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Draft – Not for Implementation

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

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 14, 2020.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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.

When final, this guidance will update and supersede the applicable sections of "Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)," issued on August 17, 2010.

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

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 1724 and complete title of the guidance in the request.

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

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. Introduction

FDA has developed this draft guidance to propose select updates to the FDA guidance document "Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)."[1] The existing guidance on devices used for the treatment of BPH remains in effect, in its current form, until this draft guidance is finalized. FDA intends to incorporate this draft guidance into one final guidance document after obtaining and considering public comment on these select updates. The proposed sections referenced below are intended to replace applicable sections of the existing BPH guidance after FDA considers public comment on this draft guidance. The sections of the existing BPH guidance that are not affected by this select update will not be substantively changed and will remain in effect.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[2] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-non-clinical-and-clinical-investigation-devices-used-treatment-benign-prostatic-hyperplasia.

[2] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

"Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[3]

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

II. Scope

In addition to the devices currently within the scope of the existing BPH guidance, FDA is proposing to add the following devices into the scope of the future final guidance document (Section II) when updated:

Product Code	Product Code Name	Regulation Number
KNS	Endoscopic Electrosurgical Unit (With Or Without Accessories)	21 CFR 876.4300
PEW	Implantable transprostatic tissue retractor system	21 CFR 876.5530
PZP	Fluid jet removal system	21 CFR 876.4350
NOY	Embolic agents for treatment of benign prostatic hyperplasia	21 CFR 876.5550

III. Non-Clinical Testing Recommendations

FDA is proposing to update only a subset of the recommendations included in Section III.K of the existing BPH guidance document.

K. Animal Study

Animal studies[4] 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

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

[4] 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.

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.

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;[5]
- 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, rectal wall, bladder neck, external sphincter, neurovascular bundle, and prostatic capsule.

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."[6]

[5] 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).

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

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.

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 Study Recommendations

FDA does not currently intend to significantly change the content in Section IV of the existing BPH guidance document. FDA is proposing the following changes:

- FDA is proposing to change the name of this section to "Pilot Clinical Study Recommendations;"
- In the fifth paragraph, FDA is proposing to revise the recommendation that if sponsors intend to pool pilot and pivotal study results, that this pooling is planned prospectively and keep the recommendation that sponsors provide a rationale showing that it is statistically and clinically valid to pool the data from the pilot and the pivotal studies; and
- In the seventh and final paragraph, FDA is proposing to include a recommendation that the methods used to characterize the temperature distribution in the prostatic and periprostatic tissues include both the rectal wall and urethra. The current recommendation includes only the rectal wall.

V. Pivotal Study Recommendations

FDA is proposing to change the title of the Section V of the existing BPH guidance to "Pivotal Clinical Study Recommendations" and recommend the use of the FDA guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices"[7] for FDA's current thinking on the principles for the design of clinical studies on medical devices. FDA only intends to significantly change the following subsections of Section V of the existing BPH guidance document.

C. Randomization and Controls

FDA is proposing to replace Section V.C of the existing BPH guidance document with these recommendations:

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.

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

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.[8] 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;
- 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.

[8] 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.

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.[9] 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.[10] Additionally, devices intended to treat BPH achieve full effectiveness quickly, while drug 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.

[9] 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.
[10] 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).

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."[11]

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.

E. Study Endpoints

(2) Primary Effectiveness Endpoint

FDA is proposing to replace Section V.E(2) of the existing BPH guidance document with these recommendations:

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

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

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.[12] 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.[13]

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 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.[14] 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.[15] 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,

[12] 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.

[13] 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.

[14] 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.

[15] 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.

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.[16]

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.

(3) Primary Safety Endpoint

FDA is proposing to replace Section V.E(3) of the existing BPH guidance document with these recommendations:

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:

- genitourinary events, i.e., events associated with the urinary tract and/or the surrounding genital region;
- damage to the bladder floor, trigone, sphincters, and rectum;
- infections;
- worsening sexual dysfunction;
- secondary surgical interventions;
- all transient post-procedure events; and
- deaths.

[16] 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.

Adverse events should be categorized according to their respective relatedness to the device or procedure, and their severity (e.g., using the latest version of the Common Terminology Criteria for Adverse Events[17]). 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 is proposing to replace Section V.E(4) of the existing BPH guidance document with these recommendations:

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;
- 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.
- 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.

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

- 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.
- Sexual function and dysfunction: Both BPH and many of its therapies adversely affect sexual function. Therefore, we recommend you incorporate a validated, gender-specific measure of sexual function assessed at each follow-up visit.
    - The recommended instrument to assess sexual function is the International Index of Erectile Function, specifically the Erectile Function domain (IIEF-5).[18] The Minimal Clinically Important Difference (MCID) has been shown to be 4 points.[19] 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.

Recommendations regarding the statistical analysis of secondary endpoints are discussed in Section IV.N of the existing BPH guidance document.

G. Statistical Hypothesis

FDA is proposing to replace Section V.G of the existing BPH guidance document with these recommendations:

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

[18] 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.

[19] 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.

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.

I. Patient Selection Criteria

FDA is proposing to replace Section V.I of the existing BPH guidance document with these recommendations:

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.

- 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: 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.
- 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.[2012]

[20] 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.

- 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).[21]
- 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 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;[22]
  - 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;

[21] 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.

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

- 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.[23] 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
  - 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.

[23] 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.

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.

M. Post-Treatment Evaluations

FDA is proposing to replace Section V.M of the existing BPH guidance document with these recommendations:

We recommend the post-treatment evaluation schedule include multiple follow-up visits spanning the entire study duration, e.g., 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;
- 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;[24]
- 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;[25] 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

(2) Primary Endpoint Analyses

FDA is proposing to replace Section V.N(2) of the existing BPH guidance document with these recommendations:

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

[24] Detrusor pressure-flow studies should be conducted in the subgroup of patients evaluated pre-treatment.

[25] 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.

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.[26]

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
- 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).[27]

(3) Secondary Endpoint Analyses

FDA is proposing to replace Section V.N(3) of the existing BPH guidance document with these recommendations:

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

[27] 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.

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 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

FDA is proposing to replace Section V.N(4) of the existing BPH guidance document with these recommendations:

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.[28] 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

[28] 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.

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.[29] Since these methods usually involve assumptions about the missing data mechanism, the plausibility of the assumptions should be assessed. As discussed in Section V.N(2), sensitivity analyses that compare results obtained under various assumptions about the missing data mechanism should be conducted.

[29] 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.

Appendix 1

FDA is proposing to replace the table in Appendix 1 of the existing BPH guidance document with the following table:

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