study using objective, unbiased outcomes to measure the safety and effectiveness of treatment. Major challenges faced when designing a clinical study to assess the safety and effectiveness of a BPH device include the placebo effect and spontaneous remissions that commonly occur with BPH, the inherent variability and subjectivity of the typical outcome measures commonly used to assess the effectiveness of treatment, and the availability of effective treatments for BPH.

This guidance identifies the key features of non-clinical and clinical investigational plans used to support investigational device exemption (IDE) applications, premarket approval applications (PMAs), De Novo classification requests, and some premarket notification (510(k)) submissions for devices used in the treatment of BPH. Some recommendations in this document may not apply to a particular device, and additional recommendations may be appropriate for novel device types or technologies. FDA will consider alternative non-clinical and clinical testing when the proposed alternatives are supported by an adequate scientific rationale. We encourage you to contact DHT3B, the Division of Reproductive and Urology Devices, when designing your clinical investigation and prior to submission of an original IDE application.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[8] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA

[3] Chute CG, Panser LA, Girman CJ, et al., The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol,* 1993, 150:85-89.
[4] Homma Y, Kawabe K, Tsukamoto T, et al., Epidemiological survey of lower urinary tract symptoms in Asia and Australia using the International Prostate Symptom Score. *Int Urol* 1997, 4:40-46.
[5] Hunter DJW, Berra-Unamuno A, Martin-Gordo A, Prevalence of urinary symptoms and other urological conditions in Spanish men 50 years old or older. *J Urol*, 1996; 155:1965-1970.
[6] Sagnier PP, MacFarlane G, Richard F, Botto H, Teillac P, Boyle P, Results of an epidemiological survey using a modified American Urological Association (AUA) symptom index for benign prostatic hyperplasia in France. *J Urol,* 1994, 151:1266-1270.
[7] Tan HY, Choo WC, Archibald C, Esuvaranathan K, A community-based study of prostatic symptoms in Singapore. *J Urol*, 1997; 157:890-893.
[8] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[9]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

This guidance document addresses the general concepts that we recommend you consider when designing an investigational plan, both non-clinical and clinical, for a medical device indicated for the treatment of BPH. We do not distinguish between indications for use that specifically identify BPH as the disease being treated, and indications for use that identify surgical treatments for BPH, e.g., prostatectomy, transurethral incision of the prostate. This guidance does not apply to devices intended to treat other diseases of the prostate, such as prostate cancer.

These concepts are generally applicable for any type of BPH treatment device undergoing non-clinical and clinical investigation to support a marketing submission. The device may be either class II or class III, and the technologies may include the following:

Product Code	**Description**	**Classification Regulation (21 CFR)**
OEL[10]	Laser surgical instrument for use in general and plastic surgery and in dermatology	21 CFR 878.4810
KNS, OEK, OEJ	Endoscopic electrosurgical unit and accessories	21 CFR 876.4300
MIK*	Device, Ultrasonic, Thermal Ablation	No corresponding CFR section
MEQ*	System, Hyperthermia, Microwave (BPH)	No corresponding CFR section
MER*	Stent, Urethral Prostatic, Permanent	No corresponding CFR section
NZC*	Stent, urethral, prostatic, semi-permanent	No corresponding CFR section
PEW	Implantable transprostatic tissue retractor system	21 CFR 876.5530
PZP	Fluid jet removal system	21 CFR 876.4350

[9] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

[10] Medical lasers with specific indications for BPH cleared prior to issue of this guidance may have been assigned GEX as a product code.

NOY	Agents, embolic, for treatment of benign prostatic hyperplasia	21 CFR 876.5550
QKA[11]	Temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia	21 CFR 876.5510

*These devices are class III and require premarket approval before marketing.

The non-clinical recommendations apply to class II and class III devices. The recommendations provide a framework for performance testing to support marketing authorization or initiation of a clinical study in humans.

The clinical recommendations in this guidance are not intended for the review of 510(k) submissions for class II devices that have traditionally been used in surgical interventions for BPH, such as cutting loops or scalpels.

For some class II devices, the submission of clinical data to support an indication for the treatment of BPH (or any equivalent term) is appropriate and may be necessary to support a 510(k) submission or De Novo request. If you plan to collect clinical performance data to support marketing authorization of a device with new technological characteristics, a new indication, or specific labeling and marketing claims, we recommend that submitters address the considerations discussed in this guidance document when designing the clinical study.

If a clinical study is needed to support marketing authorization, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR part 812, for studies conducted in the United States (U.S.). Generally, we believe the devices addressed by this guidance document are significant risk devices subject to all requirements of 21 CFR part 812. See the FDA guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[12] In addition to the requirements of 21 CFR part 812, sponsors of such trials of a device conducted in the U.S. must comply with the regulations governing institutional review boards (21 CFR part 56) and informed consent (21 CFR part 50).

III. Non-Clinical Testing Recommendations

Prior to use in humans, it is essential to demonstrate that the device will function as intended in its environment of use. The design of medical devices involves non-clinical development and verification of specifications that define basic safety and performance requirements of the device. Most design specifications are validated in non-clinical testing, which allows assessment of device function and safety under controlled circumstances. Additionally, a comprehensive, non-clinical battery of testing provides a foundation for evaluating future changes to the device. We recommend you provide comprehensive non-clinical testing with predefined performance limits (i.e., specifications) to support an IDE application, PMA, 510(k) submission, or a De Novo request for a new device intended to treat BPH.

[11] This classification regulation is subject to special controls. See https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN190020 for more information.

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

This section describes the types of testing that generally have been adequate to support applications for devices intended to treat BPH. Not all of the issues and testing discussed below are applicable to every new device intended to treat BPH, and additional issues or testing not described below may be appropriate for your device depending on its design and mechanism of action.

When you develop the non-clinical testing plan for your device, we encourage you to explore the use of other FDA guidance documents and consensus standards that directly or indirectly relate to relevant aspects of your device. For example, some of the methods frequently used to test performance characteristics of urinary catheters may be applicable to devices intended to treat BPH, such as transurethral microwave thermotherapy (TUMT) applicators. If you use other FDA guidance or consensus standards in developing your non-clinical test plan, we recommend you provide a clear rationale describing how the FDA guidance or consensus standards are relevant to your device.

For information on the recommended content and format of test reports for the testing described in Sections III.A, III.D, III.E, III.H, and III.I, refer to FDA's guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[13]

A. Material Safety

We recommend that you provide data or information that supports the material safety of all patient-contacting components of your device. Because steps in processing, manufacturing and sterilization may introduce new materials and potentially harmful agents not present in the raw material components, it is difficult to support the material safety of a device based solely upon the safety of either similar devices or the raw materials. Therefore, to demonstrate the material safety of your device, we recommend that you conduct biocompatibility testing on the patient-contacting components of your device in their final finished form, in accordance with recognized standards and applicable FDA guidance.

For guidance on the selection of biocompatibility tests, refer to "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'"[14]

To facilitate our independent assessment, we recommend you include the following for all biocompatibility testing conducted:

- a summary of the results;
- test protocols;
- all raw data sheets;
- the acceptance criteria; and

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket.
[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

- any other supporting data.

Frequently, the highest concentrations of potentially harmful materials or agents exist in a new device and may gradually diminish over time. For this reason, biocompatibility testing is often conducted on new devices with little storage time. However, for some devices, the material risks change during long-term storage. For example, long-term storage can allow potentially harmful agents removed from the surface during processing to resurface from the bulk of the device. We recommend you evaluate the impact of device storage on the material safety of your device and conduct the biocompatibility testing at time points in which the potentially harmful materials or agents are likely to be at their highest concentration.

B. Electrical Safety and Electromagnetic Compatibility (EMC)

Some BPH devices are medical electrical equipment and therefore may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance.

Electrically powered BPH devices should be tested to demonstrate that they perform as anticipated in their intended use environment. We recommend that this testing be performed as described in the currently FDA-recognized versions of the following standards for medical electrical equipment safety and electromagnetic compatibility:

- ANSI/AAMI ES60601-1: *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance.*
- ANSI/AAMI/IEC 60601-1-2: *Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic disturbances - Requirements and tests.*

If submitting a declaration of conformity to the above standards, we recommend that appropriate supplemental documentation such as an assessment of the results and how conformity was determined, and information regarding test methods used should be provided because this series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria or address assessment of results. For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance, "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices."[15]

If your device contains a thermometry system, electromagnetic interference can impair the function and accuracy of the temperature sensors. We recommend you include a discussion of how you eliminated or avoided electromagnetic interference with the temperature sensors during testing and treatment, especially if the thermometry system controls treatment delivery. We recommend your discussion include:

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/information-support-claim-electromagnetic-compatibility-emc-electrically-powered-medical-devices.

- the method used to electrically isolate the signal paths of the system's thermocouples;
- the thermocouple sheathing material;
- the filters used to decrease electromagnetic interference; and
- how electromagnetic interference will be minimized in the clinical environment.

C. Magnetic Resonance (MR) Compatibility for Passive Implants

The MR environment includes a strong static magnetic field and its associated spatial gradient, pulsed gradient magnetic fields, and pulsed radio frequency (RF) fields. The interactions of the medical device with the MR environment create safety concerns including serious patient injury, device malfunction, and poor image quality.

