CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

STUDY NUMBER: CASE 1816

Protocol Date: 03/29/2016

STUDY TITLE: Intra-operative Assessment of Cavernosal Nerve Stimulus Threshold

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SUPPORT/FUNDING: Department of Urology
Glickman Urological and Kidney Institute
Cleveland Clinic

SUPPLIED AGENT***(S):*** None

IND #: None

OTHER AGENT***(S):*** None

SUMMARY OF CHANGES

Protocol Date	Section	Change
03-29-16		Initial CASE CCC PRMC Submission per CCF IRB Requirement

STUDY SCHEMA

Patients will be randomly assigned to a cavernosal nerve electrical stimulation testing algorithm of 4 different stimulus patterns in sequence (Table 1) while intercavernosal pressure is recorded to detect penile erection. Specifically, a fixed frequency and pulse width will be set with amplitude started at 1 mA and increased by 5 mA increments, to a maximum of 30 mA or until intracavernosal pressure is observed to persistently rise. Upon pressure rise, amplitude will be decreased by 5 mA and then increased by 1 mA increments to identify the threshold level. If no pressure changes are appreciated, the contralateral neurovascular bundle will be assessed, and if no pressure changes are observed here, the procedure will be aborted.

Table 1: Stimulus Parameter Testing Algorithm

Stimulus Pattern	Frequency	Pulse Width	Amplitude (Variable)
1	10 Hz	100 μs	1 mA to 30mA
2	10 Hz	200 μs	1 mA to 30mA
3	7 Hz	100 μs	1 mA to 30mA
4	7 Hz	200 μs	1 mA to 30mA

PROTOCOL SUMMARY

Protocol Number/Title	CASE 1816
Study Phase	Pilot
Brief Background/Rationale	Erectile dysfunction persists in approximately 80% of men 1 year after prostatectomy. Various erectile rehabilitation strategies have not provided benefit. Electrical stimulation has been demonstrated to benefit neuroregeneration and the functional recovery of neuromuscular systems. Therefore, electrical stimulation of the cavernosal nerves during radical prostatectomy is being investigated for its potential development into a treatment aimed at improving recovery of erectile function after prostatectomy. This pilot study is intended to determine the threshold of electrical stimulation that results in penile erection, as defined by persistent intracavernosal pressure increase, such that future studies of sub-threshold stimulation may be pursued.
Primary Objective	Endpoint for this study is the accrual of 7 patients and collection of cavernosal nerve stimulation thresholds for induction of penile erection in each.
Secondary Objective(s)	None
Exploratory Objective(s)	None
Correlative Objective(s)	None
Sample Size	7 men age 18 years or older
Disease sites/Conditions	Prostate cancer being treated with radical prostatectomy.
Interventions	Unilateral cavernosal nerve electrical stimulation, possible contralateral cavernosal nerve electrical stimulation, and intracavernosal pressure recording.

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation

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1.0 Introduction

1.1 Erectile Dysfunction after Prostatectomy

Erectile dysfunction persists up to 1 year after radical prostatectomy in approximately 70% to 80% of cases, whether performed with open or robotic surgical approaches (O'Neil 2016). Approximately 30 years ago, it was identified that intraoperative preservation of the prostatic neurovascular bundles containing the cavernous nerves enabled some men to recover and maintain erectile function after surgery (Lepor 1985). Prior to this discovery, the surgery essentially had a 100% rate of erectile dysfunction.

Since that time, technologic advances in pelvic surgery, such as robotic surgery, have demonstrated a minimal advantage over open surgery in terms of postoperative erectile dysfunction rates. Furthermore, there is limited data to suggest current postoperative penile rehabilitation therapies provide a marked improvement in erectile function recovery after pelvic surgery. One temporal analysis found stable rates of erectile dysfunction, at 70% to 90%, from the mid-1990s through the current era (Schauer 2015). A contemporary analysis of patient-reported outcomes confirms that 78% to 88% of men demonstrate some degree of erectile dysfunction after prostatectomy (O'Neil 2016).

