NxThera

1633-001
Rev 03

Protocol, Rezūm System First-In-Man Minimally Invasive Treatment of BPH (Rezūm FIM Clinical Study)

Approvals: Signatures on File

Authored by:	Sew-Wah Tay, PhD Consultant, Libra Medical	Sew Wah Tay Signature	3/9/2012 Date
Approved by:	Michael Hoey, PhD for Chief Technical Officer	Signature	3/9/12 Date
	J. Robert Paulson Jr Chief Executive Officer	Signature	3/9/2012 Date

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	Consultant, Libra Medical	**Signature**	**Date**
Approved by:	**Michael Hoey, PhD**		
	Chief Technical Officer	**Signature**	**Date**
	J. Robert Paulson Jr		
	Chief Executive Officer	**Signature**	**Date**

Revision History			
Rev	**Date**	**Description**	**Comments**
01	**November 20, 2011**	**Initial Release**	
02	**February 24, 2012**	**Added MSHQ-EjD Short Form, updated exclusion criteria for Phase 1, updated inclusion criteria for phase 2, updated AE description for LUTS and catheterization, updated CRF requirements, added references, updated MRI requirements,**	
03	**March 9, 2012**	**Updated sample size for Phase 1 and Phase 2, updated water flow setting.**	

Rezūm FIM: First In Man Feasibility Study for the Treatment of BPH with Rezūm System

Protocol # 1633-001
Revision 03
March 9, 2012

Sponsor:
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PROTOCOL SIGNATURE PAGE

Rezūm FIM: First In Man Feasibility Study for the Treatment of BPH with Rezūm System

Protocol # 1633-001
Revision 03
March 9, 2012

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital ethics committee (EC). I will discuss this material with them and ensure they are fully informed regarding the study device and the conduct of the study according to this protocol, applicable laws, and applicable regulatory requirements including 21 CFR parts 50, and 56 and hospital EC requirements.

Clinical Site Name:

Centro Medicao Dr. Canela D.R.
Av Lertertad No. 44
La Romana, Dominican Republic

_____
Printed Name

_____ _____
Signature **Date**

Protocol Summary

Title:	**In vivo treatment with NxThera Rezūm device for acute and urinary retention with BPH**
Purpose:	**To evaluate the effect of the NxThera BPH Rezūm System on prostate tissue in subjects suffering from LUTS symptoms secondary to benign prostatic hyperplasia (BPH).**
Study Design:	**This study is a single center study. It will be carried out in two phases on subjects with benign prostatic hyperplasia.** **Phase 1: Acute study - In-vivo treatment of the prostate in subjects scheduled to have a surgical TURP or full excision of the prostate. Prostate tissue will be excised after treatment as part of the planned surgery. There is no follow up.** **Phase 2: Optimization study - Subjects with BPH symptoms will be treated with the Rezūm device with a range of thermal energies (as measured by calorie output) to optimize the setting for maximum lesion size with minimal intra and post procedure discomfort. The lesion size and ablated tissue resorption rate will be followed post-procedure via MRIs.**
Enrollment:	**Phase 1: Up to 20 BPH subjects scheduled for surgical removal of the BPH tissue** **Phase 2: Up to 15 BPH subjects suffering from BPH symptoms.**
Target Subject Population:	• **Male subjects ≥ 45 years of age who have symptomatic / obstructive symptoms secondary to BPH requiring surgical intervention.**
Follow-up:	**Phase 1 – Acute, no follow up** **Phase 2 – 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, and annually thereafter up to 5 years.**
Phase 1 Endpoint	**Lesion size and characteristics as evaluated using Tetrazolium Chloride (TTC) stain and histopathologic evaluation of representative samples.**
Phase 2 Endpoints	**Lesion characterization via MRI** **Intra and post procedure discomfort** **Catheterization post procedure** **The change (improvement) from baseline in International Prostate Symptom Scores (IPSS) at day 1, week 1, month 1, months 3,6 and 12, and annually thereafter up to 5 years**

Study and Data Management:	**Libra Medical, Inc.** **8401 73rd Ave N, Suite 63** **Minneapolis, MN 55428** **Tel: 763-477-5606** **Fax: 763-477-6357** **Email: swtay@libramed.com**
Study Monitors:	**Libra Medical, Inc.** **8401 73rd Ave N, Suite 63** **Minneapolis, MN 55428** **Tel: 763-477-5606** **Fax: 763-477-6357** **Email: swtay@libramed.com**
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1 BACKGROUND

NxThera has completed more than 60 canine studies as part of its convective vapor ablation system product development program. Collectively, these studies are best classified as a series of investigational studies that were an integral part of the Company's efforts to develop and validate the safety of the system and the treatment of the prostate with vapor therapy, and to optimize the therapeutic delivery of vapor to effectively treat benign prostatic hyperplasia (BPH).

An earlier version of the Rezūm System has been tested in human subjects. This initial study included four acute subjects and 9 chronic subjects with up to 6 months follow-up and a subset of these chronic patients with 12 month follow-up data. This study repeats the same study but using the revised Rezūm System that is intended for commercial use.

2 SUMMARY DEVICE DESCRIPTION

The NxThera BPH Rezūm System consists of the following components:

- Power Generator
- Delivery Device (which includes an insulated introducer sheath and vapor delivery needle)
- Water delivery system
- Saline flush tubing

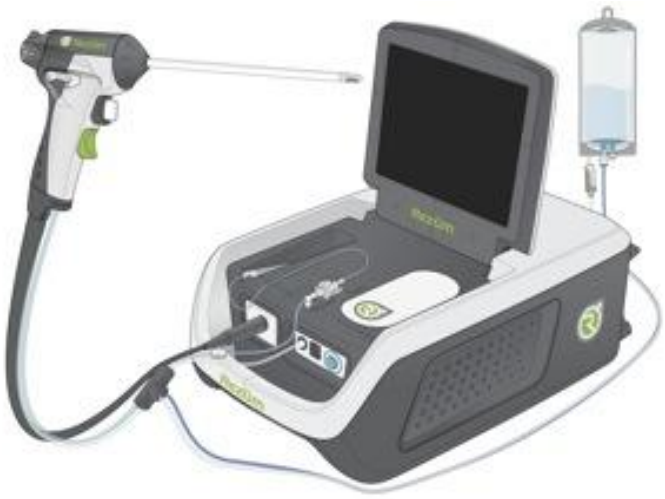

Figure 2-1: Rezūm System (not drawn to scale)

The NxThera BPH Rezūm System consists of a RF power Generator unit which controls the generation and temperature of the water vapor created at the Delivery Device and delivered to the prostate.

Within the Delivery Device is an insulated shaft with two lumens, one of which is used for a 4 mm cystoscopy optical lens. The other lumen contains the vapor delivery plastic needle. At

the distal end of the vapor needle, the vapor emitter holes are arranged circumferentially around the needle through which water vapor is delivered to the prostate when the needle is inserted within the prostate.

The Rezūm Generator system has been built in compliance with quality control system (IEC 60601-1) and both the hardware and software of the system have gone through verification and validation testing, including controlling the vapor delivery.