We recommend that you address the issues affecting safety and compatibility of your device in the MR environment as described in the FDA guidance, "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."[16] We also recommend that you consider the labeling recommendations given in the same guidance document. If you would like to market various sizes and shapes of your device, then we recommend you follow our recommendations in the FDA guidance, "Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices."[17]

D. Mechanical Testing

Medical devices are subject to mechanical forces during use. Damage or failure of the device due to mechanical forces could result in poor performance or injury to the patient. Therefore, we recommend that you conduct comprehensive mechanical testing to demonstrate that the device and its components can withstand the mechanical stresses of its environment over its expected lifetime. In addition, we recommend this set of tests simulate the mechanical stresses experienced by the device during use, e.g., the forces associated with body movement, insertion, or removal. Mechanical testing includes mechanical strength (e.g., tensile testing), cyclic loading, and simulated use.

To facilitate our review, we recommend you provide a complete description and justification for each mechanical test conducted, including:

- a description of the test article, including its size, sterilization status, age, and any modifications that were made to allow the performance of the test;
- the number of samples tested;
- the testing environment used, e.g., synthetic urine, water, air;
- the load applied, including the rate, direction, and placement;
- the predetermined performance criteria; and
- other relevant parameters used in the tests.

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishing-safety-and-compatibility-passive-implants-magnetic-resonance-mr-environment.
[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-radiofrequency-induced-heating-magnetic-resonance-mr-environment-multi-configuration.

E. Corrosion or Degradation

The urological environment can degrade materials routinely used in medical devices, impacting device performance and safety. For devices that have extended indwelling durations within the urinary tract, we recommend you include corrosion or degradation testing that assesses the effects of bodily fluids on your device. We recommend you:

- perform the testing in a natural or artificial medium that is chemically equivalent to the environment the device will experience *in vivo*;
- select a time course relevant to the proposed clinical use;
- examine the device for any visible corrosion product or encrustation;
- test the device to determine changes in structural integrity or function; and
- measure the device for any change in weight or dimensions.

We recommend you provide a complete description and justification of the following:

- the test articles, including the size, sterilization status, age, and any modifications that were made to allow the performance of the test;
- the number of samples tested;
- the methods used, including the environment and time course;
- the evaluation methods, i.e., visual evaluation, dimensional evaluation, mechanical integrity;
- the predetermined performance criteria; and
- any other relevant parameters.

F. Sterilization

If any component of your device has the potential to introduce pathogens into otherwise aseptic or sterile tissues, we recommend you provide information regarding how pathogens are eliminated from the device, such as sterilization. For any devices or components that are provided sterile, refer to the document "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[18] for the recommended information to include in your 510(k) submission. Additional information (e.g., package integrity testing) or more detailed information (e.g., the results of sterilization cycle validation testing) may be requested for IDE applications, De Novo requests, or PMAs.

If your device, or any of its components, is intended to be reused and has the potential to introduce pathogens into otherwise aseptic or sterile tissues, we recommend you provide detailed instructions on reprocessing methods and evidence that the components can be safely disinfected or sterilized through these methods.[19]

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[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled.

[19] For more information, see the FDA guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling.

G. Software

If your device includes software, we recommend you provide the information based on the risks associated with software failure prior to mitigation, i.e., "Level of Concern." We recommend you submit the information for software devices described in "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."[20]

H. Repeated Use Reliability

The performance and safety of devices, components, or accessories intended for use in multiple treatments can degrade with repeated use and sterilization. If your device contains components intended for use in multiple treatments, we recommend you provide mechanical and functional test data that support device reliability throughout the life expectancy of the components.

I. In Vitro Thermal Mapping (Phantom Study)

Some devices treat BPH by generating thermal fields within the prostate (e.g., TUMT). The magnitude and distribution of the thermal field impacts the therapeutic effect and risks associated with the device. *In vitro* thermal mapping in a tissue-equivalent phantom provides important information on the thermal field prior to use of the device in human or animal populations.

If your device is a thermal field-producing device, we recommend you map the temperature gradient (i.e., the depth of penetration and distribution of heat), in a tissue-equivalent phantom, at body temperature. We recommend that the design of the phantom studies provide the following information:

- a spatial plot of the specific absorption rate (SAR, in W/Kg);
- a spatial plot of the measured temperature as a function of time;[21]
- the value, location, and time of maximum recorded temperature; and
- data recorded at various distances along multiple radial planes (i.e., preferential side, opposite the preferential side, and on each of the lateral sides), including the value, radial distance, and time of the maximum recorded temperature in each plane, if preferential heating applies to the device.[22]

A variety of scientifically valid methods exists to conduct these types of phantom studies. We recommend you provide a detailed explanation and justification of the methods used including:

- the test apparatus, including diagrams labeled with dimensions and the location of the sensors;

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[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices.

[21] For catheter-based applicators, a spatial plot is usually most conveniently created by measuring the temperature along the length of the catheter and in multiple radial planes.

[22] Some thermotherapy applicators are specifically designed to provide preferential heating. However, preferential heating occurs to some extent in any applicator that is not perfectly axi-symmetric. Therefore, we recommend that you collect data in multiple radial planes for all devices in the initial phantom testing. If the testing verifies that the thermal fields are symmetric, you can reduce the number of planes during subsequent phantom testing.

- the sensors used, including evidence that they are not affected by the field generated by the device;
- the phantom, including its composition, thermal and physical constants (e.g., thermal conductivity, density, and heat capacity) electromagnetic properties, e.g., permittivity and electrical conductivity at the proposed frequency, and a literature reference for the phantom, if available;
- the device settings and parameters used; and
- the technological characteristics of the power control unit and the power adjustment method.

When you report the findings of thermal mapping for your device, we recommend that you include a scientifically sound rationale describing how the results obtained with the tissue-equivalent phantom relate to clinical use in humans. Specifically, we recommend the discussion include the following:

- the relationship between results and the pertinent anatomy of the lower urinary tract;
- how the data demonstrate that your device provides therapeutic heating to the prostate without clinically significant heating of the non-target tissues; and
- the impact of the heterogeneous tissue composition of the prostate and surrounding tissues including blood flow.

J. Animal Study

Animal studies[23] provide a valuable assessment of the device's functional design characteristics to evaluate the device for its intended use. The limitations of bench models can make adequate assessment of some safety and effectiveness concerns difficult with bench testing alone. For example, bench testing does not assess tissue necrosis and healing for thermal field-producing devices. For most new BPH devices, animal studies provide data to evaluate such safety and effectiveness concerns prior to use in humans.

We recommend that you assess whether animal studies are warranted in your comprehensive non-clinical testing plan. Conducting animal studies for a new device intended to treat BPH depends on factors that include:

- device design;
- material construction;
- mechanism of action;
- duration of clinical use;
- history of clinical use; and
- data from prior animal studies, human clinical investigations (foreign and domestic), or other appropriate studies.

[23] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

Animal studies intended to evaluate device safety should be conducted pursuant to 21 CFR part 58. To facilitate our evaluation of your study methods and results, we recommend that you provide complete descriptions and justifications for the following:

- choice of animal model and the number of animals tested;[24]
- the test protocol, including objectives and procedures;
- the study results, including the investigator's comments;
- the study conclusions;
- the treatment site;
- all complications;
- all device malfunctions; and
- the study results relating to the human anatomy and the intended use of the device.

In addition, animal study(ies) should include gross and histological examination of the treatment areas by a blinded, independent pathologist that includes the following:

- serial sectioning and staining with hematoxylin and eosin stain and/or a functional stain to evaluate thermal injury, as appropriate;
- representative photomicrographs of histopathological sections; and
- pathologist review and histological description of tissue changes, and extent of changes in three dimensions, in the prostate, prostatic urethra, rectal wall, bladder neck, external sphincter, neurovascular bundle, and prostatic capsule. For technologies such as prostate artery embolization that use embolic agents, we recommend the anatomy surrounding the urethra (e.g., bladder, rectum) be examined for non-target embolization leading to damage, ischemia, or necrosis.

Prior to initiating an animal study, the Agency encourages manufacturers to submit a Q-Submission to obtain detailed feedback on any animal studies for devices intended to treat BPH. For more information, see the FDA guidance document "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[25]

We recommend that the following specific animal studies be conducted for new thermal field-producing devices and stents.

(1) Thermotherapy

Thermal field-producing (i.e., thermotherapy) devices for the treatment of BPH by design generate tissue damaging temperatures. Bench testing, such as *in vitro* thermal mapping, provides partial evidence that a thermal field-producing device can raise the target tissue to therapeutic temperatures without clinically significant heating of the surrounding non-target tissues (e.g., rectum, bladder). However, these models do not capture important characteristics of the human urological system that impact device performance and safety, such as blood flow, tissue heterogeneity, and active tissue processes such as healing.

[24] We recommend that you conduct the study using an analytically meaningful number of animals for each experimental condition (i.e., each observation time point, each device operational setting).
[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

We believe animal studies examining the temperature distributions, histological changes, and safety of the non-target tissues are important in assessing the tissue effects of the treatment prior to clinical use in humans. Animal studies are important for devices in which the heating is not localized, and the entire prostate is exposed to prolonged heating (e.g., transurethral microwave thermotherapy (TUMT) devices), or for devices using new ways to generate the thermal field.

We recommend you conduct an *in vivo* animal study to provide complete thermal mapping of the prostate and non-target tissues (i.e., transperineal interstitial thermal mapping including the urethral, intraprostatic, periprostatic, and anterior rectal wall tissues) using intact male dogs of sufficient age and size to mimic the human prostate anatomy. Tissue temperatures should be recorded following treatment until they return to baseline to ensure capture of maximum temperature and time-temperature history. Due to the differences in human and animal anatomy, we recommend image verification of the location of the device components (e.g., treatment applicator, temperature probes) and the temperature sensors.

