PROCEPT BioRobotics

Official Title: WATER II
Waterjet **A**blation **T**herapy for **E**ndoscopic **R**esection of prostate tissue **II**
Clinical Investigational Protocol

NCT Number: NCT0312350

Document Date: 22-January-2020

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WATER II

Waterjet **A**blation **T**herapy for **E**ndoscopic **R**esection of prostate tissue **II**

Protocol Number:	**TP0124**
Version Number:	**C**
Date:	**22 January 2020**
Device:	**AQUABEAM® System**
Commercial Sponsor:	**PROCEPT BioRobotics Corporation 900 Island Drive, Suite 101 Redwood City, CA 94065, USA**
Geographical Region:	**United States and Canada**

Protocol Revision Number	Protocol Revision Date
Rev. A	11 April 2017
Rev. B	31 May 2019
Rev. C	22 January 2020

1 GENERAL STUDY INFORMATION

1.1 Study Acknowledgement/Confidentiality

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The WATER II study will be conducted according to the IRB approved protocol and in accordance with 21 CFR 50, 54, 56, 812 and any other applicable regulations. The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with The World Medical Association Declaration of Helsinki (59thWMA General Assembly, Seoul, October 2008) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the device relating to pre-clinical and prior clinical experience will be made available to all physicians and other personnel who participate in conducting this study. The Investigator will discuss this material with the study team to ensure that they are fully informed regarding the device and the conduct of the study.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by both the sponsor and principal investigator or such disclosure is required by laws. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The sponsor and trial participants (including the principal investigator) agree to the terms outlined in the attached Clinical Trial Agreement.

Study Role	**Signature**	**Date** (dd/mmm/yyyy)
Sponsor/Designee		
Principal Investigator		
Co-Investigator		
Co-Investigator		
Co-Investigator		

1.2 Study Summary

Title:	Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue II (WATER II)
Design:	Pivotal study to support marketing claims, single-arm, interventional clinical trial collecting patient data from use of the AQUABEAM System
Device Name and Intended Use:	PROCEPT BioRobotics has developed the AQUABEAM, a personalized image-guided waterjet resection system that utilizes a high-velocity saline stream to resect and remove prostate tissue in males suffering from Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)
Primary Safety Endpoint:	The primary safety endpoint is the proportion of subjects with adverse events rated as probably or definitely related to the study procedure classified as Clavien-Dindo Grade 2 or higher or any Grade 1 event resulting in persistent disability (e.g. ejaculatory disorder or erectile dysfunction) evidenced through 3 months post treatment
Primary Effectiveness Endpoint:	IPSS score change from baseline to 3 months
Enrollment:	101 participants who received study treatment under protocol rev. A
Clinical Sites:	Sixteen (16) clinical study centers (13 in the United States, and 3 in Canada)
Follow up Schedule:	Baseline, Discharge, 1, 3, 6, 12, 24, 36, 48, and 60 months
Target Population:	Men with lower urinary tract symptoms due to BPH resulting from a large prostate size (80-150 mL)
Sponsor:	PROCEPT BioRobotics Corporation 900 Island Drive, Suite 101 Redwood City, CA 94065, USA

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2 STUDY PLAN

2.1 Background

Benign prostatic hyperplasia (BPH), or enlargement of the prostate due to benign growth of glandular tissue, is a very common disease of older men. Prostatic tissue may compress the urethral canal, causing partial or sometimes complete obstruction of the prostatic urethra, which interferes with the normal flow of urine. Symptoms of BPH include urinary hesitancy, frequent urination, dysuria, increased risk of urinary tract infections, and urinary retention.

Therapy for BPH includes medication and various surgical approaches. While medication is first-line therapy, many men do not have adequate responses to treatment. Surgical approaches include transurethral resection of the prostate (TURP) and other less invasive approaches such as transurethral microwave thermotherapy (TUMT) or transurethral needle ablation (TUNA). TURP involves invasive removal of prostate tissue using electrocautery and/or sharp dissection. While TURP remains the gold standard for surgical treatment, it carries risks, including bleeding, clot retention/colic, bladder wall injury, hyponatremia (water intoxication), bladder neck contracture, urinary incontinence, retrograde ejaculation, and erectile dysfunction. Additional techniques using lasers or electrocautery that either ablate or enucleate the adenomatous tissues have been developed to improve the efficiency and reduce the morbidity of TURP.

2.2 AQUABEAM System Clinical Experience Outside of US

Eighty-four subjects (New Zealand, Australia and India) have been treated with the AQUABEAM System from two clinical trials (APS, N=37; ABS, N=47).

APS (AQUABEAM Pilot Study) is a prospective multicenter phase II single-arm clinical trial (n=37) conducted in India, Australia, and New Zealand. Device generations 1.0 and 1.6 were used. Treatment took place between January 2013 and July 2014. The results from this study provided early evidence to support the safety and effectiveness of Aquablation for symptomatic benign prostatic hyperplasia.

ABS (AQUABEAM Study) is a single center prospective trial (n=47) with 1-year follow-up in India using generation 2.0, 2.1, and 2.2. Treatment took place between December 2014 and October 2015. This study confirmed procedure process improvements resulting from system enhancements, with preservation of safety and effectiveness during use of a second-generation device for the treatment of LUTS attributable to BPH.

In both trials, participants were men aged 50-80 years with moderate-to-severe lower urinary tract symptoms as determined by urodynamics. All patients underwent Aquablation under image guidance. Primary endpoints included procedural and peri-operative safety. The main clinical endpoint was change from baseline in International Prostate Symptom Score (IPSS). Other secondary endpoints included uroflow measures, prostate volume by transrectal ultrasound, and detrusor pressure (Pdet@Qmax, measured at 6 months only).

Eighty-four subjects enrolled and underwent Aquablation between January 2013 and October 2015. Most procedures were done under general anesthesia; some procedures in India were done under spinal anesthesia. The average subject 67.7 ± 6.7 years old with a prostate size of 49.8 ± 22.5 mL (range 20-118 mL) with 51.8% having a median lobe. 9 subjects (11%) had a prostate size >80 mL.

All procedures were technically successful with a mean ablation time of 5 minutes. One subject required transfusion. None required intravenous electrolyte management.