The procedure utilizes a transurethral approach under direct visualization using the optics from a standard rigid cystoscope which is inserted into the Delivery Device to allow the treating physician to visualize access to the prostate through the urethra, and to facilitate proper placement of the vapor needle into the prostate to deliver the vapor therapy. Using the bladder neck and veru montanum as the anatomical guides (e.g., the transition zone of the prostate), the tip of the Delivery Device is positioned against the wall of the urethra; the physician then releases the safety and deploys the vapor needle into the prostate.

Once the needle is fully deployed, the vapor treatment button is activated to deliver the water vapor for up to 10 seconds of treatment. This process is repeated as many times as needed for each lobe of the prostate, with the first treatments delivered near the bladder neck. The standard treatment algorithm is to leave approximately 1 cm between each treatment injection, and a typical sized prostate with BPH will need three 10-second treatments in each lateral lobe. The median lobe, if present, may be treated with one or two treatments.

Potential benefits of this treatment, in contrast with other transurethral ablation treatments, are:

- **No electromagnetic energy is delivered within the body.**
- **Each treatment is up to 10 seconds; each lateral prostate lobe may receive 2-4 treatments or one treatment per 1 cm length of urethra within the prostate**
- **Median lobes of all sizes can be treated.**
- **Treatments may be done with no or minimal local anesthesia.**
- **There may be less bleeding, post procedure, than with other treatments.**
- **Symptom relief is expected within days of treatment.**

3 SUMMARY OF PROCEDURE

1. **Insert the 4 mm optical lens of a rigid endoscope into the Delivery Device;**
2. **Evaluate the Rezūm system readiness by doing a test treatment in air;**
3. **Lubricate the shaft of the Delivery Device with Lidocaine gel or equivalent;**
4. **Insert the shaft of the Delivery Device into the urethra until the tip is in the bladder using the endoscopy view to guide the Delivery Device;**
5. **Withdraw the tip of the Delivery Device to just below the bladder neck;**
6. **Press the tip of the shaft against the urethra, and press the flush button as necessary to visualize placement;**

7. Depress the trigger to deploy the vapor needle into the prostate tissue. Ensure that the indicator mark on the vapor needle is fully inserted into the prostate
8. Pull the vapor trigger to deliver the vapor therapy. The power will be automatically shut off after 10 seconds (or earlier if the vapor trigger is released prior to 10 seconds).
9. Retract the vapor needle;
10. Reposition the tip of the Delivery Device 1 cm from the first treatment position;
11. Repeat the process with the contralateral lobe and the median lobe (if present). See Figure 3-3 as an illustration of the final results

