PENILE LENGTHENING PRE-PENILE PROSTHESIS IMPLANTATION

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Study Product:	RestoreX®
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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ED	Erectile Dysfunction
HIPAA	Health Insurance Portability and Accountability Act
IPP	Inflatable penile prosthesis
PHI	Protected health information
PP	Penile Prosthesis
PTT	Penile traction therapy
RCT	Randomized controlled trial

Study Summary

Title	Penile Lengthening Pre-Penile Prosthesis Implantation
IRB Protocol Number	17-011052
Methodology	Controlled randomized study
Overall Study Duration	3 years
Subject Participation Duration	3 months
Objectives	Compare length of penile prosthesis inserted after traction therapy
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	Men undergoing placement of a penile prosthesis
Study Device	RestoreX®, penile traction therapy
Duration of Exposure	Subjects will use device for 30 minutes, 3 times a day
Reference therapy	Use of the device will be compared against a control group using no traction therapy
Statistical Methodology	Stratification of subjects prior to randomization to assure an equal representation based on baseline penile length. Statistical comparisons will be made comparing total length of prosthesis inserted between those using and not using traction, stratified by baseline penile length.

1 Introduction

This document is a protocol for a human research device study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

Men with erectile dysfunction (ED) refractory to conservative therapies are often recommended to undergo placement of an inflatable penile prosthesis (IPP). However, one of the most common complaints after surgery is that the men feel that their penis is shorter than what it was previously. This is likely due to one of several factors including the underlying disease process which resulted in loss of penile length, effects of aging on penile length (loss of elasticity; increased fibrosis), changes in abdominal physiology (development of pre-pubic fat pad that obscures the penis), and recall bias (incorrect assumptions on prior penile length).

Several attempts have been made by investigators to optimize penile length prior to placement of the penile prosthesis, including adjunctive surgical maneuvers (excision of suprapubic fat pad, release of suspensory ligament, direct penile extension), use of injectable materials, and pre-operative use of penile traction therapy (PTT). In a small pilot study of 10 men undergoing IPP, Levine and colleagues recommended the use of the Andropenis PTT ≥2 hours daily for 2-4 months.[1] At 15 months follow-up, patients achieved a +1.6 cm increase compared to pre-traction stretched length, and +0.9 cm increase following penile prosthesis (PP). Results from a non-validated satisfaction questionnaire demonstrated that no patients reported loss of length following surgery. Unfortunately, the study did not include a control group, thus limiting the conclusions which may be drawn.

Compared to other options, PTT offers several potential advantages in that it is minimally-invasive, does not increase the morbidity of surgery, and has not been shown to result in any long-term side effects.

Recently, Mayo Clinic licensed a new PTT concept to PathRight Medical, who subsequently developed the RestroreX PTT device. This is classified as a Class I device, not requiring clinical human trials. The purported benefits with the RestoreX device over other PTT systems include ability to generate constant traction, user-feedback on appropriate use, improved comfort, and ability to track improvements. The device is currently utilized in 30-minute intervals, with up to 3 sessions performed per day.

Given the clinical issue of dissatisfaction with penile length post IPP, the potential role for PTT, and limited amount of data available, we sought to perform a clinical trial evaluating the effect of PTT on increasing the total length of prosthesis which can be inserted. We additionally sought to determine if PTT resulted in improved post-operative satisfaction on total penile length achieved.

1.2 Investigational Device

RestoreX is a PTT device developed by PathRight Medical using technology licensed from the Mayo Clinic. The device is classified as class I (orthotic) and does not require clinical trials to prove safety or efficacy. Mayo Clinic is currently conducting a randomized clinical trial to evaluate several clinically relevant factors including safety, comfort, and preference and to provide preliminary data on dosing and efficacy (IRB 17-001283).

The device has two functional aspects. The first is the ability to provide direct traction on the penis. The second is the ability to provide counter-bending forces, to treat conditions such as Peyronie's disease (bent penis). In the current study, only the direct traction aspects of the device will be investigated.

Men randomized to treatment will be recommended to utilize the device for 30 minutes, 3 times daily for 3 months prior to placement of an IPP.

1.3 Preliminary Data

Currently, there is a small amount of preliminary data available on the RestoreX® instrument. During the developmental phase of the device, a quality improvement project was performed to evaluate the clamping portion. It was determined that the clamp represented the most critical aspect of the device, as this was where the majority of discomfort occurred with other devices. Additionally, the clamp needed to provide sufficient friction to allow adequate traction without having the glans of the penis dislodge from the device.