A safety summary of the 84 subjects resulted in no adverse events of urinary incontinence, erectile dysfunction, or retrograde ejaculation reported. The rates of all other adverse events were anticipated with a rate within the range observed with other minimally invasive BPH therapies. There were no reported serious adverse events related to the AQUABEAM System. The efficacy results are shown in **Figure 1** illustrating changes in IPSS, IPSS quality of life (QOL) score, maximum urinary flow rate (Qmax), and post-void residual (PVR).

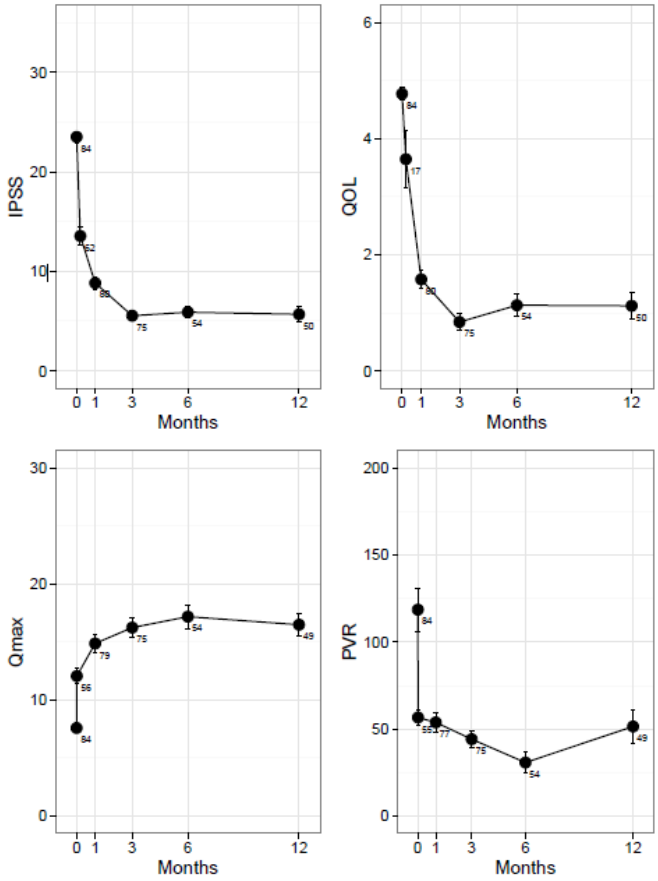


Figure 1 Twelve months IPSS, Qmax, QoL, and PVR results (mean±SE)

The AQUABEAM System offers the ability to rapidly ablate the adenomatous elements and as confirmed by the early clinical experience, the mechanism of action, controlled delivery of high-velocity saline stream, will potentially reduce complications including sexual dysfunction and result in an effective and rapid treatment option for patients with symptomatic BPH.

2.3 AQUABEAM System Clinical Experience Within US

WATER (NCT02505919) is a prospective double-blind multicenter randomized clinical trial conducted in the US and other sites. Currently, the study enrollment is completed and all subjects are in active follow-up. The study was being run under the guidance of a data monitoring committee (DMC). The DMC did not recommend any changes to study conduct or endpoints up to DMC closure. The trial was reported to FDA to support the De Novo submission which was granted on December 21st, 2017 (DEN170024).

2.4 AQUABEAM System Description

The AQUABEAM System is comprised of nine main components along with accessories. The main components are as follows:

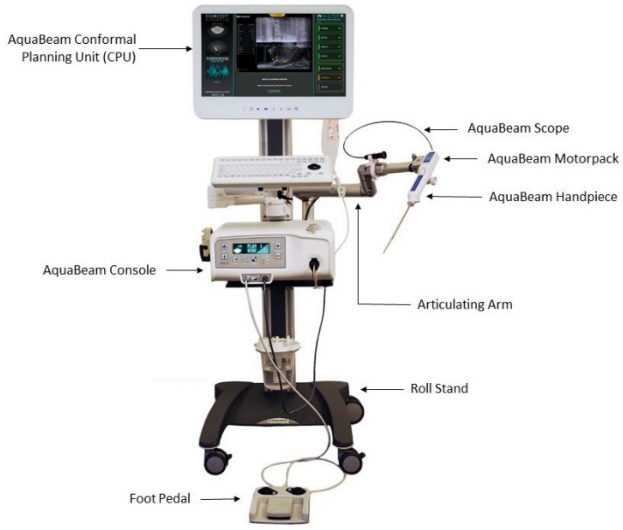


Figure 2 AQUABEAM System (TRUS Articulating Arm is not shown in this figure)

- ***AQUABEAM Conformal Planning Unit (CPU)***

Live transrectal ultrasound (TRUS) video are imported into and displayed by the CPU (**Figure 3**) allowing the operator to map the contour of the prostate. The prostatic capsule, verumontanum, and bladder are visualized allowing the operating physician to identify key anatomical markers, to optimize position of the AQUABEAM Handpiece and select the target area for treatment.

The planned parameters are downloaded to the AQUABEAM Console and Aquablation treatment can be initiated. During Aquablation treatment, the operating physician will utilize the CPU to monitor the progress of resection. At any point in time the operating physician can pause Aquablation treatment and make real-time adjustments to the target area as appropriate.

Figure 3 AQUABEAM Conformal Planning Unit

(Refer to User Manual for current configuration of the CPU interface)

- ***AQUABEAM CONSOLE***

The AQUABEAM Console (**Figure 4)** is a reusable component of the AQUABEAM System and it controls the functionality of the high pressure waterjet delivered by the Handpiece. The Console performs the following functions:

- Provides power sources to the CPU, Motorpack, and Foot Pedal
- Controls pump power and speed
- Primes the Handpiece during system setup
- Accepts planned resection angles and treatment profile from the CPU to allow the initiation of the Aquablation procedure
- Displays the status of the Aquablation procedure modes (i.e. PLAN or CUT)
- Displays pump level during the Aquablation procedure

The Console is mounted on the Roll Stand, which is then locked in place to prevent movement during the procedure. It is connected to a source of AC power via a transformer with a medical-grade grounded power cord. It is connected to the CPU via a USB cable and connected to the Motorpack and Foot Pedal through custom cables.

Prior to initiation of Aquablation treatment, the Console is attached to the AQUABEAM Handpiece providing the conduit for the saline fluid connection to be used in the subject treatment. The Console generates the saline pressure allowing controlled resection of the prostatic tissue in accordance with the AQUABEAM Conformal Planning Unit measurements. In addition, the console utilizes a peristaltic pump that assists in evacuation of saline from the bladder and prostatic urethra.