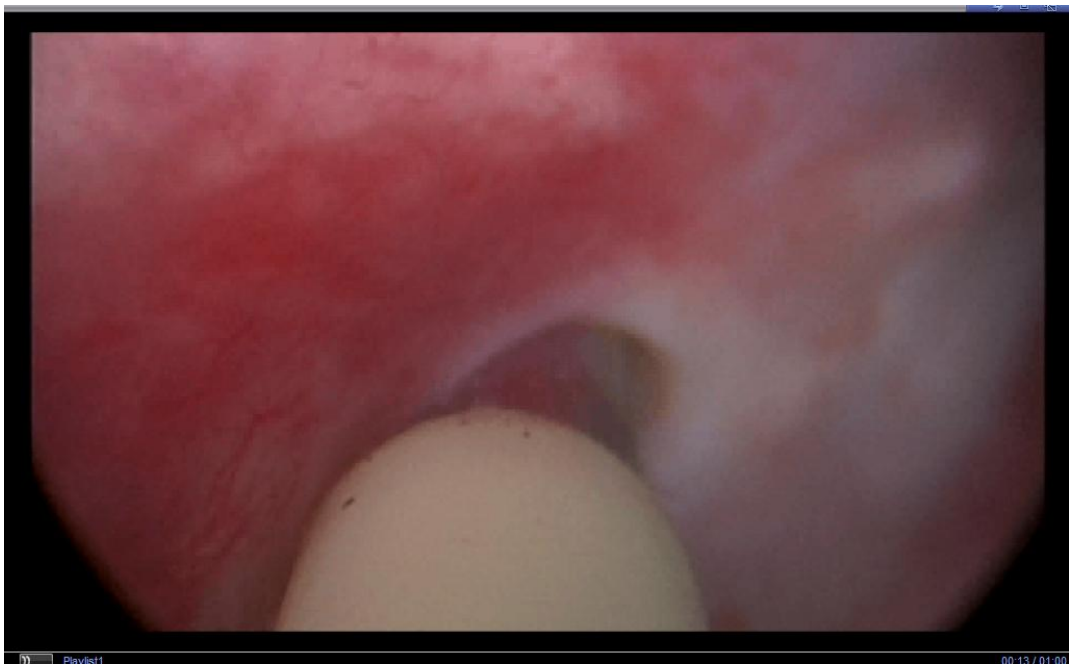

Figure 3-1: Vapor Delivered Through Vapor Needle

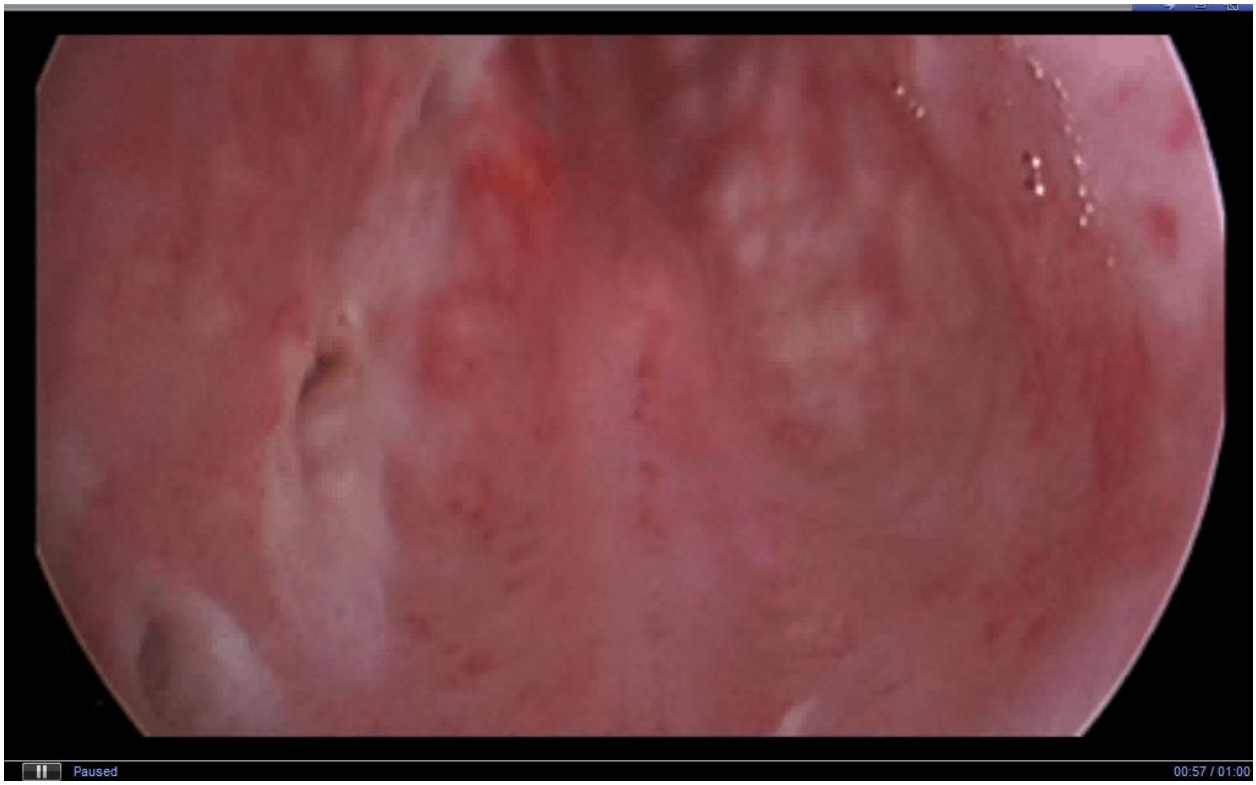

Figure 3-2: Prostatic Urethra After 3 Treatments on the Left Lobe

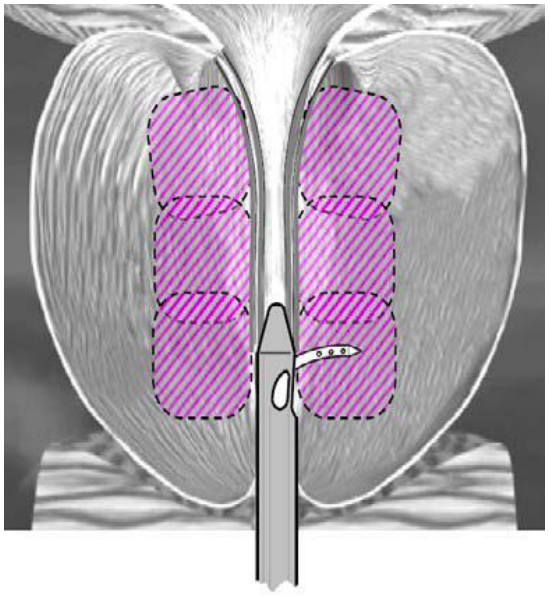

Figure 3-3: Schematic of Ablation Zone After Treatment

4 PHASE I ACUTE STUDY DESIGN

This study will be conducted in two phases. The phases will run consecutively. Both phases are part of a single arm, single center study.

4.1 PHASE 1: ACUTE STUDY

The subjects will undergo a Rezūm procedure per the IFU with the Delivery Device inserted transurethrally in order to deliver the therapy directly into the prostate. The treatment setting used will be based on the results obtained from treating extirpated prostate tissue from Rezūm Ex study. After vapor ablation, the planned prostatectomy/adenectomy surgical procedure will continue until completion. Information regarding usability, treatment settings, and correlation to the lesion size will be collected from an examination of the extirpated tissue. The lesions from the extirpated prostate tissue will be necropsied and evaluated for lesion characteristics to gain additional information to optimize the vapor ablation treatment.

4.1.1 Acute: Inclusion Criteria

1. **Male subjects ≥ 45 years of age who have symptomatic / obstructive symptoms secondary to BPH requiring invasive intervention.**
2. **Scheduled to have prostatic tissue surgically removed.**

4.1.2 Acute: Exclusion Criteria

1. **Presence of a penile implant;**
2. **Any prior minimally invasive intervention (e.g. TUNA, Microwave) or surgical intervention to treat the symptoms of BPH;**
3. **Confirmed or suspected malignancy of prostate;**
4. **Previous pelvic irradiation or radical pelvic surgery;**
5. **Urethral strictures, bladder neck contracture or muscle spasms; or,**
6. **Biopsy of prostate within 30 days prior to the date of this procedure.**
7. **Unable or unwilling to sign the Informed Consent Form**

4.2 TREATMENT MEDICATION

There are no treatment medication requirements for this portion of this study. Medication will be administered at the discretion of the Principal Investigator or his designee per the standard hospital procedure for adenectomy. .

4.3 SAMPLE SIZE

Up to 20 BPH subjects scheduled for surgical removal of BPH tissue

4.4 STUDY DURATION

There is no follow up for this acute study. Therefore, study duration is anticipated to be no more than 2 weeks.

4.5 ENDPOINT

Lesion size from the vapor treatment, as measured by TTC stain in the extirpated tissue.

5 PHASE 2: OPTIMIZATION STUDY

5.1 STUDY OBJECTIVE

The objectives of the Phase 2 study are:

Optimize the effectiveness of the BPH Rezūm System and assess the effect of treatments with different caloric values, including an assessment of subject comfort during the procedure and post-procedure

Further document the safety and post-operative effects of the Rezūm System in the treatment of obstructive BPH.

5.2 STUDY DESIGN

In this Phase 2 study, up to 15 subjects with LUTS secondary to BPH requiring surgical treatment will be treated with the Rezūm System. Treatment is ≤ 10 seconds per treatment. The power and water flow rate settings may be adjusted slightly to minimize pain and swelling to the subjects while maximizing the treatment area (e.g., lesion size). The power setting will be between 175W and 250W with a concomitant adjustment to the water flow rate of 2.7 ml/min to 5.0 ml/min. The actual power output will be recorded. For all the treatment settings, adverse and subject responses will be collected. The range of acceptable power setting have been determined in bench-top, animal studies, testing on extirpated human prostate to create lesions of a size that is adequate to treat the BPH tissue. The unknown factor that will be evaluated in this Phase 2 study is the acute response(s) to the different treatments in terms of procedural and post procedural discomfort. If the subjects are able to tolerate the higher caloric treatments, those treatments will be used in subsequent subjects. If the subjects are not able to tolerate a particular caloric treatment, the lower caloric treatment will be used in subsequent subjects.

The standard Rezūm treatment following the IFU will be followed. Information regarding the vapor needle configuration, treatment settings, treatment medications, pain or discomfort during treatment, post-treatment catheterization requirements, and the type and severity of any short term irritative or urinary obstructive symptoms will be collected. Information regarding the subjects' symptomatic response and uroflowmetry characteristics will be collected at baseline and in follow-up evaluations conducted with each subject. Any adverse events will be evaluated at each visit. Lesion characteristics and treated tissue resorption rate will be measured by gadolinium enhanced MRI imaging techniques performed post-procedure at specified intervals.

5.3 OPTIMIZATION ENDPOINTS

5.3.1 Endpoint 1: Intra-procedure Pain

Procedural pain will be assessed using the Wong Baker scale. Subjects will be asked to rate the level of pain and discomfort during the treatment.

5.3.2 Endpoint 2: Post-Procedure Catheterization

All subjects will be kept at the clinic for observation for 24 hours post-procedure. Post procedure catheterization will only be allowed if the Principal Investigator determines that

the subject has symptoms of retention (defined as failure to void within 8 hours post procedure) or requires catheterization for other safety reasons.