A total of 15 patients participated in the quality improvement project and had the clamps applied under direct supervision for 30 minutes. After the 30 minutes, all patients reported 0/10 pain, and only minimal transient erythema was documented by the physician. The clamp was again applied, and traction forces were administered to determine if the clamp was able to remain intact despite stretching forces applied. This also resulted in a successful outcome, with all patients able to successfully achieve a minimum required tension of 1 kg, with a 36% safety factor achieved before any discomfort was reported among any patient. During the testing, patients reported improved comfort with the use of a wrap such as gauze or Coban, which permitted additional traction in all patients.

Very limited data are available on the efficacy of PTT in men undergoing placement of an IPP. As previously noted in the introduction, a small pilot study of 10 men undergoing IPP demonstrated a +1.6 cm increase in penile length compared to pre-traction stretched length and 0% of men reporting loss of length following surgery.[1] The study has several notable limitations including a lack of control group and use of more relevant clinical measure such as length of device inserted.

Regarding background data on the RestoreX device, currently, Mayo Clinic is conducting a randomized clinical trial evaluating its role in men with PD (IRB 17-001283). Initial data are expected by the end of 2018.

1.4 Study Rationale and Risk Analysis (Risks to Benefits Ratio)

1.4.1 Study Rationale

PTT has been shown to improve penile length in several clinical scenarios, including following penile surgery, as a primary lengthening therapy, and in men with conditions which shorten the penis such as Peyronie's disease.[2] Very preliminary data suggest a possible role for PTT prior to placement of an IPP to optimize outcomes and address a common complaint of reduced penile length.[1] The current study is designed to address this gap in the literature.

1.4.2 Potential Benefits

There are several potential benefits to using PTT prior to IPP placement. The most notable is the ability to place a larger device. As reduced penile length is a very common complaint post-operatively, any therapy which addresses this issue offers the potential benefit of enhancing overall patient satisfaction. Perhaps more importantly though, currently there are several adjunctive surgical techniques which are used to increase penile length. These often are very morbid procedures and may result in significant consequences including necrosis of the glans penis, need for additional surgeries, infections, and early device failures, among others. Given the minimally-invasive nature of PTT, any data demonstrating efficacy of this therapy offers potential benefits over the more invasive alternatives.

1.5 Anticipated Duration of the Clinical Investigation

The overall study will be scheduled for 3 years, to permit adequate time for enrollment and follow-up. The intervention phase will include 3 months of treatment (for the treatment arm) and up to 1 year follow-up.

2 Study Objectives

2.1 Primary Objective

1. The primary objective is to assess the length of the penile prosthesis inserted into subjects following completion of RestoreX® traction therapy compared to control groups (no treatment).

2.2 Secondary Objective

1. Compare patient compliance with traction device.
2. Compare patient reported satisfaction with use of traction device.
3. Evaluate any adverse events (AEs) with use of RestoreX® for penile lengthening.
4. Compare intra- and/or post-operative complication rates.
5. Compare pre- and post-operative stretched penile lengths.
6. Compare patient satisfaction scores including satisfaction with overall penile length.

3 Study Design

3.1 Subject Selection

3.1.1 Inclusion Criteria

- Men undergoing placement of a penile prosthesis
- >18 years old
- Must be the first time a penile prosthesis is implanted
- Undergoing implantation of a 3-piece inflatable penile prosthesis

3.1.2 Exclusion Criteria

- Prior ischemic priapism
- Any prior penile prosthesis surgeries
- Any prior penile surgeries other than circumcision
- Undergoing malleable penile prosthesis or Ambicor device

3.2 Setting

The current study will be conducted at both the Mayo Clinic in Rochester, MN (Department of Urology) and Washington University in Saint Louis, Division of Urologic Surgery. All patients will be recruited from Drs. Tobias Kohler's (Mayo Clinic) and Arnold Bullock's (Washington University) clinical practices.

3.3 Recruitment

Drs. Kohler and Bullock will identify potential participants for recruitment in the study from their own practice and based on the inclusion and exclusion criteria. Patients will be notified of the study at the time of their planned clinic visit and those who would be interested in proceeding with the trial will be invited to meet with a study coordinator, at which time details of the study itself will be reviewed. No financial incentives will be provided to participate in the trial; however, participants would be given a RestoreX® device at no charge if assigned to the treatment group. Patients will not be charged for any visits related to the study, and no labs or other testing will be obtained which require payment.

3.4 Consent and Enrollment

During the patient's consultation appointment, they will receive a description of the study and if the patient expresses interest in participating, a formal consent will be reviewed (see **Attachment – Consent Form**).

If the patient successfully completes the consenting process, they will undergo initial study penile length assessments (described later in the protocol). Those wishing additional time to consider enrollment may be rescheduled to a later date if desired.

At enrollment, all participants will be assigned a study identifier, with a master list maintained in a password protected database (Mayo server) linking the patient to the identifier. A total of 20 patients will be enrolled into each arm of the study, for a total of 40 patients enrolled overall. It is estimated that 60 patients will need to be screened to enroll the 40 patients.