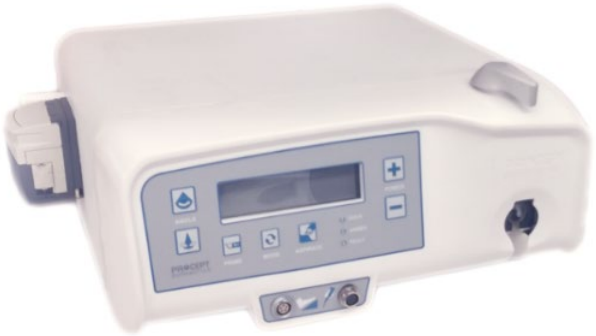


Figure 4 AQUABEAM Console
(Refer to User Manual for current configuration of the Console)

- ***AQUABEAM HANDPIECE***

The AQUABEAM Handpiece (**Figure 5**) is a sterile single use component of the AQUABEAM System. It obtains it power source and functional commands from the Motorpack. The AQUABEAM Handpiece is compatible with the AQUABEAM Scope, which is inserted into the central lumen of the Handpiece, enabling live cystoscopic visualization of the prostatic urethra and bladder during insertion and Aquablation treatment.

The tip of the Handpiece is inserted transurethral into the subject and advanced through the prostatic urethra into the bladder. Using both live TRUS and cystoscopic guidance, the operating physician positions the tip of the Handpiece to the desired location. Upon initiation of Aquablation treatment, the high-pressure sterile saline stream exits the AQUABEAM Handpiece tip at a 90º angle to the target prostatic tissue. The depth and angle of resection is based on the transferred planned contour and profile from the CPU to the Console.

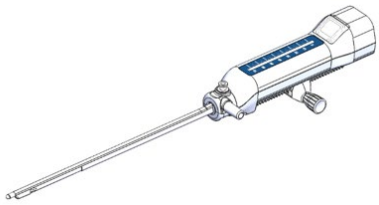
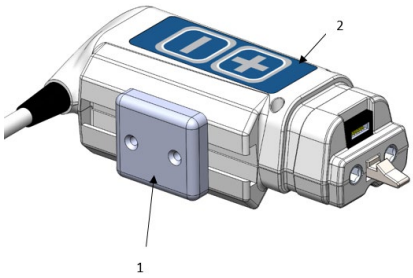


Figure 5 AQUABEAM Handpiece
(Refer to User Manual for current configurations of Handpiece)

- ***AQUABEAM MOTORPACK***

The Motorpack (**Figure 6**) is a re-usable component of the AQUABEAM System designed to dock with the disposable Handpiece and to move the Handpiece probe both rotationally and longitudinally by means of DC motors through a mechanical linkage. "Docking" means the electrical connectors and mechanical shafts of both lateral and radial motors in the Motorpack are positively engaged with the Handpiece. When complete, a LED on the Console gives a visual indication of successful docking. The Motorpack additionally has user controls consisting of two momentary switches, Power Increase Button and Power Decrease Button that signals the system to increment or decrement the High Pressure Pump power when pressed.

The Motorpack is connected to the Console with a flexible cable that carries DC power to the Motorpack as well as serial communication lines to transmit Console commands to the Motorpack/Handpiece assembly as well as to receive status and control information in return.



1. Motorpack Magnetic Strike Plate for Handpiece Articulating Arm
2. Pump Power Control Buttons (+/-)

Figure 6 AQUABEAM Motorpack
(Refer to User Manual for current configurations of Motorpack)

- ***AQUABEAM SCOPE***

The AQUABEAM Scope (**Figure 7**) consists of a semi-flexible stainless steel hypotube at the distal end (indirect patient contact) and a flexible Pebax sheath (non-patient contact), which is connected to a proximal eye piece. The semi-flexible and flexible portions of the Scope are connected by a stainless steel adapter. The Scope has no lumens, ports, or open channels. The Scope also includes 3 light adapters, one of which is used, depending upon the light source.

Prior to initiation of Aquablation procedure, the AQUABEAM Scope is inserted into the central lumen of the AQUABEAM Handpiece enabling direct visualization within the prostatic urethra during treatment.

The Scope camera is positioned just proximal to the AQUABEAM Handpiece tip to visualize the treatment zone. Cystoscopic imaging is used in conjunction with TRUS to monitor progression of tissue resection.

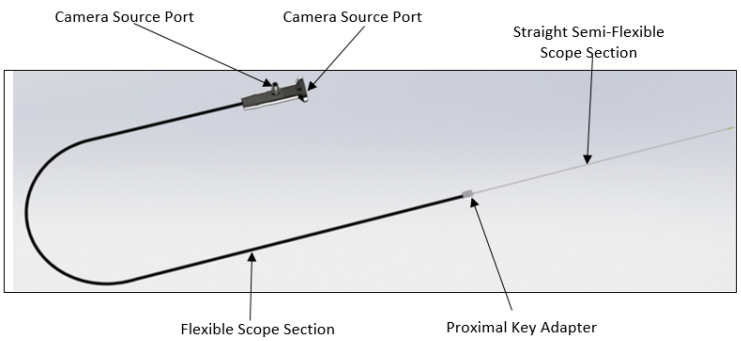


Figure 7 AQUABEAM Scope
(Refer to User Manual for current configurations of Scope)

- ***AQUABEAM FOOT PEDAL***

The AQUABEAM Foot Pedal (**Figure 8**) contains three foot-activated momentary switches. It is connected to the Console with a flexible cable. The Aquablate Pedal is the large center switch which must be depressed to enable Aquablation. The Aquablate Pedal is also used in the centering the of the Handpiece probe during the planning process. The two smaller switches at top left and top right provide controls to manual aspiration and manual priming.