5.3.3 Endpoint 3: Lesion size, as measured by MRI at Week 1 post-procedure.

5.3.4 Endpoint 4: Change in IPSS score from baseline at various points post-procedure.

5.4 INCLUSION CRITERIA

1. **Male subjects ≥ 45 years of age who have symptomatic / obstructive symptoms secondary to BPH requiring invasive intervention.**
2. **IPSS score of ≥ 15.**
3. **Qmax: Peak flow rate ≤ 15 ml/sec.**
4. **Post-void residual (PVR) < 300 ml.**
5. **Prostate transverse diameter > 30 mm.**
6. **Prostate volume between 20 to 120 gm.**
7. **Voided volume ≥ 125 ml.**
8. **Subject able to complete the study protocol in the opinion of the Principal Investigator.**
9. **Subject must be willing to undergo the procedure without anesthesia.**

5.5 EXCLUSION CRITERIA

1. **History of any illness or surgery that in the opinion of the Principal Investigator may confound the results of the study.**
2. **Presence of a penile implant.**
3. **Any prior minimally invasive intervention (e.g. TUNA,Laser, Microwave) or surgical intervention for the symptoms of BPH.**
4. **Currently enrolled in another clinical trial.**
5. **Confirmed or suspected malignancy of prostate or bladder.**
6. **Previous rectal surgery (other than hemorrhoidectomy) or history of rectal disease.**
7. **Previous pelvic irradiation or radical pelvic surgery.**
8. **Documented active urinary tract infection by culture or bacterial prostatitis within last year documented by culture (UTI is defined as >100,000 colonies per ml urine from midstream clean catch or catheterization specimen).**
9. **Neurogenic bladder or sphincter abnormalities.**
10. **Urethral strictures, bladder neck contracture or muscle spasms.**
11. **Bleeding disorder (note that use of anti-platelet medication is not an exclusion criterion).**
12. **Subjects who are interested in maintaining fertility.**
13. **Use of concomitant (or recent) medications to include the following:**
    a. **Beta blockers, antihistamines, anticonvulsants, and antispasmodics within 1 week of treatment, unless there is documented evidence of stable dosing for last 6 months (e.g., no dose changes).**
    b. **Alpha blockers, antidepressants, anticholinergics, androgens, or gonadotropin-releasing hormonal analogs within 2 weeks of treatment.**
    c. **5-alpha reductase inhibitor within the last 6 months**
14. **Subject is unable or unwilling to go through a "washout" period for the above medications prior to treatment.**

15. Subject has chronic urinary retention.
16. Significant urge incontinence.
17. Poor detrusor muscle function.
18. Neurological disorders which might affect bladder or sphincter function.
19. Bladder stones.
20. Renal impairment.
21. In the opinion of the Principal Investigator, subject will not be able to adequately tolerate a rigid cystoscopy-type procedure.
22. Unable or unwilling to sign the Informed Consent Form (ICF) and/or comply with all the required follow-up requirements.
23. Any cognitive disorder that interferes with or precludes a subject from directly and accurately communicating with the Principal Investigator regarding the study.
24. Peripheral arterial disease with intermittent claudication or Leriches Syndrome (i.e., claudication of the buttocks or perineum).
25. Biopsy of the prostate within 30 days prior to the Rezūm procedure.

6 STUDY PROCEDURES

6.1 SUBJECT ENROLLMENT

Only subjects who meet the inclusion/exclusion criteria will be eligible to participate in the study. It is recommended that only subjects that live within 90 minutes of driving distance from the study site be selected as participants in the study due to the study follow-up requirements.

Once it is determined that a subject meets the enrollment criteria (except for the use of the concomitant medication), the subject will be given an informed consent to read. Subjects that were on BPH medication will then go through a washout period. If the subject successfully goes through the washout period and still meets the selection criteria, the subject will be considered enrolled and assigned an enrollment ID.

The Principal Investigator (PI) or study coordinator will review the informed consent with the subject to be sure the subject completely understands the meaning of the consent. Upon completion, the subject will be given an opportunity to sign the informed consent. A subject will be considered officially enrolled only if treatment with the NxThera Rezūm System is attempted.

6.2 SCREENING AND BASELINE EVALUATIONS

The following evaluations will be completed for all study candidates who have provided a written informed consent:

- Complete general medical and genitourinary history (including any previous treatment for LUTS; if pharmacologic, name of drug(s) as well as dosage) and duration of subject's BPH symptoms.
- Blood analysis:
    - Complete blood cell count (CBC)
    - Blood urea nitrogen (BUN)

- **Serum creatinine**
- **Serum prostate-specific antigen (PSA) level**
- **Electrolytes**

- **Uroflowmetry:**
  - **Voided volume (must be ≥ 125 mL or test must be repeated)**
  - **Total time of voiding**
  - **Peak flow rate (Qmax; also known as PFR)**
  - **Average urinary flow rate**
  - **Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)**
- **Urinalysis**
  - **Urine culture, if indicated**
  - **Subject questionnaires:**
  - **International Prostate Symptom Score (IPSS)**
  - **BPH Impact Index (BPHII)**
  - **International Index of Erectile Function (IIEF)**
  - **Male Sexual Health Questionnaire Short Form (MSHQ-EjD Short Form)**
  - **Prostate volume (PV), length and width, as measured by TRUS**
  - **Confirmation of function of detrusor muscles via urodynamics**
- **Subjects must undergo a "washout" period of 6 months if they have been on:**
  - **5-alpha reductase inhibitor**
  - **Subject must undergo a "washout" period of 2 weeks if they have been on:**
  - **alpha blockers**
  - **antidepressants**
  - **anticholinergics**
  - **androgens**
  - **gonadotropin-releasing hormonal analogs**
  - **Subject must undergo a "washout" period of 1 week if they have been on:**
  - **Beta-blockers**
  - **Antihistamines**
  - **Anticonvulsants**
  - **Antispasmodics**
  - **Unless subjects have been on a stable dosing for the last 6 months (i.e. no changes)**

6.3 CONCOMITANT THERAPY

Therapy (medication and non-medication therapies) not restricted by a protocol requirement may be used during the study for the treatment or prevention of disease or to maintain good health. However, subjects should not take concomitant medications that affect the BPH symptoms which might confound the study result, per the PI's discretion.

6.4 SUMMARY OF PRE-PROCEDURE PREPARATION

All eligible subjects who have signed an informed consent and are on alpha blockers or beta blockers will undergo a washout period of 2 weeks or 7 days, respectively. Subjects who have been on a stable dosing of beta blockers for the last 6 months (i.e. no dose changes) do not need to undergo the 7 day washout period.

Subjects are to be given an oral anti-anxiety medication prior to treatment. This medication must be given at least 45 minutes prior to the procedure, but no more than 2 hours before the procedure. No anesthesia will be allowed. Pain killer may be prescribed at the physician's discretion.

