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Clinical Investigations for Prostate Tissue Ablation Devices

Guidance for Industry and Food and Drug Administration Staff

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For questions about this document, contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices/DHT3B: Division of Reproductive, Gynecology, 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

Preface

Public Comment

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Clinical Investigations for Prostate Tissue Ablation Devices

Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

This guidance document provides recommendations for (1) complying with the clinical testing special control under 21 CFR 876.4340(b)(8) for premarket notifications (510(k)s) for high intensity ultrasound systems for prostate tissue ablation, and (2) collecting clinical data to support marketing submissions for new types of prostatic tissue ablation devices. High intensity ultrasound systems for prostate tissue ablation transmit high intensity therapeutic ultrasound energy into the prostate to thermally ablate a defined, targeted volume of tissue. Other prostate ablation devices achieve the same clinical effect of ablating targeted tissue volumes using different sources of energy. Regardless of the energy type used for ablation, these devices may receive marketing authorization for a general indication for ablation of prostatic tissue. This guidance does not address intended uses for the treatment of a specific disease (e.g., prostate cancer or benign prostatic hyperplasia).

FDA's guidance documents, including this 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. Background

In 2015, the Agency granted a De Novo request for a high intensity ultrasound system for prostate tissue ablation.[1] The special control under 21 CFR 876.4340(b)(8) includes a requirement for clinical testing to document the adverse event profile, provide evidence of

[1] The DEN150011 transparency summary and final classification order are available at https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150011.pdf and 82 FR 45725.

prostatic ablation, and demonstrate that the device performs as intended under anticipated conditions of use. The purpose of this guidance document is to provide clinical testing recommendations for submitters seeking a general indication for ablation of prostate tissue (i.e., not intended for the treatment of any specific prostate disease), whether by high intensity ultrasound to ensure compliance with the clinical testing special control or alternative technologies.

Prior to initiating a clinical investigation, the Agency encourages manufacturers to submit a Pre-Submission to obtain detailed feedback on the clinical investigation of prostate tissue ablation devices. For details on Pre-Submissions, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[2]

III. Scope

The scope of this guidance document is limited to the clinical investigations to support marketing authorization for general indications of prostate tissue ablation systems, including devices that are regulated under the product code PLP. This guidance does not address the clinical investigations of devices that are intended to treat specific prostatic diseases (e.g., prostate cancer or benign prostatic hyperplasia). Additionally, this document does not address recommendations or other requirements for non-clinical testing, training, or labeling of prostate tissue ablation systems.

IV. Clinical Investigation Recommendations

We recommend that you conduct a clinical study to (1) comply with the clinical testing special control under 21 CFR 876.4340(b)(8) for new high intensity ultrasound systems for prostate tissue ablation and systems with changes to the ablation energy output characteristics relative to the 510(k)-cleared versions, or (2) to support marketing submissions for prostate tissue ablation devices outside the scope of 21 CFR 876.4340.

Generally, we believe prostate tissue ablation devices addressed by this guidance document are significant risk devices subject to all requirements of the Investigational Device Exemptions (IDE) regulation, 21 CFR 812, for studies conducted in the United States (US). See the FDA guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[3] In addition to the requirements of 21 CFR 812, sponsors of such trials of a device conducted in the US must comply with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50).

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

When data from clinical investigations conducted outside the United States are submitted to FDA for prostate tissue ablation devices, the requirements of 21 CFR 812.28 may apply.[4] 21 CFR 812.28 outlines the conditions for FDA acceptance of clinical data from investigations conducted outside the US when submitted to support premarket submissions. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."[5]

In some cases, "real-world data" (RWD) may be used to support changes to the ablation energy output characteristics for a device for which 510(k) clearance has already been obtained. Whether the collection of RWD for a legally-marketed device requires an IDE depends on the particular facts of the situation. Specifically, if a cleared device is being used in the normal course of medical practice, an IDE would likely not be required. For additional information regarding this topic, please refer to the FDA guidance entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[6]

The results of the clinical investigation should be presented in a complete test report, formatted to include the following elements:

- Executive summary/overview;
- Site/investigator identification;
- Patient demographics and baseline characteristics;
- Treatment data;
- Protocol deviations;
- Safety and effectiveness endpoints analysis (analyzed and raw line data formats);
- Conclusions; and
- Study protocol.

Specific clinical study recommendations for prostate tissue ablation devices are summarized below. The clinical study recommendations reflect CDRH's current thinking regarding study design for prostate tissue ablation devices. However, consistent with least burdensome principles,[7] we recognize that, for any regulatory decision, there exists some degree of uncertainty around benefits and risks. It is important to acknowledge and appropriately mitigate uncertainty in benefit-risk determinations supporting FDA premarket decisions.[8] As such, the

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[4] This applies to data from clinical investigations that began on or after February 21, 2019 and are submitted to support a premarket submission, including IDEs, premarket approval applications (PMAs), and 510(k)s.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked.

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

[7] Please see FDA's guidance "Least Burdensome Provisions: Concept and Principles" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles) for more information on this topic.