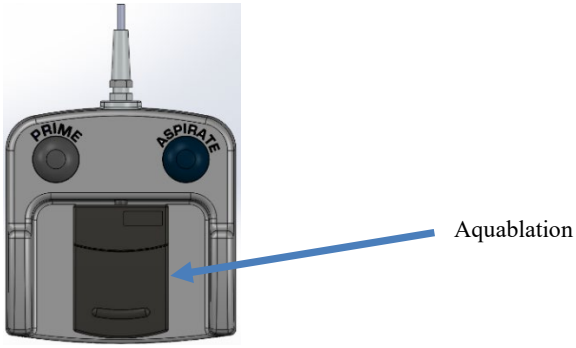


Figure 8 AQUABEAM Foot Pedal
(Refer to User Manual for current configurations of Foot Pedal)

- ***AQUABEAM ROLL STAND***

The AQUABEAM Roll Stand (**Figure 9**) is the main power source to the Console and serves as the chasis for the AQUABEAM System. The Roll Stand performs the following functions:

- AQUABEAM pump supply saline bag mount
- Adjustable CPU mount
- Console shelf
- Tissue collection container holder
- Articulating Arms storage rail (TRUS and Handpiece)
- Adjustable keyboard mount
- Foot pedal storage mount
- Serves as the storage unit for the AQUABEAM System

The power cable of the Roll Stand is plugged into the power outlet in the surgical suite or operation room to supply power to the Console.

The keyboard is the user data input to the CPU.

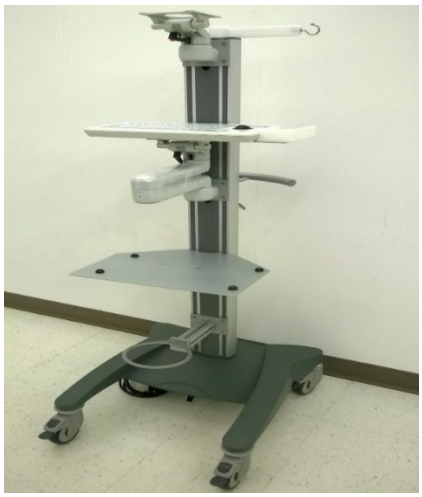
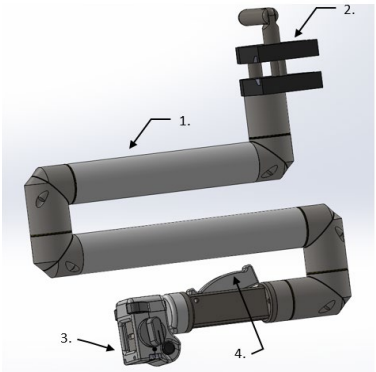


Figure 9 AQUABEAM Roll Stand
(Refer to User Manual for current configurations of Roll Stand)

- ***AQUABEAM HANDPIECE ARTICULATING ARM***

The AQUABEAM Handpiece Articulating Arm (**Figure 10)** fixes the Handpiece and Motorpack in position relative to the patient. The Handpiece Articulating Arm performs the following functions:

- Connects to standard bedrails
- Allows full freedom movement when Release Trigger is depressed
- Locks rigidly when Release Trigger is not depressed
- Connects to Motorpack/Handpiece via defeatable magnetic latch
- Allows ±20° of Handpiece rotation with 2°discrete locking points
- Provides bubble level to visualize horizontal plane
- Provides stability of Handpiece during Aquablation



1. Handpiece Articulating Arm
2. Bedrail Clamp
3. Magnetic Latch Block
4. Articulation Release

Figure 10 Handpiece Articulating Arm
(Refer to User Manual for current configurations of Handpiece Articulating Arm)

- ***AQUABEAM TRUS ARTICULATING ARM***

The AQUABEAM TRUS Articulating Arm (**Figure 11)** fixes the TRUS probe and stepper in position relative to the patient. The TRUS Articulating Arm performs the following functions:

- Connects to standard bedrails
- Allows full freedom movement when Release Trigger is depressed
- Locks rigidly when Release Trigger is not depressed
- Connects to TRUS probe and stepper
- Provides stability of TRUS probe during Aquablation

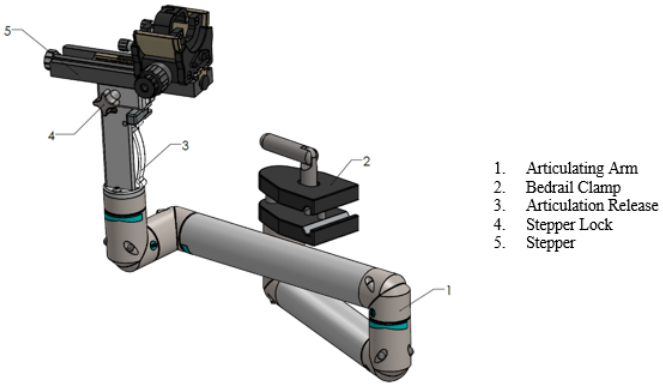


Figure 11 TRUS Articulating Arm
(Refer to User Manual for current configurations of TRUS Articulating Arm)

2.5 Regulatory Status

The AQUABEAM System received US FDA De Novo grant on December 21st, 2017 (DEN170024) and concluded that the device should be classified into Class II. It is CE marked in Europe and currently commercialized in Australia, New Zealand, Canada, the United States, and select European markets.

2.6 Indications for Use

The AQUABEAM System is intended for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia.

2.7 Overall Design

Pivotal study to support marketing claims, single-arm, interventional clinical trial collecting data from the use with the AQUABEAM System.

2.8 Study Objectives

The primary endpoint of this study is to evaluate the efficacy of the AQUABEAM System for the treatment of lower urinary tract symptoms resulting from BPH, as measured by the changed in IPSS score at 3 months.

2.9 Study Duration

Each subject is followed postoperatively through 60 months. Total study duration from first subject enrolled to last subject completing the 60 months follow-up visit is expected to take approximately six years.

2.10 Number of Sites

Sixteen (16) clinical sites will participate, 13 in the United States, and 3 in Canada.

2.11 Sample Size

One hundred and one (101) participants who received study treatment under protocol rev. A.

2.12 Study Population

Men with lower urinary tract symptoms due to BPH resulting from a large prostate size (80-150 mL). To participate, a patient must meet all inclusion criteria and none of the exclusion criteria listed in **Table 1**.