6.5 FOLLOW-UP

The following evaluations will be completed at the follow-ups as indicated:

Table 6-1: Evaluations at Follow Up

Follow up period	Description
1 day (1-2 days)	Check for AE
	IPSS
	Pain assessment
	Medications
1 week (4-7 days)	Check for AE
	Pain assessment
	IPSS, Subject Satisfaction Questionnaire
	Cystoscopy
	Uroflow
	MRI
	Medications
1 month (3-5 weeks)	Check for AE
	Pain assessment
	Uroflow
	IPSS, BPHII, IIEF, EQ5D, MSHQ-EjD SF
	MRI
	Medications
3 months (12 – 14 weeks)	Check for AE
	Pain assessment
	Uroflow
	IPSS, BPHII, IIEF, EQ5D, MSHQ-EjD SF, Subject Satisfaction Questionnaire
	PSA
	Prostate Volume
	MRI
	Medications
6 months (24-28 weeks)	Check for AE
	Pain assessment
	Uroflow
	IPSS, BPHII, IIEF, EQ5D, MSHQ-EjD SF, Subject Satisfaction Questionnaire
	PSA

	Prostate Volume
	MRI
	Medications
12 months (11-13 months)	**Check for AE**
	Pain assessment
	Uroflow
	IPSS, BPHII, IIEF, EQ5D, MSHQ-EjD SF, Subject Satisfaction Questionnaire
	PSA
	Prostate Volume
	Medications
Annually for up to 5 years. Annual check up may be within 2 months of the anniversary of the procedure	**Check for AE**
	IPSS, BPHII, EQ5D, MSHQ-EjD SF, Subject Satisfaction Questionnaire
	Medications
Unscheduled	**Check for AE**
	Pain assessment (optional)
	Medications
	IPSS, BPHII, IIEF,MSHQ-EjD SF (all optional)
	Uroflow (optional)

6.5.1 Scheduled Follow-up Visits

Table 6-2: Schedule of Visits

	Baseline Pre-Op	1 day	1 week	1 month	3 months	6 months	1 year	Annual (2-5 years)	Unscheduled
IPSS	√	√	√	√	√	√	√	√	optional
BPH Impact Index	√			√	√	√	√	√	optional
EQ5D	√			√	√	√	√	√	
Sexual function (IIEF)	√			√	√	√	√	√	optional
MSHQ-EjD Short Form	√			√	√	√	√	√	optional
Subject Satisfaction Questionnaire			√	√	√	√	√	√	optional
Subject Pain Assessment		√	√	√	√	√			
Uroflow (Qmax + PVR)	√		√	√	√	√	√		optional
Urodynamics	√								
Prostate specific antigen (PSA)	√				√	√	√	√	
Prostate Volume	√				√	√	√	√	
Cystoscopy	√		√						
MRI	optional		√	√	√	√			
Adverse event(s)		√	√	√	√	√	√	√	√
Medication(s) used	√	√	√	√	√	√	√	√	√

7 ADVERSE EVENTS

7.1 DEFINITION OF ADVERSE EVENT(S)

For the purpose of this protocol, an "adverse event" (AE) will be defined as any adverse medical condition change (i.e., *de novo* or increased severity in a preexisting condition) from the subject's baseline condition that occurs during the course of the clinical study, after starting study procedure, whether considered procedure-related or not. Therefore, conditions existing at the time of enrollment will not be reported as an AE unless the event increased in clinically significant severity during the course of the study. Events which resolve and then recur should be reported as separate AEs. Events that are a continuation of an unresolved AE should not be reported as a new AE but a continuation of the previously reported AE.

The reason for catheterization will not be considered an AE if catheterization occurs and ends within 72 hours after the procedure because this is generally considered standard of care to allow the tissue to heal.

The reason for catheterization will be considered an adverse event if the following applies:

a. **If catheterization occurs within a 72-hour window after the procedure and the duration of catheterization extends beyond that 72-hour window**
b. **If catheterization occurs outside of a 72-hour window after the procedure**
c. **If catheterization recurs after the same symptom is resolved**

Lower Urinary Tract Symptoms (LUTS) will not be considered an adverse event if LUTS occurs and ends within a 3-day window (72 hours) after the procedure.

Lower Urinary Tract Symptoms (LUTS) will be considered an adverse event if the following applies:

a. **If LUTS occurs within a 3-day window (72 hours) after the procedure and the duration of LUTS extends beyond that 3-day window (72 hours)**
b. **If LUTS occurs outside of a 3-day window (72 hours) after the procedure**
c. **If LUTS recurs after the same symptom is resolved**

Normally expected symptoms caused by the treatment will not be considered AEs for this study. For example, normal pain or minor bruising at the surgical site due to the healing of the site will not be considered an AE. "Treatment" includes all procedures and treatments administered according this protocol.

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or by physical examination by the investigator.

AEs should be classified according to their underlying cause, if known, (e.g., fever resulting from infection should be reported as "infection"). Concomitant AEs that are unrelated (in the clinician's judgment) should be reported as separate events.

AE determination is based on three levels of evidence:
Level 1 – final diagnosis

Level 2 – signs
Level 3 – symptoms

Every effort should be made to collect Level 1 evidence of any AE. If an AE has all three levels of evidence, an AE should be reported only once at the highest level of severity, which is the final diagnosis (Level 1). A single AE should not be reported as multiple AEs based on separate symptoms, signs, and diagnosis.

In cases where a diagnosis is not possible, AE determination should be based on the next highest level of evidence (signs, Level 2), followed by symptoms (Level 3), if only symptoms are available.

A corrective action itself is not an AE. The AE should always be determined based on the reason that a corrective action was taken.

Note: there may be multiple symptoms representing or associated with only one AE. In this case only one AE should be reported. The symptoms can be captured within the AE description. If the symptoms are related to LUTS, complete the LUTS form in addition to the AE form. If AE requires catheterization, then complete the catheterization form.

Figure 7-1 is an AE determination and outcome flowchart.

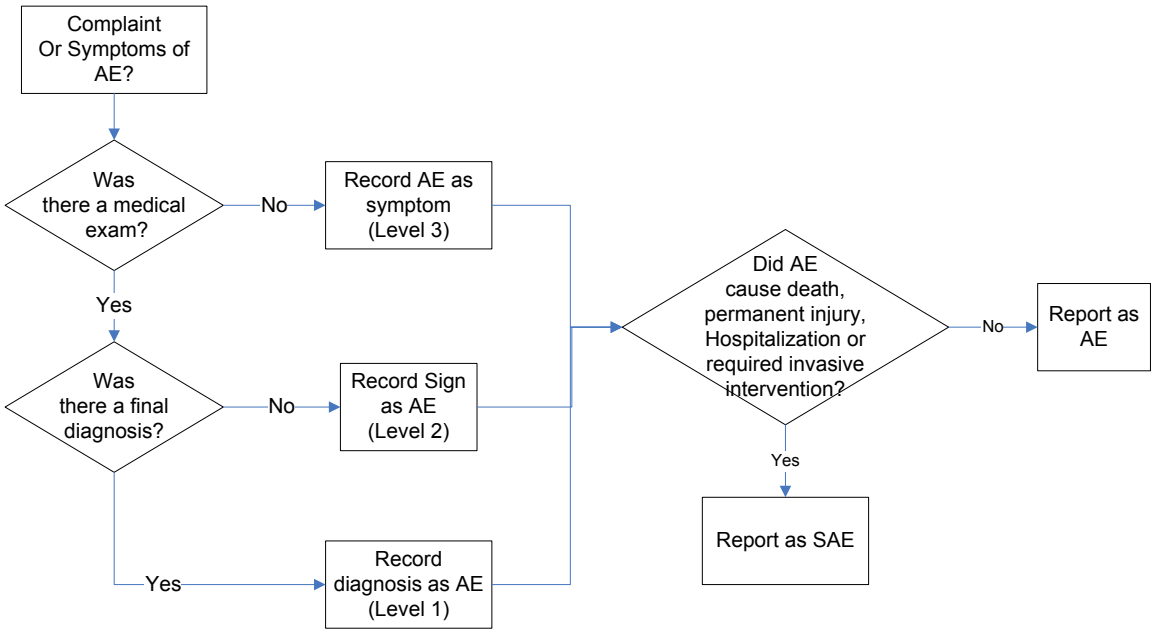

Figure 7-1: AE Determination and Outcome Flowchart

Examples
Subject is diagnosed with urinary retention and requires catheterization for more than 3 days. In addition, they have symptoms of irritation, urgency, and hematuria. Only one AE – retention should be reported. The additional symptoms should be noted in the AE description. Catheterization is the treatment.