We recommend you select device operating parameters for the animal study that mimic clinical use in humans to evaluate the safety and functional characteristics of the device design, and to validate the performance of the device for its intended use. You should evaluate the complete range of achievable power levels and temperatures, including the maximum power and time settings. If your device includes multiple applicator designs or variable operational settings (e.g., treatment time, power), we recommend you conduct complete testing for each design and setting. For example, if your device includes both a cooled applicator and a non-cooled applicator, we recommend you evaluate each applicator using minimum, mid-range, and maximum settings in your animal study. If your device includes multiple treatments, the number of treatments used in the animal study should equal or exceed your intended maximum number of treatments.

Because these devices rely on acute tissue injury, followed by necrosis and subsequent healing to achieve their intended use, we recommend you evaluate both the early tissue effects and subsequent early healing (e.g., 24 hours, three weeks after treatment).

As described above, we recommend you provide histological assessment of tissue changes and a discussion of the extent of thermal effects as they relate to human anatomy. Specifically, we recommend you compare the observed area of histological thermal effects with the relevant anatomy, including:

- in-target compared with non-target tissue; and
- the target tissue in relation to that of surrounding critical tissues, including rectal wall, urethra, neurovascular bundles.

(2) Stents

Whether we recommend conducting animal studies for prostatic stents intended to treat or relieve BPH depends on the device design, material construction, mechanism of action, duration of use, and any novel aspect. For example, we recommend animal data to evaluate the safety of a permanent prostatic stent prior to clinical use in humans.

We recommend the animal study protocol closely approximate the intended clinical methods to evaluate the safety of the procedure, functional design characteristics, and to validate the performance of the device for its intended use. In addition, we recommend you select follow-up periods and sacrifice periods that provide clinically meaningful assessment of the device effects.

We recommend the animal study include:

- placement of a single stent as per clinical protocol;
- placement of the maximum number of stents proposed for use in the clinical study;
- repositioning the device; and
- removal using the manufacturer's recommended techniques.

We recommend this animal study assess the following adverse events using imaging, gross, and histologic evaluation as indicated based on a clinical risk assessment:

- stent migration;
- encrustation;
- erosion;
- pressure necrosis;
- urothelial hyperplasia/tissue ingrowth;
- stone formation;
- urethral edema;
- cellular atypia; and
- device failure or breakage.

We recommend you conduct a macroscopic and microscopic evaluation of the stent including calcification, erosion, and epithelization.

If your stent can be explanted or removed, we recommend you conduct mechanical testing similar to the non-clinical testing on the explanted stents in order to evaluate any changes to the structural integrity of the device that may have occurred due to stent implantation.

If your stent is designed to resorb or degrade *in situ*, we recommend you evaluate the degree of absorption or degradation at multiple time points over the course of its degradation to ensure that tissue response to starting, intermediate, and final degradation products are fully assessed. We also recommend the timing of your evaluations be sufficient to determine the rate of degradation and to demonstrate that complete healing and total elimination of the stent occurs. The selection of time points for the study may depend on the nature of the material and should relate to its estimated degradation time.

IV. Pilot Clinical Study Recommendations

For BPH devices that are novel or represent a significant shift in technology or use relative to existing products, we recommend that you stage the clinical investigation of your device in phases to minimize the risks to investigational subjects, to ensure device functionality, to monitor safety, and to gain experience in use of the device prior to commencing a large clinical

study. These phases typically consist of an initial phase, commonly referred to as a "pilot" or "feasibility" study, followed by a pivotal study.

During the pilot study phase, you can gain valuable information regarding short-term safety, treatment technique, study conduct, and the optimal patient population. Additionally, information obtained from exploratory analyses of the pilot study results can be used to refine pivotal study hypothesis, identify the most suitable endpoints and estimate their response to treatment and variance, and investigate potential indications for use. Information from a pilot study may also allow a limited evaluation of the factors that may introduce bias (e.g., covariates).

A pilot study generally involves a limited number of subjects and sites, and close monitoring of all adverse events. The size and duration of the pilot study can vary depending upon the type of device being investigated. For example, a pilot study for a novel or high risk device generally begins with a smaller sample size and follows subjects for a longer period of time. We recommend the pilot study protocol prospectively define the minimum dataset (i.e., number of enrolled subjects and the minimum duration of follow-up on those subjects) to be collected to support initiation of the pivotal study. For investigations conducted under an IDE application, we recommend you submit a detailed report of the pre-specified pilot study dataset prior to, or at the time of, the request for pivotal study approval. Analysis of the pilot study dataset will help determine whether it is appropriate to initiate the pivotal study.

In situations where the performance of the control group is not well characterized, or there are logistical issues associated with randomization that require exploration, we recommend you randomize subjects in your pilot study between study groups. This information can help you adequately power and carry out the subsequent pivotal study.

We believe it is unlikely that pilot study data can be pooled with pivotal study data because there are often differences in the pilot and pivotal study protocols. If you intend to pool pilot and pivotal study results, we recommend you plan it prospectively and provide a rationale showing that it is statistically and clinically valid to pool the data from the pilot and the pivotal studies.

For thermal field-producing devices in which heating is not localized and the entire prostate is exposed to prolonged heating (e.g., TUMT devices), we recommend that you conduct a pilot study that includes transperineal interstitial thermal mapping to ensure that the pivotal study population will not be placed at unreasonable risk. We acknowledge that there are risks associated with interstitial thermometry. However, we believe that interstitial thermal mapping provides essential data needed to evaluate the temperatures achieved and to assess the safety of exposure to such temperatures, which support the reliability of the treatment effect and the safety profile of the device. We recommend you conduct interstitial thermal mapping to provide reasonable assurance that therapeutic temperatures are reached, can be controlled, and are safe.

For interstitial thermal mapping, we recommend you acquire temperature measurements at the time of the first treatment session on a small but analytically useful number of subjects, e.g., the first 10 patients treated. The methods should characterize the temperature distribution in the prostatic and periprostatic tissues, including the rectal wall and urethra, and monitor for unexpectedly high or low temperatures being produced within affected areas. These

measurements are usually accomplished by introducing at least two fiber optic thermal sensors transperineally using direct imaging control by transrectal ultrasound under local anesthesia extending into the prostatic capsule. Alternate thermosensors are acceptable if there is an adequate demonstration that they are not affected by the energy field generated by the device. We recommend you carefully collect and report all adverse events.

V. Pivotal Clinical Study Recommendations

The purpose of the pivotal clinical study is to collect the primary evidence of safety and effectiveness to support a marketing submission or application. This phase of the clinical investigation is conducted after sufficient evidence of device safety and function is available from preclinical and (if needed) pilot clinical study testing to support its use in human research subjects.

Proper pivotal study design can minimize error and bias; and facilitate an objective assessment of the investigational device. We recommend you conduct a pivotal study of a device intended to treat BPH at multiple clinical sites to demonstrate that the study results are repeatable among a wide variety of investigators and patient populations, and to increase the likelihood that the study population is representative of the general patient population.

We recommend that you address the following when designing a pivotal clinical study for a device intended to treat BPH.

A. Study Objective

The study objective forms the basic framework for the study design and helps in identifying the control, the primary endpoint, the study follow-up duration, and the primary statistical analysis. The statistical hypothesis follows directly from the primary objective of the study. For these reasons, you should state a clear study objective before you design your pivotal clinical trial. All elements of your trial design should be consistent with your study objective.

B. Minimizing Bias

One consideration in the design of any clinical study is how to minimize known or suspected sources of bias so the study conclusions can be clearly and objectively assessed. Bias occurs when any characteristic of the investigator, study population, or study conduct interferes in a systemic way with the ability to measure a variable accurately. Appendix 1 identifies common sources of potential bias and methods that are frequently employed to mitigate them. These sources of bias are discussed individually in Sections V.C (Randomization and Controls), V.D (Blinding (Masking)), V.I (Patient Selection Criteria), and V.N (Statistical Analysis Recommendations) of this guidance document.

If these sources of bias are not adequately minimized, the validity of the study's conclusions regarding the safety and effectiveness of the investigational device may be questionable. For all study designs, we recommend your protocol include a section describing how the study design intends to minimize bias.

C. Randomization and Controls

Clinical investigations of devices for the treatment of BPH pose unique challenges such as a placebo effect, spontaneous remissions, subjectivity of lower urinary tract symptoms (LUTS) and their impact on quality of life, difficulty in securing reliable measurement of LUTS and quality of life, and wide availability of effective treatments for BPH.

We believe these challenges are most efficiently overcome by using a randomized, controlled trial design. The benefit of a randomized, controlled trial is its tendency to balance confounding factors, measurable and unmeasurable, between study groups and minimize the potential for bias.

The potential advantages of a randomized, controlled trial design extend not only to the evaluation of device effectiveness, but also to the evaluation of safety. Adverse event rates may be affected by factors such as subject characteristics, device design, evolving procedural methods, and operator experience, and may be much more difficult to evaluate when using historical control data.

Randomizing subjects between study groups is a standard method to minimize selection bias and control for confounding factors. Selection bias occurs when subjects possessing one or more important prognostic factor appear more frequently in one study group than the other. The randomization process assigns subjects to an intervention or control group with a known probability and each subject has an equal chance of being selected for a group. Randomization also protects the trial from conscious or subconscious actions on the part of study investigators that could lead to study groups that are not comparable, e.g., selecting the most symptomatic patients for the therapy thought by the study investigator to be the more aggressive treatment.