Table 1 Study Eligibility Criteria

Inclusion Criteria	**Exclusion Criteria**
a) Male age 45-80 years b) Subject has diagnosis of lower urinary tract symptoms due to benign prostatic enlargement causing bladder outlet obstruction c) Subject has an IPSS score greater than or equal to 12 d) Maximum urinary flow rate (Qmax) less than 15mL/s[1] e) Serum creatinine < 2 mg/dL within 30 days of surgery f) History of inadequate or failed response, contraindication, or refusal to medical therapy g) Prostate size ≥ 80 mL and ≤ 150 mL as measured by TRUS h) Patient is mentally capable and willing to sign a study-specific informed consent form	a) BMI ≥ 42 b) Patients unable to stop anticoagulants, antiplatelet agents, or non-steroidal anti-inflammatory agents (NSAIDs, including aspirin greater or equal to 100mg) prior to treatment per standard of care c) History of gross haematuria d) Participants using systemic immune-suppressants including corticosteroids (except inhalants); unable to withhold non-steroidal anti-inflammatory agents (NSAIDs, including aspirin) prior to treatment per standard or care except for low dose aspirin (e.g. less than or equal to 100mg) e) Known coagulopathy or platelet disorder f) Contraindication to both general and spinal anesthesia g) Any severe illness that would prevent complete study participation or confound study results h) History of prostate cancer or current/suspected bladder cancer. Prostate cancer should be ruled out before participation to the satisfaction of the investigator if PSA is above acceptable thresholds i) History of actively treated bladder cancer within the past two (2) years j) Diagnosis of polyneuropathy k) Clinically significant bladder calculus or bladder diverticulum (e.g., pouch size >20% of full bladder size) l) Active infection, including urinary tract infection or prostatitis

	m) Urinary catheter use daily for 90 or more days consecutively n) Previous urinary tract surgery such as e.g. urinary diversion, artificial urinary sphincter or penile prosthesis o) Diagnosis of or has received treatment for chronic pelvic pain syndrome p) Ever been diagnosed with a clinically significant urethral stricture or meatal stenosis, or bladder neck contracture q) Known damage to external urinary sphincter r) Has had an open heart surgery, or cardiac arrest < 180 days prior to the date of informed consent s) Known illicit substance abuse t) Participants using anticholinergics specifically for bladder problems. Use of medications with anticholinergic properties is allowable provided the patient does not have documented adverse urinary side effects from these medications. u) Dementia or psychiatric condition that prevents the participant from completing required follow up v) Previous pelvic radiotherapy w) Participating in another investigational study that could affect responses to the study device x) Subject is unwilling to accept a transfusion should one be required

[1]The total voided volume must be ≥ 125mL. If the total voided volume is less than 125mL, the voided volume must be equal to or greater than 50% of the bladder capacity (defined as voided volume + PVR). The patient can repeat the test if necessary.

2.13 Screening and Baseline

Potential study participants will undergo screening at the study center. A patient must sign a study-specific, IRB approved informed consent form prior to any baseline testing for eligibility that goes beyond standard care. Each patient will be assigned a study ID after signing the informed consent form.

Baseline assessment consists of the tests listed below. Please refer to **Table 2** for detailed test list and requirement:

- Medical history focusing on urinary symptoms
- Uroflowmetry for Qmax and PVR
- Transrectal Ultrasound (TRUS) for measuring prostate volume
- Questionnaires for assessing BPH symptoms and sexual functions (see schedule of assessments)
- Concomitant medications
- Blood tests (see schedule of assessments)

2.14 Surgical Procedure

The surgical procedure should take place within 90 days of baseline tests.

2.15 Preoperative Instructions

Patients must avoid taking non-steroidal anti-inflammatory agents (NSAIDs) or antiplatelet agents (e.g., aspirin, clopidogrel) prior to surgery per standard of care.

2.16 Anesthesia

All surgical procedures will be performed under general or spinal anesthesia.

2.17 Device Usage and Malfunction Reporting

A brief description of use of the AQUABEAM System is provided below. The study investigator will be trained in device use through didactic, practicum training and proctoring. Complete details on the preparation and use of the AQUABEAM System can be found in the device's instructions for use and user manual documents. Should any device defect or malfunction be noticed at any point, whether prior to, during, or after a procedure, this defect or malfunction will be reported through PROCEPT's standard medical device reporting process.

AQUABEAM Device Use. The AQUABEAM device will be used according to the manufacturer's instructions for use. The Handpiece is removed from the urethra and the Investigator uses a balloon catheter inflated in the prostatic fossa for approximately 3-5 hours to achieve adequate hemostasis.

Analysis of Excised Tissue. Histopathology of the excised tissue will be performed. The study sponsor will be allowed access to the high-definition photographs of the tissue slides.

2.18 Post-Procedure Management

Post-procedure care is defined as care provided to the subject during the period starting after the procedure to hospital discharge. The subject will be managed post-operatively and discharged as per standard practices. At 1 month, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months the subject will return for follow up visits. The 60 months visit concludes the subject's participation in the study. Please refer to **Table 2** for detailed test list and requirement for this visit.

2.19 Study Assessments

The schedule of assessments is shown in **Table 2** below.

Table 2 Schedule of Assessments

Evaluation	Baseline w/in 90 days of Tx	Treatment	Discharge	1 Month (+/-5 days)	3 Months (+/-10 days)	6 Months (+/-30 days)	12 Months (+/-60 days)	24,36, 48, 60 Months (+/-60 days)
Medical History + Demographics	X							
Serum Blood Test – CBC & BMP[1]	X		X					
PSA	X					X	X	X
Uroflow + PVR	X			X	X	X	X	X
Incontinence Severity Index	X			X	X	X	X	
IPSS	X			X	X	X	X	X
Pain Intensity Scale (NRS) & Dysuria Questionnaires	X			X	X	X		
Sexual Function (IIEF-15, MSHQ-EjD)[2]	X			X	X	X	X	
Quality of Recovery			X	X	X	X	X	
TRUS	X	X			X			
Concomitant Medication	X	X	X	X	X	X	X	X[3]
Adverse events		X	X	X	X	X	X	X[4]

[1]Basic metabolic profile
[2]Required for patients who are sexually active 4 weeks prior to the questionnaire completion date
[3]Only urological SAEs and urological adverse event related medication and all BPH medication
[4]Only urological SAEs and urological adverse events

Medical history: During the baseline assessment, the investigator or coordinator will record details of medical history as they relate to BPH.

Serum Blood Test: A blood sample should be collected prior to the surgical procedure to measure PSA, complete blood count (CBC), and Basic Metabolic Panel (BMP) to include at least levels of creatinine, sodium, and blood urea nitrogen. A CBC and BMP should also be collected following the first voiding trial and prior to discharge. PSA will also be repeated at 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months follow-up visit.