7.2 STUDY RELATED AE DEFINITION

This section applies particularly to the Phase 2 part of the study. The transurethral intervention with a rigid scope similar in size to the Rezūm device commonly is associated with transient symptoms. For the purpose of this study, these types of transient symptoms will not be considered an adverse event. The corollary to a surgical procedure is bleeding. Bleeding will occur in all surgical BPH procedures, and bleeding, therefore, is not clinically significant and typically not reported as an AE. The following types of signs and symptoms that are attributed to the procedure, last less than or equal to 72 hours, AND do not result in intervention, re-hospitalization, or prolonged unplanned hospitalization, will not be considered AEs.

- **Dysuria**
- **Hematuria**
- **Storage (irritative) LUTS**
- **Urgency/frequency**
- **Nocturia**
- **Urge incontinence**
- **Voiding (obstructive) LUTS**
- **Hesitancy**
- **Decrease flow**
- **Increase residual**
- **Pain/discomfort**
- **Catheterization**

7.2.1 Erectile Dysfunction and Retrograde Ejaculation

Erectile dysfunction (ED) is commonly present in this population group. Therefore, only *de novo* ED and retrograde ejaculation attributable to the procedure within the first 3 months will be considered an AE. ED is a progressive disease and is expected to increase in frequency with age regardless of the procedure.

7.3 ANTICIPATED ADVERSE EVENT(S)

Anticipated adverse device events are those that may be reasonably expected to occur in association with a surgical BPH procedure, and include those listed here or reported in the literature associated with a minimally invasive BPH ablation procedure:

- **Pain**
- **Bleeding**
- **Infection / fever**

- **Perforation**
- **Retrograde ejaculation**
- **Urinary symptoms including:**
- **Dysuria**
- **Frequency**
- **Urgency**
- **Nocturia**
- **Urinary retention**
- **Temporary acute incontinence**
- **Sensation of not emptying bladder completely**
- **Transient incontinence**
- **Urethral stricture**
- **Urethritis**
- **Irritative urinary symptom**
- **Urethral injury**
- **Urinary clot retention**
- **Chronic pain at site**
- **Bladder spasm**
- **Rectal, perianal findings**
- **Anal irritation**
- **Flu-like symptoms**
- **Hematospermia**
- **Epididymitis**
- **Blood pressure change during therapy**
- **Flank pain**
- **Blood loss (> 50 ml)**
- **Bowel irritation**
- **Erectile dysfunction**
- **Retrograde ejaculation**
- **Pressure sensation**
- **Prostatitis**

7.4 SERIOUS ADVERSE EVENT(S)

An AE is considered to be serious if it:

- **Results in death (as part of any surgical procedure there is a chance of this SAE);**
- **Is life threatening;**
- **Requires subject hospitalization or prolongation of existing hospitalization;**
- **Results in persistent or significant disability/incapacity;**
- **Is considered an important medical event**
-

Important medical events that may not meet one of the above definitions could be considered SAEs if they jeopardize the health of the subject, or require surgical intervention to prevent one of the outcomes listed in the above definition. Serious adverse events may or may not be related to the Rezūm procedure.

7.5 UNANTICIPATED ADVERSE DEVICE EFFECT(S) (UADE)

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the "investigational plan" or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.6 REPORTING OF ALL ADVERSE EVENTS

All AEs that occur to any subject during the study must be documented on the Adverse Event CRF, including the following information: event description, treatments given, intensity of the event, relationship with the device, and the outcome of the event.

If the Principal Investigator determines that an AE is a SAE or a UADE, all as defined in this protocol, it is to be reported to the Sponsor as soon as possible but no later than 10 working days after the Principal Investigator first learns of the incident. The Sponsor will investigate any reported SAE or UADE to determine if the event type and severity was anticipated in the investigational plan.

Investigators are required to report all UADEs to the reviewing ethics committee (EC) no later than 10 working days from the date that the Principal Investigator first became aware of such UADE. In addition, the Principal Investigator must comply with any other reporting requirements of the reviewing EC.

A Sponsor who conducts an evaluation of a UADE shall report to all reviewing EC's and participating Investigators within 10 working days after the Sponsor first receives notice of the effect.

The Sponsor also must take the appropriate action regarding termination of the study when it is determined that an AE presents an unreasonable risk to subjects. Any such termination must occur no later than 15 working days from receipt of notice of the adverse event.

7.7 RELATIONSHIP OF AES TO THE STUDY DEVICE

How any AE related to the study procedure will be reported on the Adverse Event CRF and be determined by the Principal Investigator using the following definitions:

***Definite*: The AE follows a reasonable temporal sequence from the time of index procedure. This includes an AE that occurs during the index procedure and during the follow-up period.**

***Probable*: The AE follows a reasonable temporal sequence from the time of index procedure and the possibilities of factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded.**

***Possible*: The AE follows a reasonable temporal sequence from the time of index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.**

***Unlikely*: The AE has an improbable temporal sequence from the time of index procedure, or it can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.**
***Not related*: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.**

7.8 DEGREE OF SEVERITY

The degree of severity of the AE to the subject's health will be determined by investigator and documented on an Adverse Event CRF:

***Minimal*: Awareness of the event but easily tolerated**
***Moderate*: Discomfort enough to cause interference with usual activity**
***Severe*: Inability to carry out usual activity**

8 TRAINING

The training of appropriate clinical site personnel will be the responsibility of NxThera, as the study Sponsor. All physicians proctored by NxThera or another trained physician must sign the site Proctoring Form. To ensure proper surgical technique, uniform data collection and protocol compliance, NxThera will present a formal training session to study site personnel. At this training session, the study protocol, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up and regulatory requirements will be reviewed.

9 DEVICE MALFUNCTIONS

All failures and malfunctions of the study device must be documented on the Device malfunction/Performance CRF and faxed to the Sponsor, preferably within 24 hours of knowledge of the event. In the event of a device malfunction every effort must be made to return the suspected device to the Sponsor for analysis. All device performance issues and malfunctions will be reported in the clinical results (e.g. final report).

10 STUDY MANAGEMENT

This study is being conducted following "good clinical practices" (GCP). The Sponsor or a Sponsor representative will monitor the progress of the study as required by GCP and as specified by the study monitoring plan. This monitoring will include routine, periodic visits to study sites to compare reported results with source documentation.

10.1 SUBJECT IDENTIFICATION

Subjects participating in the study will be assigned a unique identification code (ID) using the format "XXX-YYY" where:

XXX = Institution Number, assigned by the Sponsor to each study site
YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study.