We recommend you:

- pre-specify the randomization method in the study protocol;
- balance the assignment of subjects within each site, e.g., stratification by site, block randomization;
- preclude investigators and other study personnel from predicting or influencing the assignment of subjects; and
- prevent natural patterns of patient behavior from influencing study assignment.

When designing a randomized, controlled study, we recommend you select an appropriate control therapy. There are a variety of scientific and ethical issues that may influence the choice of control.[26] Typically, the current standard of care for the targeted patient population represents the most clinically meaningful control. However, other factors may also influence this decision. We recommend you address each of the following specific factors when choosing a control:

- standard of care;
- indications for use of the investigational device;
- any desired representations of device performance in future labeling;

[26] Temple R, Ellenberg SS, Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Ann Intern Med*, 2000, 133(6):455-461.

- risks versus benefits, i.e., to permit a clinically meaningful comparison, it is desirable for the risk-to-benefit ratio of the control treatment to be comparable to that of the investigational device;
- ability to effectively mask the investigator, subject, and evaluator;
- time to treatment effect; and
- device design characteristics.

Potential control therapies for clinical investigations for the treatment of BPH include:

- an accepted surgical procedure, e.g., transurethral resection of the prostate (TURP);
- a medical device cleared or approved for the treatment of BPH; and
- sham treatment.

TURP is considered the gold standard surgical treatment for BPH and there are many successful clinical trials using TURP as a control.

A control that consists of a treatment with a legally marketed device, similar in design to the investigational device, is often a desirable option because study design, patient enrollment, and data analysis may be straightforward. For example, it might be both simple and appropriate to use a randomized study to compare the safety and effectiveness of a new implantable transprostatic tissue retractor system to a legally marketed system with similar design and operational characteristics.

Sham effect during BPH procedures has been shown to be significant, on the order of change seen with commonly used medications.[27] Sham controlled studies represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design may be most appropriate for studies with subjective endpoints, such as reduction in patient-reported symptoms. Sham surgical procedures/treatments typically involve more risk than the placebo control arm in drug trials and these risks should be considered when designing a clinical trial. This study design should be considered when it is methodologically warranted, i.e., when designs that are unblinded are methodologically unacceptable (e.g., because endpoints are subjective) and when a "no treatment" control is methodologically warranted. Furthermore, the withholding of treatment should not lead to serious injury, such as irreversible morbidity, or death. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned.

While potentially useful to certain stakeholders, the use of an approved drug therapy as a control is complicated because devices used to treat BPH generally have significantly dissimilar expected risks and different mechanisms of action compared to approved drug therapies.[28] Additionally, devices intended to treat BPH achieve full effectiveness quickly, while drug

[27] Welliver C, Kottwitz M, Feustel P, McVary K, Clinically and Statistically Significant Changes Seen in Sham Surgery Arms of Randomized, Controlled Benign Prostatic Hyperplasia Surgery Trials. *J Urol*, 2015, 194:1682-7.
[28] AUA Guideline "Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms (2018, amended 2019)" (https://www.auanet.org/guidelines/benign-prostatic-hyperplasia/lower-urinary-tract-symptoms).

therapies often take many months to reach full effectiveness. Consequently, the results of drug-controlled studies can be difficult to interpret when assessing the safety and effectiveness of a device.

It is often difficult to obtain adequate, dependable, and directly applicable historical information from published literature or a prospective chart review due to variations in patient demographics, selection criteria, and evaluation methodologies. Consequently, we believe using an historical control complicates the demonstration of safety and effectiveness in most investigations.

You can employ several strategies to facilitate subject recruitment and retention. For example, 2:1 (or other) randomization schemes increase the likelihood that a given subject will receive the investigational treatment. Study designs may allow sham subjects, for example, to receive treatment with the investigational device after a pre-specified time or significant disease progression.

We generally recommend a randomized, controlled trial to address the challenges described in this guidance document; if you use an alternative study design, we recommend you discuss how it is scientifically sound and will address relevant safety and effectiveness questions. While we recognize that there is no unique "best design" for investigations of BPH treatments, we consider the elements discussed in this document as core features of well-designed studies. As noted, we will consider alternative study designs, but we recommend that you clearly explain the scientific reasoning supporting your alternative design (e.g., How will bias be minimized? How does the study address placebo effects? How does the control compare with current patient characteristics and standards of clinical care?). Prior to initiating a clinical study with an alternative design, FDA encourages manufacturers to submit a Q-Submission to obtain detailed feedback on such studies. For details on Q-Submissions, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[29]

For all study designs, we recommend you collect detailed baseline and demographic information on all study subjects so that the study groups can be assessed for imbalances in prognostic factors.

D. Blinding (Masking)

Sources of bias in a clinical trial include investigator bias, evaluator bias, and placebo or sham effect (defined in Appendix 1). To protect the study against these sources of biases, we recommend you incorporate blinding (masking) into the study design. Single-blind designs mask the subject from knowing what intervention was assigned. Double-blind studies mask both the subject and the investigator. In cases where single- and double-blind designs are impossible or not feasible, it is usually possible to use a masked third party evaluator to evaluate certain outcome measures, e.g., symptoms scores, quality of life, cystoscopy, adverse events.

Blinding is usually accomplished by coding the interventions and having an individual who is not on the patient care team control the key to the code. Since bias introduced by breaches in

[29] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

blinding can be very difficult to assess in the analysis, we recommend you do not to break the code until the analysis is completed. If your study incorporates blinding, the protocol should describe the blinding methodology and prospectively define the conditions for breaking the blinding code.

E. Study Endpoints

Your clinical protocol should clearly specify and support the study's primary and secondary endpoints. To ensure the collection of meaningful results, these endpoints should be clinically relevant to the patient population you intend to target in the study. Additional factors to consider when selecting the optimum endpoints for your clinical investigation are described below.

(1) Primary Endpoints

The primary safety and effectiveness endpoints are the clinical measures that best characterize the safety and effectiveness of the device and are used to judge the overall success of the study. For a BPH device study, the primary endpoint specified in the statistical hypothesis is usually an effectiveness endpoint, which, in turn, directly impacts the indications for use. Generally, study success is based on the ability of the study to achieve both the primary effectiveness endpoint and the primary safety endpoint.

(2) Primary Effectiveness Endpoint

The primary effectiveness endpoint should be one that is clinically meaningful and should fully characterize the effect of treatment. Due to the subjective nature of BPH symptoms, it is difficult to find an effectiveness measure that is objective and repeatable (i.e., has low test-retest variability), yet is also meaningful to patients and relevant to their reasons for seeking treatment.

Since its development, the most widely used primary outcome measure used in studies of therapies for BPH has been the American Urological Association Symptom Index (AUA-SI) and the equivalent International Prostate Symptom Score (IPSS). These measures consist of seven questions assessing LUTS associated with BPH (i.e., incomplete emptying, frequency, hesitancy, urgency, weak stream, straining, and nocturia). Each question is scored on a 0-5 scale and summed to form a final score from 0-35, where higher scores reflect more severe symptoms.[30] An additional disease-specific quality of life question scored separately on a 0-6 scale is included in the IPSS. These instruments are considered reliable measures of LUTS due to BPH and have been validated in multiple languages.[31]

Bothersome LUTS is usually the primary reason a patient seeks treatment for his BPH, and most devices used to treat BPH are designed to provide symptomatic relief. In most clinical trials, the

[30] Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al., The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*, 1992, 148:1549.

[31] Barry MJ, Adolfsson J, Batista JE, et al., Measuring symptoms and health impact of benign prostatic hyperplasia and its treatments. In: Denis L, Griffiths K, Khoury S et al. (eds). Fourth international consultation on BPH. Plymouth: Plymbridge Distributors: 1998: 265-321.

primary effectiveness endpoint should demonstrate improvements in symptom severity. Specifically, we recommend you base the primary effectiveness endpoint upon the improvement in AUA-SI (or IPSS) compared to baseline.

Generally, patients are unable to discern an AUA-SI (or IPSS) score difference of less than 3 points.[32] However, the minimal clinically significant difference following treatment depends on the baseline symptom score. Investigations evaluating the minimal clinically significant difference in AUA-SI used drug therapy for BPH. FDA is unaware of studies that identified the minimal clinically significant difference in AUA-SI following device treatment. Furthermore, many trials enroll subjects across more than one symptom severity classification. Therefore, identifying an appropriate minimal clinically significant difference for the AUA-SI following device therapy can be challenging.

One study of men with moderate to severe LUTS used a balanced Likert score to investigate the extent to which patient satisfaction is influenced by a change in BPH symptoms.[33] This study identified a range of improvement in AUA-SI across symptom severity classifications needed to achieve certain satisfaction levels. An improvement of at least 30% in the AUA-SI was used for a "Satisfied" or "Very Satisfied" response. This is an appropriate level of response given the difference in risk profiles between drug and device therapies. Based on this literature, we recommend an improvement of ≥ 30% over baseline as the minimum clinical improvement in AUA-SI following device therapy. Higher risk devices may warrant a more significant benefit. We recommend a 12-month analysis of the primary effectiveness endpoint(s) for an active control trial. For a study design that does not include an active control, we recommend incorporating a sham control. Given the challenge in maintaining a sham control for 12 months, we recommend a shorter timepoint for head-to-head comparison between the treatment and sham arms. However, stability of effectiveness should still be demonstrated at 12 months for the *treatment arm* in a sham-controlled trial.