Uroflowmetry: Uroflowmetry test is performed at baseline, 1 month, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months follow-up visit. For Qmax to be valid for a patient, the total voided volume must be ≥ 125mL. If the total voided volume is less than 125mL, the voided volume must be equal to or greater than 50% of the bladder capacity (defined as voided volume + PVR). The patient can repeat the test if necessary.

Incontinence Severity Index: ISI[1] is a validated means of assessing incontinence and will assist in isolating *de novo* incontinence rather than pre-existing incontinence secondary to Bladder Outlet Obstruction (BOO). This questionnaire will be completed at baseline, 1 month, 3 months, 6 months and 12 months follow-up visit.

International Prostate Symptom Score (IPSS): IPSS[2] is a validated measure of urinary dysfunction due to BPH. This questionnaire will be completed at baseline, 1 month, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months visit.

Pain Severity Assessment (NRS) and Dysuria Score: NRS and Dysuria Scores are a method of measuring post-operative pain and pain on micturition. This questionnaire will be completed at baseline, 1 month, 3 months and 6 months follow-up visit.

International Index of Erectile Function Questionnaire (IIEF-15): IIEF-15[3] is a validated, fifteen-item questionnaire designed to diagnose the presence and severity of erectile dysfunction. This questionnaire will be completed at baseline, 1 month, 3 months, 6 months, and 12 months follow-up visit. IIEF-5 is a subset of IIEF-15 that has also been validated for the measurement of erectile function.[4]

Male Sexual Health Questionnaire to assess Ejaculatory Dysfunction (MSHQ-EjD): MSHQ-EjD[5] is a validated, four-item questionnaire that assesses ejaculatory function and related distress or bother. This questionnaire will be completed at baseline, 1 month, 3 months, 6 months, and 12 months follow-up visit.

Quality of Recovery. This is a validated visual analog scale rating of quality of recovery from surgery[6]. The scale extends from "poor recovery" to "excellent recovery."

Transrectal ultrasound (TRUS): TRUS will be performed to assess eligibility for prostate volume, length, transverse width, anterior/posterior width, and general condition of the prostate. Presence of a middle or intravesical lobe should be documented by sagittal images. TRUS will be conducted at baseline, treatment, and 3 months follow-up visit.

Concomitant Medications: The following will be recorded on a rolling log: BPH medication, post-operative pain medication, all AE related medications up to the 12 months visit, and all urological SAE and urological AE related medications for the 24 months, 36 months, 48 months, and 60 months visits.

2.20 Adverse events

The occurrence of all adverse events will be documented in all study subjects throughout the study treatment and 12 months follow-up period. Only urological SAEs and urological events will be collected at 24 months, 36 months, 48 months, and 60 months follow-up visits. AE information (start and stop date, description of event, severity, relatedness to the treatment procedure, the device itself or other study-related procedures) will be assessed and recorded on CRFs. Whether an AE meets the definition for serious adverse event will be determined by the study investigator using **Table 3.** All urological events consistent with a SAE must be reported to the Sponsor within 24 hours of awareness of the event. Relatedness of the AE to the surgical procedure or the study device itself will be judged by the clinical events committee (CEC) for adverse events up to 12 months according to **Table 4**.

The classification of surgical complications shall be done per **Table 5** by the CEC. Note that persistent ejaculatory or erectile dysfunction, the need for re-catheterization after postoperative day 3, and urinary incontinence related to surgery are considered to be surgical complications.

Table 3 Adverse Event Definitions

Term	Definition
Adverse event* (AE)	Any untoward medical occurrence in a subject.

Serious adverse event* (SAE)	An adverse event that:
	• led to a death,
	• led to a serious deterioration in the health of the subject that
	  • resulted in a life-threatening illness or injury,
	  • resulted in a permanent impairment of a body structure or a body function,
	  • required hospitalization or prolongation of existing hospitalization,
	  • resulted in medical or surgical intervention to prevent permanent impairment to body structure or function,
	  • led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Adverse device effect (ADE)	Any untoward and unintended response to a medical device. This term includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or any event resulting from user error.
Serious adverse device effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
Unanticipated Adverse Device Effect (UADE)	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.

*Note that these definitions do not imply a relationship between the adverse event and the AQUABEAM System.

Non-Reportable Events - Mild to moderate symptoms that are typically associated with the usual post-operative course including but not limited to dysuria, decreased urinary flow, gross hematuria within 7 days post treatment.

Ejaculatory dysfunction – The absence of seminal emission

Erectile dysfunction – The inability to achieve and maintain an erection sufficient for satisfactory sexual activity

Urinary Retention – Subjects with an episode of the inability to urinate without the use of a catheter

Urinary Retention Adverse Event – Subjects who present beyond 7 days post-index treatment and are unable to void requiring catheterization to resolve their symptoms

Urinary Incontinence – Subjects who didn't require incontinence pads prior to Aquablation treatment and require 1 or more incontinence pads per day post-index treatment.

Table 4 Adverse event relatedness categories

Term	Definition
Unrelated	No evidence that AE related to Aquablation procedure or AQUABEAM System
Unlikely	AE has a low likelihood of being related to Aquablation procedure or AQUABEAM System
Possible	AE could be related to Aquablation procedure or AQUABEAM System but an alternative explanation is also likely
Probably	AE likely to be related Aquablation procedure or AQUABEAM System even though alternative explanations are possible
Definitely	AE almost certainly related to Aquablation procedure or AQUABEAM System

Table 5 Clavien-Dindo grading system[7]

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.†
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.*
Grade 3	Requiring surgical, endoscopic or radiological intervention.
Grade 3a	Intervention not under general anesthesia.
Grade 3b	Intervention under general anesthesia.
Grade 4	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
Grade 4a	Single organ dysfunction (including dialysis).
Grade 4b	Multi-organ dysfunction.
Grade 5	Death of a subject.

*Note that the need for medications related to BPH (e.g., alpha blockers) is likely related to lack of effectiveness (not safety) and is not considered to meet criteria for a Grade 2 event.