In addition to the ID, each subject's initials will be used as an identifier included on documentation submitted to the Sponsor.

For Phase 1 Acute subjects, an "A" will be added as a Prefix to the subject ID.
For Phase II Optimization subjects, an "O" will be added as a Prefix to the subject ID.

10.2 CENTRAL DATABASE

All study documentation will be collected and compiled in a central database by the Sponsor. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

11 REGULATORY RESPONSIBILITIES

11.1 ETHICS COMMITTEE (EC) APPROVAL

The Principal Investigator must submit the study protocol to their EC and obtain the EC's written approval before being allowed to conduct and participate in the study. The Principal Investigator also is responsible for fulfilling any conditions of approval imposed by the EC, such as regular reporting, study timing, etc. The Principal Investigator will provide Sponsor or its designee with copies of such approvals and reports.

11.2 INFORMED CONSENT FORM (ICF)

The Sponsor will provide a template ICF to each site for EC submission. This template may be modified to suit the requirements of the individual study site. The Sponsor must pre-approve all changes to the ICF prior to initial submission to the EC.

The Principal Investigator or assigned designee must administer the EC -approved version of the ICF to each prospective study subject, and obtain the subject's signature or a legally approved designee's signature along with the date of consent prior to enrollment in the study. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also informed that withdrawal from the study will not jeopardize their future medical care. A copy of the signed ICF must be given to each subject enrolled in the study.

11.3 CONFIDENTIALITY

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The Principal Investigator consents to the visits by the staff of the Sponsor and its authorized representatives and the U.S. FDA or any other local governmental body to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., cystograms).

11.4 AMENDING THE PROTOCOL

Neither the Principal Investigator nor the Sponsor will modify the Investigational Protocol without first obtaining concurrence of the other in writing. All changes must be submitted to the EC for review and approval. Any change that would require alteration of the ICF must receive approval from the EC prior to implementation. Following approval, the protocol amendment will be distributed to all protocol recipients at the site.

11.5 PROTOCOL DEVIATIONS

A Protocol Deviation CRF must be completed for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion / exclusion criteria, not performing required testing, missed follow-up window, etc.). An investigator must notify the Sponsor and the reviewing EC of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five working days after the emergency occurred.

11.6 SITE NONCOMPLIANCE

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations (21 CFR §812.46(a)).

11.7 DEVICE ACCOUNTABILITY

A Device Tracking Log (DTL) will be maintained at each investigational site and will be provided by the Sponsor. The BPH Rezūm Systems and Delivery Devices allocated for investigational site use will be recorded in the log upon delivery to the investigational site and will be stored in a secured area until use. Each site will be responsible for tracking the receipt and disposition of all investigational BPH Rezūm Systems and Delivery Devices. All unused BPH Rezūm Systems and Delivery Devices at the end of the study must be returned to the Sponsor.

The DTL will be updated as each BPH Rezūm System is delivered, used, or returned. The DTL will contain delivery dates, used dates, returned-to-sponsor dates, serial numbers, expiration dates and model and/or unit numbers of the BPH Rezūm Systems and/or Delivery Devices delivered to the site, and the subject IDs associated with all BPH Rezūm Systems and /or Delivery Devices that are used.

11.8 SPONSOR RESPONSIBILITIES

NxThera, Inc. is the Sponsor of this study. NxThera's responsibilities in the study include:

Provide training to Principal Investigator, other physicians, and the staff of the study site.

Select the Principal Investigator, all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.

Provide financial support to each study site.

Ensure completion of site monitoring of clinical data at clinical study sites.

Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.

11.9 PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The Principal Investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol and applicable laws and regulations. Also, the Principal Investigator may not begin enrollment until Sponsor or its designee receives and approves (when necessary) the following documents:

- Signed Investigator Agreement

- **Financial Disclosure Forms for all participating investigators**
- **EC Roster**
- **EC Protocol and ICF Approvals**
- **Investigators' current curricula vitae (CV)**
- **Signed Site Delegation Log**

11.10 CASE REPORT FORMS (CRFS)

CRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the data must be legible and complete.

CRFs will be provided by the sponsor representative via eDC.
All subject questionnaires will be provided by the sponsor representative as paper CRFs.

MRI Core Lab Forms will be provided by the sponsor representative as paper CRFs. These will then be sent to Libra Medical for data entry into the database.

All paper CRFs must be completed using a pen. Corrections of data on the CRF should be made by crossing out, but not obliterating, the incorrect data with a single line; writing the correct value next to that crossed out; and, at each change, initialing and dating by the person making the change. Correction fluids and covering labels must not be used. If the original CRFs have already been submitted to the data management, the Sponsor will initiate a Data Clarification Form to be completed by study site personnel.
eCRFs must be signed by the study investigator.
Queries will be created in the database if there are missing data or if there is a question about the data submitted following a data review. The site representative will answer the query or correct the data accordingly. The query must be approved by a monitor, data manager or project manager.

12 MONITORING PROCEDURES

The site will be monitored to ensure compliance during the study. Monitoring will consist of review of subject records, source documents, and other required documentation, including EC approvals and correspondence. The site staff must be available to meet with the monitor or other study Sponsor representative during site visits.

The monitoring will be performed in accordance with study Monitoring Plan. The monitoring will be done by the Sponsor representative:

Libra Medical, Inc.
8401 73rd Ave N, Suite 63
Minneapolis, MN 55428
Tel: 763-477-5606
Fax: 763-477-6357
Email: bschnabel@libramed.com

13 REPORTS AND RECORDS

13.1 REPORTS

Table 13-1 displays a list of the reports that are the responsibility of the Principal Investigator to report to the Sponsor. Each study investigator must follow their site's reviewing EC reporting requirements. If applicable regulations or EC requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 13-1: Reports Required from Investigators to Sponsor

Type of Report	Time Constraints of Notification (from the time study site personnel learned about the event)
Subject death	Written reports (e.g., via e-mail) within 48 hours
SAE or UADE	Within 10 working days
Report of subject enrollment	Daily
Subject withdrawal	Within 5 working days (e.g., by fax, e-mail)
Withdrawal of EC approval	Immediately by telephone/e-mail followed by a copy of the notification within 5 working days
Significant deviations from Study Protocol	Within 5 working days
Informed consent not obtained	Within 5 working days

13.2 RECORDS

The Principal Investigator must maintain the following accurate, complete, and current records relating to the conduct of the investigation. The final responsibility for maintaining such records remains with the Principal Investigator. These include:

- All correspondence with another investigator, an EC, a laboratory, Sponsor or its designee (e.g., monitor);
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;
- Any other records that applicable regulation requires to be maintained

14 OTHER STUDY ELEMENTS

14.1 INVESTIGATORS AND PATIENT POPULATION

The Principle Investigator (PI) for this study is Dr. Edwin Rijo from the Canela Clinic in La Romana, Dominican Republic.

Subjects for this study will be recruited from the PI's practice, will have been diagnosed with BPH and scheduled for surgery (Phase 1 Acute) or would otherwise be treated surgically or with other minimally invasive BPH treatment (Phase 2 – Optimization).