1.2 Cavernosal (Cavernous) Nerve Electrical Stimulation

1.2.1 Preclinical Data: Electrical Stimulation and Nerve Regeneration

Electrical stimulation elsewhere in urology, specifically the sacral and pudendal nerves, has been applied with permanently implanted devices, and used successfully to treat voiding dysfunction. Laboratory studies have shown that temporary pudendal nerve stimulation in animal models of incontinence can improve neuroregeneration by increasing neurotrophin levels within the nerve, a phenomenon observed in other peripheral nerves (Jiang 2013). This beneficial effect of temporary nerve stimulation, and the practice of urologic patients treated with nerve stimulators undergoing temporary percutaneous test stimulation before implantation, led to our overall hypothesis for a long-term series of clinical studies: temporary percutaneous stimulation of the cavernous nerves after prostatectomy will improve neuroregeneration, and the subsequent postoperative recovery of postoperative erectile function, as defined by a reduced erectile dysfunction rate, better quality of erections, shorter time to functional recovery, and improved patient satisfaction.

The stimulation assessed in the animal models of pudendal nerve recovery was performed with sub-threshold (20 Hz frequency, 0.3 mA amplitude, 100μs pulse width) parameters, which did not result in end-organ activation (anal sphincter contraction). The ideal application of electrical stimulation to facilitate recovery of erectile function will similarly utilize sub-threshold (i.e. stimulation parameters will not result in an erection) parameters. Previous work during intraoperative cavernous nerve mapping studies confirmed the ability of intraoperative stimulation (20 Hz frequency, 1-10 mA amplitude, 220μs pulse width) to produce erections (Rehman 1999). However, the stimulus

thresholds at which sub-threshold stimulation became supra-threshold stimulation are unknown.

1.2.2 Clinical Data: Cavernosal Nerve Stimulation for Anatomic Localization

The use of electrical stimulation has been applied to prostatectomy for the purpose of cavernous nerve localization to facilitate their anatomic preservation. Commercially available devices for this purpose have been developed; however, current surgical approaches and improved understanding of pelvic anatomy have resulted in intraoperative electrical stimulation providing no advantage in preserving the prostatic neurovascular bundles and cavernous nerves. The implantation of permanent electrodes for stimulating (20 Hz frequency, 5mA - 60 mA amplitude, 260 𝞵s pulse width) the cavernous nerves to produce erections has been investigated, but this has never gone beyond initial clinical trials (Burnett 2008).

1.3 Study Rationale

Various laboratory studies have investigated using biologically active molecules to facilitate neuroregeneration of the cavernous nerves. These include various growth factors, such as neurotrophins, as well as the use of stem cells. While animal models have shown some promise with these, the clinical investigation of such treatments has been limited by their unknown systemic effects and other potential adverse risks they pose. These challenges highlight the potential for application of non-biologic therapies, such as electrical stimulation, to augment neuroregeneration. Electrical stimulation, which has been demonstrated safe and well tolerated in many other human appilcations, has been shown to enhance neuroregeneration. As cavernosal nerve electrical stimulation can result in penile erection, determining sub-threshold stimulation parameters is necessary such that men can undergo stimulation after surgery and not develop penile erection with an indwelling foley catheter. This will facilitate both their comfort and social acceptance of the treatment.

2.0 Objectives

2.1 Primary Objective

To determine the cavernosal nerve electrical stimulation amplitude thresholds at which an erection, as indicated by persistent increases in intracavernosal pressure, occurs for various stimuli of fixed frequency and fixed pulse-width.

2.2 Secondary Objective

There are no secondary objectives of this study.

3.0 Study Design

3.1 Prospective Pilot Study

This is a prospective pilot study used to determine a threshold range of cavernosal nerve electrical stimulation parameters that result in penile erection. Assignment to the order of stimulation paradigms will be randomized. No placebos are used. No blinding is used.