Separation of the irritative and obstructive symptom questions in the AUA-SI (or IPSS) is psychometrically valid, but at this time it is not clear that such sub-score analyses are clinically meaningful.[34]

We recognize that other outcome measures may be appropriate as well due to specific device design characteristics or desired marketing claims. For example, claims for reduction of obstruction could be based on documented improvement in flow rate, results of "pressure/flow" studies (cystometry), and post-void residual urine volume. If you choose an alternative outcome measure, it is important that you provide a scientifically valid rationale that explains its appropriateness for your device.

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[32] Barry MJ, Willlifred WO, Chang Y, et al., Benign prostatic hyperplasia specific health status measures in clinical research: How much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients. *J Urol,* 1995, 154:1770-1774.

[33] Roehrborn CG, Wilson TH, Black LK, Quantifying the Contribution of Symptom Improvement to Satisfaction of Men with Moderate to Severe Benign Prostatic Hyperplasia: 4-Year Data from the CombAT Trial. *J Urol*, 2012, 187:1732-1738.

[34] Barry M.J., et al., Filling and voiding symptoms in the American Urological Association symptom index: the value of their distinction in a Veterans Affairs randomized trial of medical therapy in men with a clinical diagnosis of benign prostatic hyperplasia. *J Urol*, 164:1559-1564, 2000.

(3) Primary Safety Endpoint

We recommend you base the primary safety endpoint on the incidence and severity of adverse events. However, if the device is associated with, or intended to mitigate, a specific safety concern, then it may be appropriate to base the primary safety endpoint on the specific adverse event(s) of interest associated with that concern, while still recording all adverse events.

To collect safety information reliably, we recommend your protocol instruct the investigators to record all adverse events, regardless of whether you believe they are device-related or anticipated. Regardless of study design, we recommend you follow subjects during the premarket follow-up period for one year following treatment to monitor adverse events. We recommend you routinely record the following events at baseline and at follow up time points, noting the severity of each event:

- genitourinary events, i.e., events associated with the urinary tract and/or the surrounding genital region, including, but not limited to, stress urinary incontinence, urge urinary incontinence, and urinary retention (defined by any need for catheterization ≥ 7 days post-procedure);
- damage to the bladder floor, trigone, sphincters, and rectum;
- infections;
- worsening or new onset erectile and/or ejaculatory dysfunction;
- secondary surgical interventions;
- all transient post-procedure events; and
- deaths.

Adverse events should be categorized according to their respective relatedness to the device or procedure, and their severity (e.g., using the Clavien-Dindo classification of complications or the latest version of the Common Terminology Criteria for Adverse Events[35]). This categorization should be based on pre-defined criteria and can be accomplished by study investigators or an independent, third-party Clinical Events Committee (CEC). Because of the difficulty of determining the root cause of genitourinary events, we recommend you categorize events conservatively as either device- or procedure-related unless there is clear evidence of other causation. Additionally, we recommend that investigators document the onset and resolution times of each adverse event, noting the method of resolution.

We recommend the safety analysis include a descriptive assessment of the types and frequency of adverse events observed in the study, with comparison to the control therapy, as appropriate.

(4) Secondary Endpoints

FDA believes secondary endpoints, by themselves, are not sufficient to fully characterize treatment benefit. However, these measures may provide additional characterization of the treatment effect. Specifically, secondary endpoints can:

- supply background and understanding of the primary endpoints;

[35] For more information, see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- be the individual components of a composite primary endpoint, if used;
- aid in the understanding of the treatment's mechanism of action;
- be associated with relevant sub-hypotheses (separate from the major objective of the treatment); or
- be used to perform exploratory analyses.

Assuming that the primary safety and effectiveness endpoints of the study are successfully met, we recommend you analyze the secondary endpoints to provide supportive evidence concerning the safety and effectiveness of the device, and to support device performance if you plan to make such representations in your labeling.

Although there are many possible secondary endpoints to consider for clinical investigations of devices intended to treat BPH, we recommend your protocol include the endpoints discussed below:

- Prostate volume: Many devices intended to treat BPH, such as transurethral microwave thermotherapy (TUMT), can reduce prostatic volume. Increases in prostatic volume can also indicate the progression of BPH. Therefore, we recommend that you evaluate prostatic volume throughout the study for those devices where the mechanism of action depends on reduction in prostate volume.
- Uroflowmetry: Decreased peak urine flow rates are common in men with BPH. We recommend you conduct uroflowmetry including peak and average flow rates, total void time, and total void volume at each follow-up visit.
- Post void residual (PVR) urine volume: PVR has generally been considered to reflect the severity of bladder outlet obstruction. We recommend you measure PVR at each follow-up visit to monitor impairment or improvement of bladder emptying due to the treatment or disease progression.
- Quality of life: BPH is associated with impairment of quality of life. Therefore, we recommend you incorporate a validated quality of life measure specific to BPH into the study. The measure most commonly used is the disease-specific quality of life question included with the AUA-SI (or IPSS) questionnaire.
- Return to "Normal" symptom severity: There is value in knowing the percentage of subjects whose symptoms improve to what is considered "normal" (i.e., AUA-SI < 8) after therapy. Conversely, the proportion of subjects whose symptoms worsen after therapy is also important to know. Therefore, we recommend you collect pre- and post-treatment AUA-SI scores.
- Return to normal activities: The time to recovery is also important to patients. Recovery time may be assessed by recording the days to return to normal activities or to return to pre-operative activity level.
- Sexual function and dysfunction: Both BPH and many of its therapies adversely affect sexual function, including erectile and ejaculatory dysfunction. Therefore, we recommend you incorporate a validated, sex-specific measure of sexual function assessed at each follow-up visit.

- The recommended instrument to assess erectile function is the International Index of Erectile Function, specifically the Erectile Function domain (IIEF-5).[36] The Minimal Clinically Important Difference (MCID) has been shown to be 4 points.[37] However, the MCID is a function of baseline erectile function. For example, the MCID is 2, 5, or 7 for men with mild, moderate, or severe erectile dysfunction, respectively. If your study population is limited to men in only one subgroup of erectile dysfunction (mild, moderate, or severe), it is appropriate to use the specific MCID for your study group. However, if you choose to include men across two or more ranges of erectile dysfunction (e.g., mild and moderate, moderate and severe, or mild, moderate, and severe), then a responder analysis using the appropriate MCID considering baseline values is more appropriate.
- We recommend you assess ejaculatory function using a validated instrument.

Recommendations regarding the statistical analysis of secondary endpoints are discussed in Section V.N(3) of this guidance document.

F. Study Duration

You should design your clinical study to assess whether the treatment effect, assessed using the primary and secondary effectiveness endpoints, persists for a clinically meaningful period of time. For devices intended either as a curative treatment for BPH or for long-term management, we recommend you follow subjects during the premarket follow-up period for 1 year following treatment to document the stability of the treatment effect and to monitor adverse events. However, it is possible that longer follow-up may be appropriate depending upon a variety of device-specific factors or study design considerations. For example, for devices in which retreatment is needed or permitted, we recommend the follow-up duration refer to the period following final treatment. As another example, if either the device or the control is expected to have a significant delay in the time to achieve the full treatment effect, we recommend the duration of the study be extended accordingly.

In addition to the premarket follow-up considerations discussed above, long-term postapproval studies may be appropriate for class III (premarket approval) devices to assess the stability of the treatment effect and any specific long-term safety and effectiveness concerns that arise during the premarket study. For devices for which postapproval studies are anticipated or possible, we recommend your study continue to follow subjects annually beyond marketing approval. In the event FDA requires a postapproval study as a condition of PMA approval,[38] incorporating this extended follow-up in the original pivotal study will allow you to convert the premarket study into a postapproval study, eliminating the need to obtain additional informed consent from study subjects for follow-up and recruiting new subjects.

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[36] Rosen RC, Riley A, Wagner G, et al., The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997,49:822–30.

[37] Rosen RC, Allen KR, Ni X, Araujo AB. Minimal Clinically Important Differences in the Erectile Function Domain of the International Index of Erectile Function Scale. *Eur Urol*, 2011, 60:1010-1016.

[38] 21 CFR 814.82(a)(2).

G. Statistical Hypothesis

The statistical hypothesis follows directly from the primary objective of the study and establishes the framework for the design of your study. The statistical hypothesis is also used to calculate the sample size and helps determine the statistical methodology that will be used to analyze the primary study endpoint. For these reasons, you should formulate a clear statistical hypothesis that is consistent with the primary objective of your study when you design your pivotal clinical trial and include it in your protocol. All other elements of your clinical study design should be consistent with your statistical hypothesis.

For non-inferiority studies, we recommend the hypothesis incorporate a non-inferiority margin that reflects a maximum tolerable difference that is "clinically insignificant" (i.e., "not clinically meaningful") in the analysis of the primary effectiveness endpoint. Larger values of the non-inferiority margin may be selected by demonstrating significant benefits in the safety of the investigational device.

H. Sample Size

We recommend your protocol include the calculation of the estimated sample size appropriate to test the statistical hypothesis. For this calculation, we recommend using a statistical formula that is appropriate for the proposed statistical hypothesis. We recommend you state and support all statistical assumptions associated with the sample size calculation. For additional recommendations, see the FDA guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices."[39]

Since patient drop-out and other forms of missing data may occur in any clinical study, we recommend adjusting the calculated sample size upward by the anticipated loss to follow-up rate. Additionally, upward adjustment of the sample size can minimize the likelihood of having inadequate statistical power due to incorrect assumptions regarding the treatment and placebo effects and their variance.