No limitations will be applied to either clinical site for enrollments, such that it is possible that one clinical site may enroll 100% of the patients.

3.5 Study Schema

During the initial scheduled clinic appointment, the patient will receive a description of the study, and informed consent. Those consenting to the procedure will receive initial study assessments and be educated on how to use the device properly. Once consent and study assessments are completed, the patients will be randomized into one of two groups: PTT for 30 min 3x/day for 3 months, or control (no treatment).

Patients will then be given a baseline questionnaire to complete and, if assigned to the treatment group, begin using the device. Patients in the treatment arm will record a daily journal of their usage of the device.

After 3 months (+1.5 months permitted), patients in the treatment arm will return for their scheduled procedure (control arm patients will undergo surgery without a 3-month delay). Only those who utilized the device for 3 months will be asked to complete a follow-up questionnaire at this time. Patients will also be encouraged to self-report any additional adverse events (AE's) that they encountered over the 3 months of using the therapy.

During surgery, data will be recorded by the surgeon to indicate type, length and approach taken for penile prosthesis implanted as well as any complications of penile prosthesis implantation. These complications may include urethral perforation, corporal perforation, device malfunction, bowel injury or vascular injury; all of which are standard potential complications of the surgery.

Following surgery, patients will be seen in the clinic based on the standard routine clinical practice. During these follow-up appointments, penile length measurements will be performed and recorded.

Patients will also be sent questionnaires by email or by mail (if email not available) at 3, 6, and 12 months post-operatively. If a patient has not returned their questionnaire within 2 weeks, a follow up phone call to the patient will be placed as a reminder. Alternatively, patients may answer the questions over the phone if that method is preferable.

The subject's clinical records will also be reviewed up to 12 months post-operation to check for any complications relating to the surgery including a need for revision surgery, infection or hospitalizations.

3.6 Randomization Protocol

Following enrollment and completion of the initial length assessment, patients will be categorized into the appropriate strata based on their baseline stretched penile length (strata categorized from 8-20 centimeters stretched length). Each stratum will have a separate randomization table provided such that one of two possible outcomes will occur no less frequently than every other case. This is done to better account for baseline variables that may impact outcomes and to assist with matching groupings appropriately. Separate strata will be provided for each operative site (Mayo Clinic, Washington University), to limit the possibility of one site enrolling more in one arm compared to another.

The explanation of which grouping the patient is assigned will then be reviewed, and if the patient subject is assigned to the treatment group, a RestoreX® device will be provided.

4 Study Procedures

4.1 Initial Study Assessments

- Obtained prior to randomization
- Objective assessments
    - Penile length – measured from pubic symphysis to glanular corona
- Subjective questionnaires (attached)
    - IIEF-15
    - Patient Disease History
    - Device usage diary provided for treatment group

4.2 Follow-up Visit – Treatment Group

- Questionnaire after penile traction, but before IPP surgery

4.3 Intra-op Variables and Follow-up Visits

- Objective assessments (intra-operative surgery)
    - Size of penile prosthesis implanted at time of surgery
    - Approach for implantation of penile prosthesis
    - Type of penile prosthesis implanted
    - Any intra-operative complications of penile prosthesis surgery to be recorded by surgeon
- Follow-up visits - conducted per surgeon's individual protocols. May include one or more visits performed for up to 12 months after surgery.
    - Stretched penile length assessed
    - Notation of any interval complications or AEs

4.4 Follow-up Surveys – Performed via Redcap Survey, Mailer or Telephone Follow-up

- Performed at 3, 6, 12 months
- Subjective questionnaires for all patients (treatment and controls)
    - IIEF-15
    - Follow-up questionnaire
- Patients records to be reviewed 12 months post-operation to check for interval complications
    - Revision surgery, infection or hospitalizations

4.5 Assessment of Length

Penile length measurements will be obtained by a member of the clinical team using a measurement from the pubic symphysis to the corona of the glans penis. Measurements will be obtained pre-operatively and at all clinical visits post-operatively up to 12 months.

Size, type and approach of penile prosthesis implanted will be recorded by surgeon on operative note.

See **Attachments – Device Usage Diary, Disease Specific History, IIEF-15, Questionnaire After Penile Traction but before IPP Surgery, Follow Up Questionnaire**

4.6 Schedule of Events

Table 1: Schedule of Events for Treatment Group

Study Activity	Baseline	3 Month	6 Month (3 months post-op)	9 Month (6 months post-op)	15 Month (12 months post-op)
Consent	X				
Baseline Questionnaire	X				
Length Assessment	X				
Patient Diary Provided	X				
PTT Experience Questionnaire		X			
Penile Prosthesis Implanted		X			
Penile Prosthesis Length Recorded		X			
PP Follow-Up Questionnaire			X	X	X
Chart Review of Post-Op Complications					X

Table 2: Schedule of Events for Control Group

Study Activity	Baseline	3 Month	6 Month	12 Month
Consent	X			
Baseline Questionnaire	X			
Length Assessment	X			
Penile Prosthesis Implanted	X			
Penile Prosthesis Length Recorded	X			
PP Follow-Up Questionnaire		X	X	X
Chart Review of Post-Op Complications				X

5 Statistical Plan

5.1 Data Handling

All data will be recorded either by the patient themselves or by the provider directly onto printed forms (Attachments). Information will remain de-identified throughout the remainder of the study period and will remain on password protected, Mayo servers.