3.2 Number of Subjects

This study will enroll a total of 7 men, over age 18, who are undergoing prostatectomy for prostate cancer.

3.3 Replacement of Subjects

If men do not respond to intraoperative electrical stimulation, as evidenced by intracavernosal pressure increase, they will not be replaced. These men will be deemed non-responders. If men opt out of stimulation preoperatively, they will be replaced. If the cavernous nerves are sacrificed intraoperatively, these men will be replaced. In total, only 7 men will undergo stimulation testing.

3.4 Expected Duration of Treatment and Subject Participation

Treatment will be performed intraoperatively and take approximately 20 to 30 minutes. Thereafter, patients will be monitored as part of standard care, for approximately 24 hours postoperatively. Following this, they will be reassessed at the standard postoperative outpatient follow-up visit approximately 7 to 21 days after prostatectomy.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

Below are common examples: Edit per protocol or see further examples hyperlinked above.

___ 4.1.1 Subjects must have prostate cancer being treated via radical prostatectomy by a single surgeon (primary investigator) with planned intraoperative nerve sparing.

___ 4.1.2 Subjects must have intact preoperative erectile function, sufficient for penetrative intercourse without medication nor assistive device, as defined by a SHIM / IIEF-2 score 22 or higher, which is collected as part of routine care.

___ 4.1.3 Age $\geq$ 18 years, as prostate cancer is not routinely treated in children.

___ 4.1.7 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Baseline erectile dysfunction, as defined by the use of medications or devices to assist erection, lack of baseline erections, or a SHIM / IIEF-2 21 or lower, which is collected as part of routine care.

___ 4.2.2 Lack of successful intraoperative nerve sparing.

___ 4.2.3 Neurologic, metabolic, or vascular diseases that may negatively impact erectile function, such as: diabetes mellitus, peripheral vascular disease, coronary artery disease, stroke, multiple sclerosis, parkinson's disease, multiple systems atrophy, epilepsy, or spinal cord injury.

___ 4.2.4 Inability to provide a fully informed consent.

4.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Women are not eligible due to the lack of a prostate and penis.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator listed on the cover page.

Subjects will be randomized to the order of the four stimulus paradigms being studied.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

All cavernous nerve electrical stimulation patterns (labeled 1 – 4 in Table 1) will be tested in each patient in a randomized order.

Table 1: Stimulus Parameter Testing Algorithm

Stimulus Pattern	Frequency	Pulse Width	Amplitude (Variable)
1	10 Hz	100 µs	1 mA to 30mA
2	10 Hz	200 µs	1 mA to 30mA
3	7 Hz	100 µs	1 mA to 30mA
4	7 Hz	200 µs	1 mA to 30mA

Treatment will only be administered intraoperatively.

Appropriate dose modifications for the Electrical Stimulation are described in Section 7.0.

Reported adverse events and potential risks of Electrical Stimulation are described in Section 8.0.

There are no restrictions on other investigational or commercial agents or therapies that may be administered with the intent to treat the subject.

6.1.1 Electrical Stimulation

In addition to a dosing schema, please add a narrative description of the investigational agent administration.

Investigational Agent Administration

Subjects will receive stimulation patterns 1 – 4 in a randomized order. Specifically, a fixed frequency and pulse width will be set with amplitude started at 1 mA and increased by 5 mA increments, to a maximum of 30 mA or until intercavernosal pressure is observed to persistently rise. Upon pressure rise, amplitude will be decreased by 5 mA and then increased by 1 mA increments to identify the threshold level.

If no response is observed on the cavernosal nerve assessed, the contralateral cavernosal nerve will be tested with the same stimulus pattern. If no response is seen on the contralateral nerve, the procedure will be aborted.