†This includes the following: persistent ejaculatory dysfunction, erectile dysfunction or urinary incontinence and urinary retention requiring re- catheterization after 3 days post-procedure. Note that bladder catheterization itself is considered a Clavien-Dindo Grade 1 event

2.21 Study Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal: the subject voluntarily chooses not to further participate in the study.
- Subject death.

- At the discretion of the Principal Investigator, or where the ongoing participation of the patient involves a risk greater than perceived benefit.
- The Sponsor may terminate the study at any time.

2.22 Lost to Follow-Up

A subject will be considered "lost to follow up" and terminated from the study when he can no longer be reached by study staff and has missed two consecutive follow up visits. Documentation of the unsuccessful attempts by the Investigator or his/her designee to contact the subject or next of kin need to be filed with the study exit form.

2.23 Study Termination

The sponsor has the right to discontinue the study at any time for any reason.

2.24 Case Report Forms (CRF)

Data will be entered into an EDC system. If a consented subject is not treated, a study exit form will be completed to record the reason for screen fail or withdrawal.

2.25 Study Exit

The subject's participation in the study is considered complete at the end of the 60 months visit or if the subject withdraws from the study or loss to follow-up. A study exit form shall be completed.

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in total IPSS score at 3 months as compared to baseline.

3.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects with adverse events rated as probably or definitely related to the study procedure classified as Clavien-Dindo Grade 2 or higher or any Grade 1 event resulting in persistent disability (e.g. ejaculatory disorder or erectile dysfunction) evidenced through 3 months post treatment. Note that the Clavien-Dindo classification scheme is for grading postoperative complications not events that reflect lack of effective treatment.

3.3 Secondary Endpoints for Marketing Claims

Secondary endpoints are:

- Length of procedure time as defined as AQUABEAM Handpiece insertion to insertion of indwelling catheter. Mean and 95% confidence intervals will be calculated. There is no statistical hypothesis for this endpoint; it is considered informational.
- Proportion of subjects, who were sexually active at baseline and experienced either ejaculatory or erectile dysfunction (per protocol definitions) at 3 months. An exact binomial confidence interval will be calculated; there is no statistical hypothesis.
- Change from baseline to 3 months in Qmax. For a patient with a urinary catheter in place at the time testing, the Qmax value will be zero. Mean and confidence intervals will be calculated and a historical semi-quantitative comparison will be made with WATER Study data or other studies.

- Change from baseline to 3 months in PVR. For a patient with a urinary catheter in place at the time testing, the PVR value will be Not Applicable. Mean and confidence intervals will be calculated and a similar semi-quantitative comparison will be made.
- Change from baseline to 6 months in PSA. Mean and confidence intervals will be calculated. A t test will be used to compare PSA change vs. a null hypothesis of no change.
- Mean change from baseline in MSHQ-EjD score at 3 months. Preservation of ejaculatory function, meaning a change non-inferior to -4 points. A t test with 95% confidence intervals will be used to evaluate this hypothesis.
- Mean change from baseline in IIEF-5 (aka SHIM, part of IIEF-15) at 3 months. Preservation of erectile function, meaning a change score non-inferior to -6 points. An approach similar to that listed for MSHQ-EjD will be used.
- Re-intervention rate at 3 months. Re-intervention is defined as the need for additional tissue resection following the index procedure. An exact binomial confidence interval will be calculated. No statistical hypothesis is proposed.
- Subjects who entered the trial using a urinary catheter at any time 45 days prior to enrollment will yield more than 50% not needing a catheter at any time 45 days prior to the 3 months visit. An exact binomial confidence interval will be calculated. No statistical hypothesis is proposed.

3.4 Additional Endpoints

Additional analysis of data collected may be performed and reported.

4 STATISTICAL ANALYSIS

4.1 General Approach

Continuous Outcomes. Continuous outcomes will be summarized with mean, standard deviation and other relevant statistically summaries. When not normally distributed, medians and quantiles will be reported. A confidence interval approach may be used, if appropriate, to compare outcomes with historical information. Repeated measures analysis of variance may be used for outcomes assessed multiple times over the course of follow-up.

Binary Outcomes. Binary and ordinal outcomes will be tabulated. Rates will be expressed as a percentage taking into account denominators as listed above. If required, confidence intervals for proportions will be calculated using the exact binomial distribution. A confidence interval approach may be used to compare outcomes with historical information. Comparisons of proportions will be done with chi-squared or Fisher's exact test. Multivariate analysis may also be performed.

4.2 Primary Endpoint Calculation and Sample Size Determination

Prior studies have shown that IPSS scores are reduced by approximately 16 points after Aquablation,[8,9] values similar to those observed after TURP.[10] In patients with moderate-to-severe BPH, the mean change in IPSS score representing slight improvement is approximately 5 points.[11] Therefore, showing a mean reduction in IPSS scores that statistically exceeds 16-5 = 11 points will be interpreted as study success. The study's primary endpoint hypothesis is a one-way statistical test (alpha=.025 for interpretation):

H_0: Mean(IPSS change score at 3 months) ≤ 11
H_a: Mean(IPSS change score at 3 months) > 11

With 100 patients and assuming 10% subjects lost to follow, 90 evaluable subjects with an underlying change of 16 points and a change score SD of 7.5 points yields a 99% power to detect an improvement of more than 11 points.

The WATER study (IDE#G150089) used an assumption that a TURP rate for the same safety definition provided in this protocol would by 65% for a range of prostate sizes 30-80mL. The same safety target will be used for this protocol treating large prostates of 80-150mL. The assumed true rate for the Aquablation patients will be 50% (10% greater than WATER in order to account for treating larger prostates). The study's primary endpoint hypothesis is a one-way statistical test (alpha=.025 for interpretation):

H_0: Mean (safety rate at 3 months) $\geq$ 65%
H_a: Mean (safety rate at 3 months) $<$ 65%

The primary safety endpoint with 90 evaluable subjects has an 80% power to detect a safety rate of less than 65%.

5 RISK/BENEFIT ANALYSIS

The study protocol has been designed to provide the greatest benefits while assuring the safety of participating subjects by mitigating the occurrence, limiting the severity, and ameliorating the effects of any possible adverse events. The following describes the benefits subjects will receive as well as possible adverse events which have been identified as risks and for which subjects will be carefully monitored.