After completion of the study, de-identified information will be shared with individuals associated with PathRight Medical, Inc. who may assist with portions of the data analysis and/or manuscript drafting. No identifiable information will be sent.

5.2 Statistical Analysis

Analyses will be performed using comparisons within patients of same baseline penile stretch length and between groupings of varying lengths. Comparison of device length implanted will be made for subjects using the traction device compared to those who did not utilize traction. Comparisons will also be made on other subjective and objective variables obtained including number of adverse events, complications, subjective responses to questionnaires, or other information. Pre- and post-operative penile lengths will also be compared within individuals. All data will be normalized based on pre-operative stretched penile length.

6 Safety and Adverse Events

Definition of Adverse Event

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) - any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) breach of confidentiality and (6) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, AND

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event - an untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- Death
- Life threatening adverse experience
- Hospitalization
- Inpatient, new, or prolonged; disability/incapacity

- And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All AEs that do not meet any of the criteria for serious, should be regarded as non-serious AEs.

6.1 Adverse Event Reporting Period

For the current study, the treatment follow-up period is defined as 3 months following implantation of the penile prosthesis.

6.2 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

6.3 Post-study Adverse Event

All unresolved AEs will be followed by the study team until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. A review of AEs which the subject or subject's physician believe might reasonably be related to participation in the study will be performed up to 12 months following surgery.

6.4 Hospitalization, Prolonged Hospitalization or Surgery

Any AE related to the study intervention that results in hospitalization or surgery should be documented and reported as a serious AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

6.5 Recording of Adverse Events

The study team will seek information on adverse events by specific questioning between baseline and the 3 month visit. Information on all adverse events will be recorded immediately in the adverse event section of the specific questionnaire as well as in an adverse event form (see Attachment – Adverse Event Form).

All adverse events occurring during the study period will be recorded. The clinical course will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period will be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation will be recorded and reported immediately.

6.6 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Adverse Event Form. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

6.6.1 Sponsor-investigator Reporting: Notifying the Mayo IRB

An adverse event form will be completed for any serious adverse event. This will be reported to the Mayo IRB in a de-identified manner.

The study team will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event form (and entered into the research database)

- Subject's ID
- Description of adverse event
- The date the adverse event occurred and resolved (if applicable)
- Intensity
- Outcome
- Action taken to address
- Relationship to study
- Impact on study withdrawal
- Classification as serious or not

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event

report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

6.6.2 Stopping Rules

Any serious adverse event which is determined to reasonably be related to the study device by the sponsor-investigator will result in immediate discontinuation of the therapy. If 5 patients develop serious adverse events, the study will be halted with re-review required by the Mayo IRB prior to consideration of study resumption.

6.6.3 Medical Monitoring

Medical monitoring of serious adverse events will be performed by the study investigator on a monthly-basis if serious adverse events have been reported.

7 Data Handling and Record Keeping

7.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

7.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at

medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

7.3 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports during the study and for the longer of the following;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717,

   OR

2. A period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

8 Study Finances

8.1 Funding Source

This study is a Mayo Funded study.

8.2 Conflict of Interest

Dr. Landon Trost is the inventor and developer of the RestoreX® device. His conflict has previously been reviewed with the Mayo Clinic Conflict of Interest Review Board, and following review, it has been determined that Dr. Trost is able to conduct these studies as a Primary Investigator.

8.3 Subject Stipends or Payments

Subjects will not receive payment for their participants; however, they will be able to keep the study device following completion of the study.

8.4 Regulatory Information

PathRight Medical has registered the RestoreX® device with the FDA as a Class I device, similar to limb orthotics (see Attachment – RCRI Position Paper). The device is available without a prescription and may be purchased by the general public. As such, clinical studies are not required prior to its routine use, and the current studies are being done as an investigator-initiated project to determine its potential role in length of penile prosthesis inserted.

9 References

1. Levine, L. A., Rybak, J.: Traction therapy for men with shortened penis prior to penile prosthesis implantation: a pilot study. J Sex Med, **8:** 2112, 2011
2. Trost, L. W., Munarriz, R., Wang, R. et al.: External Mechanical Devices and Vascular Surgery for Erectile Dysfunction. J Sex Med, **13:** 1579, 2016