6.2 Electrical Stimulation Dose Escalation

Dose escalation will proceed within each stimulus pattern according to the following scheme. The pulse width and frequency will be fixed. Amplitude started at 1 mA and increased by 5 mA increments, to a maximum of 30 mA or until intercavernosal pressure is observed to persistently rise. Upon pressure rise, amplitude will be decreased by 5 mA and then increased by 1 mA increments to identify the threshold level.

If no response is observed on the cavernosal nerve assessed, the contralateral cavernosal nerve will be tested with the same stimulus pattern. If no response is seen on the contralateral nerve, the procedure will be aborted.

6.3 Definition of Dose-Limiting Toxicity (Applicable for dose escalation studies only)

No dose-limiting toxicities are anticipated in this study. The ranges of electrical stimulation that will be tested have been proven safe and effective in prior work on intraoperative cavernosal nerve stimulation for anatomic mapping.

Management and dose modifications are outlined in Section 7.

6.4 General Concomitant Medications and Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, antiemetics, etc. when appropriate. All routine care for prostatectomy patients will be provided. There is no contraindication to routine care due to participation in this study.

6.5 Criteria for Removal from Study

• Intercurrent illness that prevents further administration of intraoperative treatment.

• The investigator considers it, for safety reasons, to be in the best interest of the subject.

• Unacceptable intraoperative adverse events related to the surgical course.

• Subject decision to withdraw from the study (full consent).

• Death during surgery.

• Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.
The date and reason for discontinuation must be documented.
Every effort should be made to complete the appropriate assessments.

6.6 Duration of Follow Up

Subjects will be followed for toxicity and adverse events as part of routine post-prostatectomy care (approximately 24 hours) during the immediate postoperative hospitalization. Subsequently, they will undergo a full postoperative assessment (approximately 7 – 21 days) at their initial postoperative visit for foley catheter removal. Subsequent reassessment will occur at the second postoperative visit (approximately 2 to 4 months) assessing cancer control.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the

study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 Dose Delays/Dose Modifications

Dose delays and dose modifications will not occur as part of this intraoperative study.

8.0 Adverse Events and Potential Risks

The risks of this study are low relative to those of prostatectomy. No adverse events related to electrical stimulation are anticipated based upon its transient use intraoperatively and experience electrical stimulation in other segments of urology, as well as the published literature. The potential adverse events and risks intercavernosal needle insertion are mild in severity and are familiar to urologists on account of the use of intercavernosal injection therapy and intercavernosal aspiration in treating urologic conditions. Overall, these adverse events pose a low risk to the patient and are all easily treatable with minimal likelihood of requiring a secondary intervention.

8.1 Adverse Events

8.1.1 Electrical Stimulation

Adverse Event	Action on Study Drug	Recommend Management
Erectile Dysfunction	N/A	Expectant management as in routine care following prostatectomy.
Pareasthesia or Pain	N/A	Standard clinical care.

8.1.2 Intracavernosal Pressure Recording

Adverse Event	Action on Study Drug	Recommend Management
Bleeding	N/A	Tamponade
Hematoma	N/A	Observation
Infection	N/A	Oral antibiotic therapy directed at skin flora
Pain	N/A	Standard clinical care.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the

research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:

- Expected potential complications and outcomes of prostatectomy

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples

of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

For the purpose of this study the following events would not be considered serious adverse events and would not be recorded in the database:

- Expected potential complications and outcomes of prostatectomy

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant and requiring treatment or causing apparent clinical manifestations related to the electrical stimulation or intracavernosal pressure recording should be reported as an adverse event. Those related to expected potential complications and outcomes of prostatectomy will not be.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent (as determined by consensus of the primary and co-investigators)**
- Action taken as a result of the event
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 Serious Adverse Event Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur from the time of initial stimulation attempt through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Eric Klein – kleine@ccf.org
    - Bradley Gill – gillb@ccf.org
    - Yaw Nyame – nyamey@ccf.org
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Manufacturer Reporting Requirements:

- None - The device used to provide electrical stimulation (Medtronic NIM 3.0 Nerve Monitoring System) is commercially available and designed for intraoperative nerve stimulation.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.5 Serious Adverse Events s and OnCore™

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 TREATMENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.1.