I. Patient Selection Criteria

Although BPH is predominantly confined to older men, age and other baseline characteristics of the patient population can impact the effectiveness and safety of different device therapies for BPH. Therefore, we recommend you develop inclusion and exclusion criteria for your clinical trial that select a cohort representative of the population that will be treated clinically, while limiting characteristics that could confound the interpretation of the data.

We recommend your protocol define inclusion criteria that identify an appropriate target population. Specifically, your study should enroll men clinically diagnosed with BPH for which treatment is recommended. The patient characteristics we recommend you consider in developing the inclusion criteria for your study include the following.

[39] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

- Age: The protocol should state the age range eligible for enrollment. Because BPH is generally confined to older men, we recommend you include men over 50.
- Diagnosis: Investigators should diagnose subjects as having symptomatic BPH. We recommend the diagnosis criteria specified in the protocol be consistent with the current standard of care.
- Prostate size and shape: Frequently, devices intended to treat BPH are specifically designed to treat prostates of a specific size in terms of volume and length. We recommend your inclusion criteria prospectively define intended prostate size within lower and upper limits based on the parameters of the particular therapy. Prostate size and shape should be determined according to current AUA BPH guidelines.
- Symptom severity: Generally, patients seek treatment for BPH due to bothersome symptoms. We recommend your protocol prospectively define a range of AUA-SI (or IPSS) scores consistent with the severity of symptoms your device is intended to treat. For example, an AUA-SI > 20 is consistent with the current clinical definition of severe BPH.[40]
- Peak urine flow rate: Reduced urinary flow rates are indicative of bladder outlet obstruction and are suggestive of BPH. We recommend you include subjects with peak urine flow rates that are indicative of obstruction (e.g., < 12 ml/sec).[41]
- Subject compliance and suitability: We recommend enrolling subjects who are able to understand all study requirements and have life expectancies greater than the study period. Further, we recommend enrolling subjects who are able to tolerate the procedure (e.g., good surgical candidates) and agree to baseline and follow-up evaluations specified in the protocol.

Investigational devices present some unknown risk to study subjects. For this reason, patients with substantial comorbidities are more vulnerable and should be protected from this unknown risk by appropriately devising exclusion criteria for a clinical trial. However, FDA recognizes that a device intended to treat BPH could potentially offer an advantage, especially suitable for those subjects with substantial comorbidities (e.g., shorter procedure time, local anesthesia instead of general anesthesia, minimal bleeding risk). We recommend justifying inclusion of such subjects with a clear explanation of the expected benefits and risks if these patients are intended to be included in the study.

We recommend your study protocol define exclusion criteria that prevent enrollment of subjects with characteristics that could confound the interpretation of the data or that suggest that your device poses undue risk. The patient characteristics we recommend you consider in developing the exclusion criteria for your study include the following.

- Confounding conditions: We recommend your protocol exclude men with a history of any illness that might confound the results of the study, produces symptoms that might be

[40] Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al., The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*, 1992, 148:1549.

[41] Using current techniques, an adequate minimum voided volume (i.e., 125 ml) is needed to obtain accurate measurement of flow rates. Also, we recommend that you base the baseline flow rates on two separate measurements.

confused with those of BPH, or poses additional risk to the patient based on device design. Examples include:

- cardiac arrhythmias, cardiac disease including congestive heart failure, uncontrolled diabetes mellitus, significant respiratory disease, known immunosuppression, or bleeding disorders;
- neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes;
- a post void residual (PVR) volume > 250 ml measured by ultrasound or acute urinary retention;[42]
- compromised renal function (i.e., serum creatinine level > 1.8 mg/dl, or upper-tract disease);
- confirmed or suspected bladder cancer;
- recent (within three months) cystolithiasis or hematuria;
- urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology;
- a history of prostatitis within the last two years; or
- an active urinary tract infection.

- Prostate cancer: We recommend your protocol exclude men with confirmed or suspected malignancy of the prostate based on the digital rectal exam (DRE), prostate biopsy, transrectal ultrasound (TRUS), or prostate specific antigen (PSA) level. We recommend your protocol include testing the PSA level of all subjects. Currently clinical guidelines indicate that a PSA level > 10 ng/ml is indicative of prostate cancer. We recommend your protocol include a prostate biopsy prior to enrollment, if indicated, based on DRE, or if the subject's PSA level is > 2.5 ng/ml and ≤ 10 ng/ml and his free PSA is < 25% of total PSA.[43] Finally, we recommend you follow the aforementioned American Urological Association (AUA) guidelines to help determine in which subjects prostate cancer screening is appropriate based upon age, ethnicity, family history.
- Surgical history: We recommend your protocol exclude men with a history of any surgery that might confound the results of the study, or that poses additional risk to the patient based on device design. Examples include:
    - previous rectal surgery (other than hemorrhoidectomy) or history of rectal disease if the therapy may potentially cause injury to sites of previous rectal surgery, e.g., if a transrectal probe is used;
    - previous pelvic irradiation or radical pelvic surgery;
    - previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate; or

[42] Subjects with acute urinary retention should be excluded or treated as a separate cohort due to confounding problems in this group.

[43] We recognize that current thinking on best clinical practices on the use of PSA in screening for prostate cancer and the minimum normal value for PSA is under debate in the clinical community (see Barry MJ, Prostate-specific-antigen testing for early diagnosis of prostate cancer, *N Engl J Med*, 2001, 344:1373-1377; and "Early Detection of Prostate Cancer (2018)," AUA Guideline, https://www.auanet.org/guidelines/prostate-cancer-early-detection-guideline). We believe that it is important to exclude subjects with prostate cancer from clinical studies of devices used to treat BPH and, therefore, recommend that you adopt the more conservative limits for PSA as described.

  - cardiac pacemaker or metallic implants in the pelvic/femoral area, if warranted, based on device design (unless electromagnetic compatibility and safety with these implants are prospectively demonstrated).
- Future fertility: We recommend your protocol exclude men interested in future fertility, if your device has the potential to impact fertility.
- Concomitant medications: We recommend your protocol exclude men on medications that affect BPH symptoms as these medications can confound the study results. However, we recognize that requesting men discontinue their BPH medications to participate in the study could put them at risk for adverse events including worsening LUTS, hematuria, infection, or urinary retention. Furthermore, excluding men who cannot or will not discontinue these medications eliminates men who might benefit the most from the device from the study. Therefore, it is reasonable to include men on BPH medications if their dose has been stable after an appropriate period and the dose is not changed throughout the study unless medically warranted.

  BPH medications include prescription and over-the-counter drugs, and dietary supplements. If potentially confounding medications are clinically appropriate to be taken concurrent with the study, we recommend your protocol indicate that the dosage should not change during the study period unless medically warranted. If you intend to include such medications in your study, subjects should be on them for at least a minimal amount of time prior to the study ("wash-in"), and the recommended wash-in period should be specified. The recommended wash-in and wash-out periods are the same and are described below. If you intend to exclude specific medications from your study, we recommend your protocol specify wash-out periods after which subjects can be enrolled or treated.

  For example, we recommend excluding men using:
  - Antihistamines, anticonvulsants, and antispasmodics within one week of treatment unless there is documented evidence that the patient was on the same drug dose for at least six months with a stable voiding pattern (the drug dose should not be altered or discontinued for entrance into or throughout the study);
  - α blockers within four weeks of treatment;
  - Anticholinergics within two months of treatment;
  - Androgens, and gonadotropin-releasing hormonal analogs within two months of treatment; and
  - 5-alpha reductase inhibitors within six months of treatment.

  Your clinical study protocol should justify wash-in or wash-out periods for medications not listed above (e.g., PDE-5 inhibitors, β3 agonists, tricyclic antidepressants).

  Subjects who receive new BPH medications or an increased dose of a current BPH medication during the course of a trial should be considered treatment failures.

J. Pre-Treatment Evaluation Schedule

We recommend your protocol clearly describe all baseline tests, measurements, and examinations you plan to conduct at the pre-treatment evaluation. To ensure consistency among investigators and investigational sites, we recommend your protocol specify clearly defined, well-recognized measures for all tests and measurements. The pre-treatment urological evaluation should rule out any significant coexisting disease that might simulate BPH and document all of the inclusion and exclusion criteria contained in the study protocol.

To accomplish this, we recommend pre-treatment evaluation include the following:

- a complete history and physical examination, including a focused genitourological exam with peri-anal sensation and anal sphincter tone, and total duration of the patient's symptoms;
- patient questionnaires including AUA-SI (or IPSS), quality of life assessment, and sexual function and dysfunction assessment;
- uroflowmetry including voided volume with a prospectively defined minimum to ensure meaningful analysis (e.g., > 125 ml), total time of voiding, peak flow rate, and average flow rate, and post void residual volume (PVR);[44]
- cystometry (liquid or gas) on all patients with simultaneous assessment of intravesical and intra-abdominal pressure for determination of detrusor pressure;[45]
- blood and urine chemistry including urinalysis, urine cultures, complete blood count (CBC), PSA, blood urea nitrogen (BUN), creatinine, and electrolytes;
- prostate length and weight using DRE and TRUS;
- prostate biopsy with a minimum of 12 cores[46, 47] if clinically indicated; [48]
- cystoscopic examination to document bladder neck obstruction, the presence or absence of urethral strictures or bladder pathology, the condition of the prostatic urethra, and the anatomy of the gland (e.g., size, lobar distribution and anatomy, length from the verumontanum to the bladder neck); and
- proctoscopy if the therapy may potentially cause rectal injury.