[8] Please see FDA's guidances on this topic: "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device), "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-

acceptable level of uncertainty in benefit-risk determinations to support premarket decisions is flexible in some cases, and is tailored to the type and intended use of the device and the type of decision we are making. Therefore, FDA will consider alternatives to the study design when the proposed alternatives are supported by an adequate scientific rationale.

A. Purpose/Objective

The objective of the clinical investigation is to demonstrate the safety and effectiveness of the device for its intended use – as a general surgical tool for the ablation of prostate tissue. FDA notes that the endpoints in this clinical investigation should address safety by determining whether the device does not ablate or damage tissue outside of the targeted volume as reflected in the adverse event profile, and effectiveness by determining whether the device ablates tissue within the targeted volume.

B. Study Design and Sample Size

FDA recommends that the clinical evidence to support a marketing submission consist of either an internally- or externally-controlled trial. While a benefit of an internally-controlled trial is the collection of robust data on the subject and comparator devices from the same patient population that was followed in the same manner, a benefit of an externally-controlled trial is the reduced burden of enrolling and following only a single patient cohort (study arm) to be compared to the clinical results of an existing prostate tissue ablation device.

To adequately estimate the adverse event profile with clinically meaningful precision, including the incidence of infrequent device- or procedure-related complications, FDA recommends that the dataset include a minimum of 100 patients treated with the subject device and who were clinically followed as recommended below in Sections IV.C, G, and H, respectively.

Indirect measures of ablation effectiveness, such as prostate biopsy, prostate-specific antigen (PSA) levels, and prostate volume, should be analyzed in the same patient population of at least 100 patients that was followed for safety. Alternatively, if ablation effectiveness is instead supported by "treat and resect" data (i.e., whole-mount histopathology analysis of the extent and position of ablation, obtained from patients undergoing prostate tissue ablation prior to scheduled radical prostatectomy) collected from a separate study cohort, the sample size of this effectiveness population should be scientifically justified. While studies with separate safety and "treat and resect" cohorts will, by design, enroll a greater total number of subjects than studies in which both safety and indirect measures of ablation effectiveness are evaluated in the same

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consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de), "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k), and "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de).

cohort, a benefit of the former approach is avoiding the burden of collecting post-ablation biopsy data, PSA levels, and imaging.

C. Study Duration and Follow-up Schedule

FDA recommends that the minimum duration of scheduled follow-up for studies to support a marketing submission is one year. This recommended minimum follow-up duration is based on the delayed onset or presentation of known probable adverse events (e.g., urethral stricture, rectal fistula, and osteomyelitis pubis), as well as the time course for potential resolution of other anticipated complications (e.g., erectile dysfunction, urinary incontinence). The protocol should prospectively specify collection of adverse event information at regular intervals, with specific assessment of known probable device- and procedure-related adverse events.

Effectiveness measures should be collected post-ablation at time frames that are scientifically justified for the specific endpoint measure(s) being collected. For example, prostate biopsy, PSA levels, and prostate volume should be analyzed one year post-ablation, while "treat and resect" data may be collected and analyzed less than one month post-ablation. The study duration and timing of follow-up for all endpoints should be clinically justified, and the timing of assessments should be uniform within the study.

D. Inclusion/Exclusion Criteria

The study should enroll men for whom prostate tissue ablation is clinically warranted. To minimize confounding in the review of the clinical data, patient and treatment characteristics should be uniform with respect to:

- The underlying clinical condition for the prostate ablation (i.e., benign versus malignant disease);
- The prostate treatment history prior to the ablation procedure (e.g., "treatment naïve," post-external beam radiotherapy, post-brachytherapy, post-cryotherapy);
- The prescribed extent of ablation (e.g., whole gland ablation, hemiablation, focal ablation);
- Anatomical limitations associated with the specific technological characteristics of the ablation device (e.g., excluding subjects with prostate volumes above a certain size); and
- General clinical safety precautions (e.g., excluding subjects with uncontrolled bleeding disorders or active urinary tract infection).

E. Patient Demographics

Patient demographic information should be reported using descriptive statistics. Refer to the FDA guidance "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies"[9] for details on reporting this demographic information. This information should include, but is not limited to, the following:

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies.

- Patient age and race/ethnicity;
- Body mass index (BMI);
- Prostate volume;
- Prostate disease characteristics (as appropriate for the enrolled population), for example:
  - PSA level;
  - Clinical cancer stage;
  - Gleason scores and sum; and
  - Prior therapies (including surgeries, radiation, and hormone therapy).
- Imaging findings (e.g., suspicious regions on multi-parametric MRI); and
- Related medical history and physical exam details (including baseline erectile function and urinary continence status).

F. Treatment Parameters/Protocol (including post-operative regimen)

The protocol for the clinical study should pre-specify, and the complete test report should describe, the following treatment parameters and related information:

- Extent of ablation (e.g., whole gland ablation, hemiablation, focal ablation);
- Prostate tissue volume targeted for ablation;
- Concurrent interventions (e.g., transurethral resection of the prostate, bladder neck incision);
- Ablation time and parameters;
- Malfunctions or interruptions;
- Anesthesia or sedation used;
- Hospitalizations; and
- Catheterizations.