14.2 STATISTICAL ANALYSIS

Descriptive statistics will be calculated and reported for study variables, as appropriate. Continuous variables (e.g., symptom score, uroflowmetry, quality of life assessments) will be summarized using statistics such as means, standard deviations and absolute change from baseline. Categorical variables (e.g., adverse events) will be summarized as frequency

distributions. Adverse events and technical observations will be reported by frequency of occurrence, severity and relationship to the vapor treatment device.

All subjects enrolled in this study (including those withdrawn from the study or lost to follow-up) will be accounted for and documented.

14.3 UNSCHEDULED FOLLOW-UP VISITS

If subjects are seen for unscheduled/interim visits because of an AE, appropriate Clinical Report Form(s) (CRF(s)), including the AE CRF, will be completed, if applicable.

14.4 LOST TO FOLLOW-UP

If a subject fails to comply with follow-up evaluations, the investigational site must make repeated attempts (at least three) to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records. A last unsuccessful attempt to contact a subject must be documented by a returned, registered letter sent to the subject.

If a subject misses one of the follow-up evaluations but is present at the subsequent follow-up, the subject can be readmitted into the study and queried retrospectively for basic information; however, the missed evaluation must be documented on a Protocol Deviation CRF.

14.5 SUBJECT WITHDRAWAL FROM STUDY

14.5.1 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that there is documentation for the reason for the withdrawal. If the subject had an AE, the subject should be followed until the resolution of the AE, if possible.

14.5.2 Withdrawal Due to Exclusion Criteria

A subject may be withdrawn from the study if subject is later found to not meet study selection criteria.

14.5.3 Involuntary Withdrawal

A subject may also be withdrawn from the study at the discretion of the investigator (e.g., for non-compliance with medical advice).

14.6 END OF STUDY

Subjects may be exited from the study at the end of the study (i.e., study discontinuation by the Sponsor) or when the subject has completed the 5 year follow-up visit. An End of Study CRF will be completed at the time of study completion or discontinuation.

14.7 DESCRIPTION OF TESTS AND EVALUATIONS

14.8 SUBJECT QUESTIONNAIRES

All questionnaires are self-administered and will be completed at baseline and at each follow-up visit. Questionnaires completed at baseline will be compared to those completed at each follow-up visit to assess any effect of treatment. The following assessments will be administered.

14.8.1 IPSS[1]

The IPSS is a standardized, validated, and reliable self-administered questionnaire that utilizes 7 questions to assess the frequency and severity of a subject's obstructive and irritative symptoms, with each question scored on a scale of 0 (not at all) to 5 (almost always). Total scores on the IPSS can range from 0-35; a score of 7 or less represents subjects with mild symptoms; 8-19 represents those with moderate symptoms; and subjects with scores from 20-35 typically have severe symptoms.

14.8.2 IIEF[2]

The IIEF is a validated self-administered questionnaire designed for detecting treatment-related responses in patients with erectile dysfunction. In addition, the IIEF provides a broad measure of sexual function.

14.8.3 MSHQ-EjD Short Form[3]

The MSHQ-EjD Short Form is a self-administered questionnaire designed to assess ejaculatory dysfunction. The questionnaire consists of three ejaculatory function questions and one ejaculation bother question.

14.8.4 BPH Impact Index[4]

The BPH Impact Index is a self-administered questionnaire that measures the impact of BPH symptoms on the subjects' quality of life. The questionnaire assesses the extent to which the symptoms cause physical discomfort, anxiety/worry, bothersomeness, or otherwise affect activities of daily living.

14.8.5 EQ5D™[5]

EQ-5D is a standardized instrument used to measure health outcomes. The EQ-5D is a self-reported generic preference-based measure of health, developed by the EuroQol Group. The instrument can be applied to, and has been shown to be valid for, a wide range of health conditions. The EQ-5D has been used in many studies as a way of capturing the health-related quality of life of patients, trial participants and the general public.

14.8.6 Subject Satisfaction Questionnaire

This questionnaire is specific to the NxThera Rezūm System treatment and will measure overall satisfaction with the procedure, recommendation of treatment to friends/family and if the subject would undergo the treatment again if symptoms were to recur after 5 years.

14.8.7 Magnetic Resonance Imaging (MRI) with Gadolinium:

MRI T2 imaging, with dynamic gadolinium enhancement, will be performed on all subjects one week following the study treatment. Size and location of gadolinium defects will be independently assessed using Analyze® imaging software, a multi-dimensional, biomedical image display and analysis application.

14.8.8 Necropsy and TTC Stain

For Phase 1 of this study, gross necropsy will begin by placing the treated prostate specimen on a board for closer visual and tactile observation, measurements and pictures. Digital pictures will be taken of the treated prostate, and the prostate then will be sliced serially and the slices exposed for visual observation and digital documentation. Each of these tissue slices then will be submerged into tetrazolium hydrochloride to enhance the visual distinction between treated and untreated tissue. Treatment volume will be estimated from these slices. Observation and measurements will be recorded on the data sheets for each specimen. The sliced, stained tissues will be placed in formalin for the pathology histology examination.

14.8.9 Post Void Residual (PVR)

PVR will be determined using abdominal ultrasound, bladder scanner, or in/out catheterization. Prior to the enrollment of any subject, the study machine at each site will be identified and its accuracy verified.

14.8.10 Uroflow

The uroflow meter parameters will be measured using the uroflow meter. The print-out of the uroflowmeter must be sent to Libra Medical for adjudication.

14.8.11 Prostate Size:

For Phase 1, the extirpated prostate tissue mass/volume will be determined by submerging the treated prostate in isotonic saline in a graduated cylinder or a weight scale.

14.8.12 Transrectal ultrasound (TRUS)

For Phase 2; a TRUS will be performed on each subject during screening prior to treatment in order to obtain the subject's prostate dimensions and assist the PI in the development of each subject's treatment plan. TRUS also will be used to monitor the subject's prostate size at the follow up.

14.8.13 Urinary Tract Infection (UTI) Assessment:

UTI assessment data will be collected per normal laboratory standards. Investigators may conduct a urinalysis using a standard dipstick or may send a urine sample to the laboratory for culture.

14.8.14 Wong Baker Pain Scale

The Wong Baker scale is a validated measurement instrument intended to measure the amount of pain that a patient feels which ranges across a continuum from none to an extreme amount of pain. The pain scale is shown in pictorial form instead of a line. Each subject selects the response that he feels best represents his perception of his then current pain level.

14.9 SUSPENSION OR EARLY TERMINATION OF THE CLINICAL INVESTIGATION

If the clinical study is terminated prematurely or suspended, NxThera, as Sponsor, will promptly inform the Principal Investigator of such termination or suspension, and the reason(s) for this decision. The EC also shall be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Principal Investigator.

15 REFERENCES

[1] Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care. 1995 Apr;33(4 Suppl):AS145-55.

[2] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, and Mishra A. (1997) The international index of erectile function (IIEF): A multimentional scale for assessment of erectile dysfunction. Urology 49(6) 822-830

[3] Rosen, R.C. et al. Development and Validation of Four-Item Version of Male Sexual Health Questionnaire to Assess Ejaculatory Dysfunction. Urology. 2007 May; 69 (5): 805-809.