9.1 Investigational Agents

9.1.1 Electrical Stimulation

Product description:
Current delivery from a stimulus generator through a lead to a monopolar stimulus electrode applied to a specific nerve. The delivered stimulus is returned through a stimulus return electrode affixed to the lower extremity. A separate grounding electrode is also attached to the lower extremity to further ensure safety.

Product preparation:
The electrodes are sterile and disposable. A new set of electrodes is used for each patient. The leads are attached to the stimulus generator and the electrode end is maintained in a sterile fashion for application in the operative field. Stimulus settings are configured via

touch screen by the appropriately certified operating room personnel or co-investigator charged with data recording.

Storage requirements:
The electrodes are stored with surgical supplies and disposed of upon their expiration date if unused.

Stability:
The electrodes have a finite shelf life and are disposed of when their expiration date is reached.

Route of administration:
Electrical stimulus via electrical current is supplied to the targeted nerve by placing the stimulus electrode on the nerve and depressing the stimulation button.

Procurement:
Electrodes are commercially available from Medtronic and will be purchased for the study.

Packaging and labeling:
The commercially available electrodes are pre-packaged and labeled.

Accountability:
The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study treatment. All treatments must be accounted for, including any accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational treatment to be used other than as directed by the protocol.

Treatment Destruction:
Only the necessary number of electrodes will be ordered for this study. If a surplus of electrodes is noted (for instance due to early study closure) they will be disposed of or returned to the manufacturer refund, if possible.

10.0 EXPLORATORY or CORRELATIVE STUDIES

Not applicable for this study.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

Study parameters include persistent intracavernosal pressure rise to indicate penile erection in response to stimulus. This will be documented for each stimulus variable tested. Pressure will be recorded

11.1.1 Screening Evaluation

There is no screening evaluation besides information on erectile function gathered from the history acquired during standard care that is used to confirm study eligibility.

11.1.2 Treatment Period

Treatment is entirely intraoperative and will be done over a course of 20 to 30 minutes.

11.2 Calendar

All follow-up as part of this study will be performed as standard post-prostatectomy care, as outlined below. Deviations from the following time points are permissible and will not require exclusion from the study.

Postoperative Care (0 - 24 hours postoperative): overall assessment, drain removal
First Postoperative Visit (7 - 21 days postoperative): overall assessment, catheter removal
Second Postoperative Visit (2 - 4 months postoperative): assessment of cancer control

12.0 MEASUREMENT OF EFFECT

12.1 Intercavernosal Pressure Measurement

Effect in this study will be measured by intracavernosal pressure recording. This is perfomed via sterile 20-22 guage needle inserted perpendicularly into the right corpora cavernosa at the 9 o'clock position, which is connected to sterile arterial line tubing. Pressure will be recorded with a standard blood pressure transducer on the anesthesia cart.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or

inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

This is a pilot study aimed at determining the range of sub-threshold cavernosal nerve electrical stimulation parameters. No statistical comparisons are being made as part of this study. Only descriptive statistics of the stimulus parameters will be calculated.

Sample size was determined based upon other pilot studies of intraoperative cavernosal nerve stimulation. In one study by Lue, et al (J Urol. 1995, 154: 1426-1428) two differing stimulation types were assessed with groups of 6 and 16 men, respectively. Similarly, another study by Rehman, et al. (BJUI. 1999, 84: 305-310) investigated stimulation in groups of men with (N=4) and without (N=10) erectile dysfunction. Our study is a pilot study for dose-ranging sub-threshold neurostimulation parameters and we anticipate a sample size of 7 men will provide a sufficient assessment of the range of parameters that is clinically relevant.

Anticipated accrual rate is approximately 2 patients per month.

REFERENCES

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