G. Safety Endpoints and Data Analysis

To support a general indication for ablation of prostate tissue (i.e., not intended for the treatment of any specific prostate disease), a clinical investigation should address safety by demonstrating that the device does not ablate or damage tissue outside of the targeted volume. Safety endpoints should consist of prospectively collected adverse events, with emphasis on key safety issues that may reflect damage to the surrounding, non-target tissues. These key safety issues include, but are not limited to, erectile dysfunction, urinary incontinence, voiding symptoms or dysfunction, urethral stricture, rectal fistula, and osteomyelitis pubis.

To ensure robust collection of safety information, adverse events should be:

- Prospectively collected without regard to device-relatedness;
- Defined using pre-specified, standardized criteria (such as when reporting erectile dysfunction);

- Graded for severity according to a standard adverse event grading system (e.g., Common Terminology Criteria for Adverse Events[10]);
- Categorized according to whether they meet the established serious adverse event definitions;[11]
- Assessed for resolution status; and
- Adjudicated by an independent clinical events committee.[12]

H. Effectiveness Endpoints and Data Analysis

To support a general indication for ablation of prostate tissue (i.e., not intended for the treatment of any specific prostate disease), a clinical investigation should address effectiveness by demonstrating that the device ablates tissue within the targeted volume. Effectiveness endpoints may be either direct measurements of the extent of ablation (e.g., histopathology data from a "treat and resect" study cohort), or alternatively, indirect measurements using a composite of the following surrogate measures of prostate tissue ablation:

- Histological findings from prostate biopsies consisting of 12-core systematic transrectal biopsy of the entire gland, with heightened sampling in the region that was targeted for ablation (using image-guided targeting to direct the biopsy);
- Ultrasound or MRI follow-up of prostate volume or non-perfused volume; and
- PSA levels.

FDA believes that either effectiveness endpoint (i.e., the single "treat and resect" histopathology endpoint, or the three-part composite endpoint of histological findings from prostate biopsies, prostate volumes from imaging, and PSA levels) is equally valid. Regardless of the endpoint used, the data should collectively provide evidence of the extent to which the intended region of tissue is ablated to support marketing authorization.

FDA recommends that you report the applicable effectiveness endpoints of your study as follows:

- Biopsy results: Report the percentage of patients who had a negative biopsy post-ablation. For this endpoint, only biopsy cores taken within the region targeted for ablation should be included in the negative biopsy rate analysis, and patients with missing biopsy information post-ablation should be imputed as "positive;"
    - The following biopsy information should be reported in the raw line data listing: date of biopsy, total number of cores taken, location of each core with respect to the region targeted for ablation (i.e., "within" or "outside" the targeted region), number of positive cores, and the Gleason scores and sum of each positive core;
- Prostate volume results:

[10] For more information, see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
[11] For the purposes of this guidance, the term "serious adverse event" is used consistent with the FDA guidance "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device.
[12] For more information, see "Establishment and Operation of Clinical Trial Data Monitoring Committees," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees.

  - Report the percent decrease in total prostate volume (from baseline), as determined by pre- and post-ablation imaging (e.g., ultrasound, MRI). For this endpoint, men without both pre- and post-ablation measurements should be imputed as having a zero change in volume; or
  - Compare the volume of non-perfused prostate tissue, as determined by post-ablation imaging (e.g., ultrasound, MRI), to the volume targeted for ablation. For this endpoint, missing non-perfused volume measurements should be imputed conservatively using statistically valid methods;
- PSA levels: Report the overall percent reduction in PSA levels from baseline. Additionally, studies involving whole-gland ablation should report the percentage of patients achieving a pre-specified post-ablation PSA nadir (i.e., the lowest PSA level measured post-ablation). For this endpoint, missing PSA data should be imputed conservatively using statistically valid methods; and
- "Treat and resect" histopathology results: Report the extent/percent volume of viable tissue within the targeted region.

If effectiveness is assessed in a "treat and resect" study, it is impossible to determine whether subsequent adverse events in these patients are due to the ablation procedure or the subsequent radical prostatectomy. For this reason, safety should be assessed in a separate cohort of patients who are similarly treated with the ablation device and prospectively followed for one year post-ablation. The safety assessment in this cohort should follow the recommendations in Sections IV.B, C, and G above. In this scenario, you should demonstrate that the "treat and resect" and safety cohorts are similar with respect to patient demographics, disease characteristics, prostate treatment history, and extent of ablation (e.g., whole gland ablation, hemiablation, focal ablation).

I. Statistical Analysis Considerations

The safety and effectiveness endpoints should be analyzed using an intent-to-treat (ITT) approach. The extent of missing data should be reported and justified.

For each effectiveness endpoint, means and 95% confidence intervals should be reported in your complete test report. The safety and effectiveness endpoints should be descriptively compared to those reported for an existing prostate ablation device (either an internal or external control), with the goal of clinically demonstrating that the subject prostate ablation device has an equivalent or better benefit-risk profile.