5.1 Potential Benefits

The primary potential benefit of participation is the potential occurrence of successful treatment of lower urinary tract symptoms using the AQUABEAM System. Additional benefits may be decreased post-operative duration of pain, decreased need for urinary catheter postoperatively, and faster overall recovery. In a patient with urinary retention, the need for catheter use (indwelling or intermittent) may be reduced.

5.2 Potential Risks

The AQUABEAM System is used during a surgical procedure on the lower urinary tract. Risks associated with surgical procedures, some of which could be fatal, include:

- Irritative symptoms of urgency, hesitancy, dysuria, and nocturia
- Bleeding
- Lower urinary tract infection
- Bladder, rectum, or prostate injury
- Reaction to anesthesia
- Sphincter damage
- Urinary extravasation
- Swelling or irritation of the prostate, bladder, perineum, or urethra
- Pain
- Changes in ejaculatory function
- Reproductive system disturbances
- Blood Transfusion
- Perforation

5.3 Risk Mitigation

Risks during study participation will be minimized by the following:

- The study protocol was developed in concert with the study's principal investigator, who is well-known in the area of BPH treatment
- The site was chosen because of proven expertise in the field of urological surgery
- The investigator will receive specific training and instruction in the use of the AQUABEAM System
- Study subjects undergo intensive monitoring throughout the study by a multidisciplinary team
- Pre-clinical, in vitro, and in vivo testing has been performed in order to optimize the device safety and function
- Clinical testing in previous human subjects has been performed in order to optimize the device safety and function

6 STUDY ADMINISTRATION

6.1 Clinical Events Committee

An independent Clinical Events Committee (CEC), consisting of three physicians who are not study Investigators will be utilized for this trial. This CEC will be responsible for the review and adjudication of reported adverse events up to 12 months related to the device or the procedure that occur over the course of the study per the CEC Charter. Additionally, the CEC may adjudicate other events at the request of the Data Monitoring Committee or Sponsor. The CEC adjudicators shall classify (assign relatedness) the above described adverse events based on severity and association to the procedure or other attribution.

Device- or procedure-related events which are associated with the secondary safety endpoint analysis will be as adjudicated by the CEC. In the event the CEC differs from the Investigator in classification of events, the resulting CEC adjudication will be used for final analysis and reporting.

A CEC Charter will be developed prior to the start of study enrollment. The CEC Charter shall include consistent definitions for each type of event and shall outline the review process.

6.2 Data Monitoring Committee

The Data Monitoring Committee (DMC) will consist of a minimum of three (3) members and this group shall also act as the steering committee chartered with advising the sponsor on the design and execution of the study, monitoring the overall implementation of the study, including subject enrollment, protocol compliance, and reviewing the final primary endpoint analysis (3 months follow-up).

Membership will include only independent members and therefore will not include a study investigator or a representative from the sponsor. The DMC meetings will consist of open and closed sessions (i.e. "open" denotes sponsor staff present; "closed" denotes without sponsor staff present).

The sponsor or designate will provide the DMC with reports related to subject enrollment, procedural outcome, follow-up visits, adverse events, and any other material the DMC may deem necessary to carry out its responsibilities as established at the outset of the committee in the DMC charter. The DMC will assess if early evidence exists for dramatic benefit or harm for subjects while the clinical study is in progress. The DMC will make recommendations to the sponsor concerning continuation, modification, or termination of the study.

The DMC will establish and maintain a Charter detailing specific operating procedures. Names and contact information for all DMC members will be on-file at the sponsor and available on request.

6.3 Data Collection/Electronic Case Report Forms (e-CRF)

Case report forms will be used to collect all subject data during the study within the EDC system and are referred to as eCRFs. The EDC system enables rapid data acquisition and cleaning through extensive data checking and query processing. Monitor visits will be conducted in regular intervals through the study based upon site enrollment rates.

Data will be entered into a secure EDC system, which allows 21 CFR Part 11 compliance. Subjects' follow up visits data will be entered directly by the site with corresponding source documents maintained at the site level.

6.4 Clinical Monitoring

The study will be monitored to ensure that applicable regulations are followed. Written procedures will be established by PROCEPT BioRobotics or their authorized designee to ensure the quality of the study and to ensure that each person involved in the monitoring process carries out the required duties.

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following:

- IRB approval has been obtained and documented
- The Investigators and study personnel are appropriately trained and clearly understand the study
- The Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

Periodic monitoring visits will be made at all active study sites throughout the clinical study to assure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are followed. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the IRB, device and device inventory are controlled, and the Investigator is carrying out all agreed activities.

A study termination visit will be conducted at the completion of the clinical investigation to ensure that all subject data are properly documented and that all clinical materials are returned to PROCEPT BioRobotics.

If a clinical monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of Investigational Device Exemption regulations (21 CFR 812), or any conditions of approval imposed by the IRB, PROCEPT BioRobotics will either secure compliance or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation.

7 STUDY REPORT AND PUBLICATION STRATEGY

7.1 Final Study Report

A Final Study Report will be prepared by PROCEPT BioRobotics.

7.2 Publication Strategy

The study will be registered with a clinical trials database, as recommended by the International Committee of Medical Journal Editors.

The Principal Investigator agrees to provide copies of any and all proposed manuscripts to PROCEPT BioRobotics at least 30 days in advance of submitting such proposed manuscripts to a publisher or other third party to evaluate the proposed manuscript for the following purposes:

- For accuracy and consonance with the study database,
- To ascertain whether confidential information or other proprietary information of PROCEPT BioRobotics (including trade secrets and patent protected materials) is being inappropriately utilized and/or released,
- To provide Principal Investigator with information which may not yet be available to them, and
- To provide input from other Investigators and Co-Investigators in the study, if any, regarding the content and conclusions of the proposed manuscripts.

For the avoidance of doubt, PROCEPT BioRobotics may not require any amendments to be made to the clinical data, omissions to be made to it or amendments to the Principal Investigator's interpretation thereof. The decision as to whether to amend the manuscript to include any or all of the opinions or information provided by PROCEPT BioRobotics remains that of the Principal Investigator.

If PROCEPT BioRobotics makes a good faith determination, within such 30-day period, that the publication or presentation would be detrimental to its intellectual property interests, the Principal Investigator shall refrain from submitting such proposed manuscript to a publisher or other third party for another 365 days or such earlier time that notifies PROCEPT BioRobotics to allow time to file PROCEPT BioRobotics patent applications or take other steps to protect its intellectual property interests.

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