K. Investigator Selection and Training

We recommend you select study sites and investigators that are capable of recruiting sufficient numbers of eligible subjects, who are representative of the target population for your particular

[44] PVR can be measured by ultrasound or catheterization, but consistent methods should be used pre- and post-treatment and across investigational sites.

[45] LUTS can arise from several pathophysiological conditions besides BPH. Pressure-flow urodynamics are helpful in establishing the mechanism of action for a device, particularly a novel treatment. We recommend that you conduct detrusor pressure-flow studies in as many subjects as possible, preferably greater than 30% of subjects. Additionally, in order to minimize bias we recommend that this sub-group consist of both treatment and control subjects and that you prospectively define the means for selecting subjects for the sub-group.

[46] Escew LA, Bare RL, McCollough DL, Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. *J Urol,* 1997, 157:199-203.

[47] Levine MA, Ittman M, Melamed J, et al. 2 consecutive set of transrectal ultrasound guided sextant biopsies of the prostate for the detection of prostate cancer. *J Urol*, 1998, 159:471-476.

[48] We recommend that a prostate biopsy be performed if indicated based on DRE or if the subject's PSA is > 2.5 ng/ml and ≤ 10 ng/ml and his free PSA is < 25% of total PSA (see Barry MJ, Prostate-specific-antigen testing for early diagnosis of prostate cancer, *N Engl J Med*, 2001, 344:1373-1377).

device. Sites that have a large proportion of protocol deviations can complicate pooling and statistical analysis of the results, and ultimately may invalidate the study conclusions.

To ensure the safe, proper, and consistent use of the device, prospective investigators often benefit from training, particularly if the investigational device is novel in clinical design or application or necessitates different procedures and settings than those used for similar devices. Therefore, we recommend the protocol describe a training program that will be used to educate investigators on the use of the investigational device during the study. We recommend training consist of didactic instruction covering the device functions and principles of operation and include proctoring by an experienced physician. If the plan includes proctored training, we recommend you prospectively identify the number of proctored subjects per investigational site and state how these subjects will be included in the analysis. Additionally, it may be useful for the training to highlight the important or unique aspects of the clinical study, such as screening, obtaining informed consent, the randomization process, study blinding, the follow-up schedule, data collection methodology, and adverse event reporting.

L. Treatment Information

To promote consistency across investigators and investigational sites, the study protocol should describe the investigational and control treatments. This information should include the following:

- patient preparation;
- need for, and details of, anesthesia;
- device directions for use (e.g., sizing, route of administration, technique, placement, settings/treatment parameters);
- recommended instrumentation and imaging;
- surgical technique; and
- post-operative care.

Additionally, if the investigational or control therapy involves multiple or staged treatments, or if the protocol allows the option of retreatment during the study, we recommend your protocol describe these aspects of treatment in detail. In the case of retreatment, we recommend your protocol specify the criteria for retreatment, the minimum and maximum time intervals between treatments, the maximum number of treatments, and any special treatment instructions for performing retreatment.

M. Post-Treatment Evaluations

We recommend the post-treatment evaluation schedule include multiple follow-up visits spanning the entire study duration, e.g., 2 weeks (unless there is follow-up at an earlier timepoint) and one, three, six, and 12 months post-treatment. For thermotherapy devices, we recommend a follow-up visit shortly after treatment, (e.g., 8-10 days after removal of a post-treatment catheter), consistent with the standard of care. For devices in which a post-market study is possible or anticipated, we recommend the post-treatment evaluation schedule include periodic follow-up visits, e.g., yearly for all subjects until marketing approval.

Your protocol should clearly describe the follow-up schedule, and identify all tests, measurements, and examinations you plan to conduct at each post-treatment evaluation. To ensure consistency with the investigators and investigational sites, we recommend all tests and measurements be performed using well-recognized methods clearly defined within the protocol. To allow comparisons to the baseline data, we recommend you perform all applicable post-treatment tests using the same methodology as the pre-treatment evaluation. Additionally, we recommend the control population undergo evaluation identical to the investigational group.

We recommend that post-treatment evaluations include the following tests and assessments:

- Physical examination;
- Updated medical and surgical history, including medications and procedures (especially if needed to address treatment failure or complication);
- AUA-SI (or IPSS);
- Quality of life assessment;
- Sexual function assessment;
- Adverse events;
- Uroflowmetry including voided volume with a prospectively defined minimum to ensure meaningful analysis (e.g., 125 mL), total time of voiding, peak flow rate, average flow rate, and post void residual volume;
- Cystometry on all patients at later visits, e.g., 6 and 12 months post-treatment, with simultaneous assessment of intravesical and intra-abdominal pressure for determination of detrusor pressure;[49]
- Blood and urine chemistry, e.g., urinalysis, urine cultures, CBC, PSA, BUN, creatinine, and electrolytes;
- Biopsy, if clinically indicated;
- DRE at each follow-up, if appropriate;
- TRUS at 6 and 12 months post-treatment (to include measurement of prostate volume and other relevant dimensions);
- Cystoscopic examination as medically or technically warranted;[50] and
- Proctoscopy, if medically or technically warranted, to monitor any observed rectal injury.

Unless you plan to contraindicate patients interested in future fertility from treatment, we recommend you assess the effects of your device on future fertility by evaluating semen quality and quantity.

N. Statistical Analysis Recommendations

The protocol should include a comprehensive statistical analysis plan that prospectively describes how the study results will be analyzed. All statistical analyses used in an investigation should be appropriate for its analytical purpose and thoroughly documented. We recommend the statistical analysis plan include the information discussed below.

[49] Detrusor pressure-flow studies should be conducted in the subgroup of patients evaluated pre-treatment.
[50] For some devices, it may be acceptable to conduct the cystoscopic follow-up examination in a subgroup. This subgroup should be randomly selected to minimize bias and consist of at least 30% of the study patients.

(1) Statistical Analyses

We recommend your protocol prospectively state all planned statistical analyses of the primary and key secondary endpoints. If you plan that the study subjects and investigators (or other evaluators) be blinded to the subject's treatment allocation (i.e., investigational devices vs. control therapy), your protocol should collect information to assess the effectiveness of the blinding (e.g., by asking subjects which study group they think they are in). Your protocol should also specify when blinding will be broken.

When reporting the findings of your clinical trial, we recommend you:

- compare all treatment data to the control;
- stratify the safety and effectiveness data by relevant covariates including pre-treatment patient characteristics and treatment parameters;
- account for all patients at each follow-up period;
- provide graphical presentation of data and results;
- provide summary tables for all important parameters (including summary tables presenting the raw data for each patient and cohort analysis);
- provide a justification for pooling results across investigational sites and a stratification of the data as a function of investigational site; and
- consider the addition or increase in BPH medications, or treatment of BPH with additional modalities as treatment failure.

(2) Primary Endpoint Analyses

The primary statistical analysis of the study generally uses the primary endpoint to assess the study's overall success or failure. Therefore, we recommend you describe and document the details of this analysis in your protocol. To reduce bias, we recommend performing this primary analysis using the intention-to-treat (ITT) population. The ITT population includes all subjects randomized into the study regardless of whether the subjects received the treatment to which they were randomized. Using the ITT population preserves the comparability of patients with respect to (observed and unobserved) baseline characteristics. The ITT population is generally regarded as the preferred method for evaluating a new therapy.[51]

In addition to the ITT analysis, we recommend your protocol specify other analyses of the primary endpoint to assess the robustness of the study results. We recommend you conduct these additional analyses to assess whether the results are consistent with the conclusion of the primary ITT analysis and, therefore, are supportive of your study conclusions. You should assess the plausibility of the underlying assumptions for each sensitivity analysis. We recommend these additional analyses include at least the following:

- Analysis of the "per protocol" population (e.g., subjects treated and followed per the protocol);
- Sensitivity analyses using a pre-specified variety of methods for imputing missing data;
- Longitudinal or repeated measures analysis to assess impact of "time post-treatment" upon the results; and

[51] Ellenberg JH, Intent-to-treat analysis versus as-treated analysis. *Drug Inf J*, 1996, 30:535-44.

- Assessment of the number of subjects who are "significantly improved," "not significantly improved," and "worse" at each follow-up period relative to baseline.

To investigate the potential impact of subject-related and treatment-related factors upon the primary safety and effectiveness endpoints and to uncover any important prognostic factors, we recommend that you consider subgroup analyses. To minimize bias associated with these analyses, we recommend your protocol prospectively define all important factors. Important factors may include, but are not limited to:

- Investigational site;
- Age;
- Weight or body mass index;
- Ethnicity;
- Duration of BPH symptoms;
- All baseline measures of BPH (e.g., prostate size/volume, peak and mean flow rates, PVR, AUA-SI (or IPSS), and a BPH-specific quality of life score);
- Retreatments;
- Medication usage; and
- Important device-related covariates (e.g., device settings, size).[52]

(3) Secondary Endpoint Analyses

We recommend your protocol prospectively define the statistical analysis plan for important secondary endpoints if you intend to include secondary endpoints in your labeling. If any of the secondary endpoint analyses are intended to support the indications for use or to describe device performance in the labeling (e.g., comparing treatment and control groups using p-values or confidence intervals), we recommend you pre-specify this intention in your study protocol and provide a detailed description of the statistical methods you plan to follow. We recommend that you ensure that the overall Type I error rate is controlled when you plan such analyses. If the secondary endpoint analyses are intended as exploratory analyses or are not intended to support the indication for use or representations of device performance, we recommend you submit simple descriptions of the analyses.

One of the statistical challenges in supporting the indications for use or device performance through multiple statistical tests is the control of the overall type 1 error rate at 0.05 or below. There are many valid multiplicity adjustment strategies available for use to maintain the type 1 error at or below p=0.05, including:

- Bonferroni procedure;
- Hierarchical closed test procedure; and
- Holm's step-down procedure.

Because each of these multiplicity adjustment strategies involves balancing different potential advantages and disadvantages, we recommend you carefully consider each of the adjustment strategies when you design your clinical study and prospectively define the strategy that you

[52] All characteristics of the treatment mode (e.g., size, power level, treatment time) should be analyzed. The data should support the complete range of device sizes and treatment parameters that will be available.

intend to use. We recommend your protocol prospectively state a statistical hypothesis for each secondary endpoint for which you intend to make representations about device performance in your labeling.

(4) Missing Data

Missing data can represent a significant source of potential bias. Although many statistical methods exist for imputing missing data, excessive missing data can introduce an unacceptable level of uncertainty in the results and invalidate the study conclusions. Therefore, we recommend every effort be made to minimize the incidence of missing data through trial design and conduct.[53] We recommend your protocol incorporate the elements listed below:

- Efforts to minimize missed visits and drop-outs: We recommend that you design the study to reduce missing data. Strategies to consider include providing incentive for patients to remain in the study, such as randomization (e.g., 2:1) schemes or options for control patients to switch to the investigational device after completion of follow-up or the assessment of the primary effectiveness endpoint. We recommend you describe in the protocol the efforts to be used during the course of the study to monitor and minimize the incidence of patient drop-outs, such as monitoring activities, special incentives to subjects for study compliance, methods to remind subjects of scheduled visits, and specific efforts to contact subjects who miss their visit (e.g., telephone calls, postcards, contact next-of-kin); and
- Efforts to document the reasons for missing data: We recommend you identify the steps to document:
    - The reason for each missed visit, e.g., complications, difficulty getting transportation to the site;
    - The reason for each drop-out, e.g., seeking alternate therapy, complications or intolerance to the device, dissatisfaction with the device, moved away; and
    - The cause of any death, e.g., autopsy report or death certificate.

To facilitate a complete and detailed accounting of all study subjects, we recommend you collect complete information on each subject's follow-up status during the study. Because loss to follow-up jeopardizes the conclusions that can be made about the long-term safety and effectiveness of a device, we recommend you limit the overall rate of loss to follow-up to less than 20% over the course of the study.

The protocol should specify how you plan to handle missing primary effectiveness endpoint data for the primary analysis. To conduct the ITT analysis in the presence of missing primary endpoint data, we recommend that you use existing statistical methods for missing data, such as multiple imputation.[54] Since these methods usually involve assumptions about the missing data mechanism, the plausibility of the assumptions should be assessed. As discussed in Section

[53] National Research Council. (2010). *The Prevention and Treatment of Missing Data in Clinical Trials.* Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington DC: The National Academies Press.

[54] National Research Council. (2010). *The Prevention and Treatment of Missing Data in Clinical Trials.* Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington DC: The National Academies Press.

V.N(2), sensitivity analyses that compare results obtained under various assumptions about the missing data mechanism should be conducted.

O. Risk Analysis

The protocol should contain a clinically sound risk analysis in support of the proposed investigation. In clinical studies that require an approved IDE application,[55] the risk analysis must include the elements specified in 21 CFR 812.25(c), which are listed below:

- a description and analysis of all increased risks to which subjects will be exposed by the investigation;
- the manner in which these risks will be minimized;
- a justification for the investigation; and
- a description of the patient population, including the number, age, sex, and condition.

We recommend the risk analysis section of your protocol include the risks of the device itself and the risk associated with the treatment procedure. In addition, we recommend you convey these risks to potential subjects using easily understood terminology in the informed consent document.

P. Study Monitoring

We believe that proper study monitoring is critical to assure the safety of study subjects, investigator adherence to the investigational plan and the applicable requirements of 21 CFR parts 50 and 812, and the quality and integrity of the resulting clinical data. Therefore, we recommend that the investigational plan incorporate a comprehensive, written monitoring plan that investigators agree to follow during the study. In clinical studies that require an approved IDE application, the IDE application must include written monitoring procedures in accordance with 21 CFR 812.25(e). In addition, see the Agency's guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees"[56] on recommended approaches to monitoring clinical investigations involving FDA-regulated products.

Written monitoring procedures help to assure that each person involved in the monitoring process carries out their duties. In addition to the elements required by 21 CFR part 812 and 21 CFR part 50 and recommended in the FDA guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees," we recommend you include the following elements into your monitoring procedures:

- identification of a trained and qualified monitor;
- description of pre-investigation and periodic visits, including the timing of these visits and the specific monitoring activities to be performed;
- criteria for the review of representative subject records for completeness and accuracy; and

[55] An approved IDE is required before beginning a clinical study of a significant risk device in the United States as defined in 21 CFR 812.3(m).

[56] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees.

- elements for an adequate record of on-site monitoring visits, including findings, conclusions, and action taken to correct any deficiencies.

We recommend the study monitor overseeing the trial identify potential weaknesses during the study that may necessitate modifying the protocol. The study monitor should also have contingency plans available for unforeseen problems that may occur and have a means to rapidly implement those plans. We recommend you and the monitor carefully devise any contingency plans for the study with the goal of preserving the integrity of your study design. We also recommend your monitor assure that study subjects are entered, interventions are assigned, follow-up data are collected at the appropriate times, and data are completely and accurately recorded, as specified in the protocol.

Q. Case Report Forms

To ensure all information collected during the course of the clinical study is documented, we recommend your study incorporate case report forms for investigators to complete separately for each subject. To facilitate the documentation of all subject, treatment, and study data, we recommend you record all information described in your protocol on case report forms including:

- a pre-treatment evaluation form;
- a treatment information form;
- post-treatment evaluation forms;
- a concomitant medication form;
- a protocol deviation form;
- an adverse events form; and
- a patient discontinuation information form.

We recommend the content of these forms reflect the following information:

- A pre-treatment evaluation form includes all relevant information from pre-treatment evaluation, such as medical history, physical exam, baseline screening measures, and documentation of inclusion and exclusion criteria.
- A treatment information form includes all relevant information regarding the treatment procedure for both the investigational device and the control therapy, such as date, pre-operative preparation, anesthesia usage, device directions for use (e.g., sizing, placement, settings or treatment parameters), instrumentation and imaging usage, surgical technique, post-operative care, protocol deviations, and complications. If retreatment is permitted during the study, similar information should be recorded at that time.
- Post-treatment evaluation forms include all data collected at each follow-up visit. We recommend a separate post-treatment evaluation form be completed at each follow-up visit.
- A concomitant medication form lists all medications and dietary and herbal supplements taken by the subject at baseline and during the study, specifying the dates of usage and dosage.
- A protocol deviation form identifies and describes each protocol deviation, indicating the date, type of deviation, and clinical justification for the deviation.

- An adverse events form identifies and describes each adverse event, including the onset date, type and description, device-relatedness, severity, method of intervention or resolution, and resolution date.
- A patient discontinuation information form includes the date and reason for a patient's discontinuation from the study. Typical reasons for study termination include study follow-up completed, consent withdrawn by the subject, the subject exited to receive alternate treatment, the investigator chooses to exit the subject, death of the subject, and the subject became lost to follow-up.

VI. Conclusions

Our intent of this guidance is to assist you in developing non-clinical and clinical trials for devices to treat BPH. In addition, we encourage you to contact us to discuss any questions you may have regarding your specific device, its intended use, clinical study design, or other considerations. If you are proposing an alternative approach to the study design recommendations in this guidance, we also encourage you to request a Pre-Submission meeting.

Appendix 1.

Sources of Bias	Common Bias Mitigation Methods
Selection Bias occurs when patients possessing one or more important prognostic factors appear more frequently in one of the comparison groups than in the others.	• Randomization • Objective diagnostic and outcome measures • Homogeneous study population • Pre-specified protocol, endpoints, and statistical plan
Investigator Bias occurs when an investigator consciously or subconsciously favors one study group at the expense of the others.	• Blinding • Pre-specified protocol, endpoints, and statistical plan
Evaluator Bias is a type of investigator bias in which the person measuring the outcome variable intentionally or unintentionally records the measurements in favor of one intervention over another intervention. Studies that have subjective endpoints (e.g., quality of life) are particularly susceptible to this form of bias.	• Blinding • Objective diagnostic and outcome measures
Placebo or Sham Effect is a bias that occurs when a patient exposed to an inactive therapy believes that he (or she) is being treated with an intervention and subsequently shows or reports improvement.	• Inclusion of a sham arm • Randomization • Blinding • Objective diagnostic and outcome measures
Missing Data can introduce bias when subjects who do not report for follow-up experience a different outcome from those who do.	• Option for active device for sham arm patients after completion of follow-up • Documentation and enhanced compliance • Plan to conduct sensitivity analyses