Penile Length Restoration in Men with Diabetes Mellitus, Type II

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PENILE LENGTH RESTORATION IN MEN WITH DIABETES MELLITUS, TYPE II

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Study Product: RestoreX®

Protocol Number: 18-006696 (IRBe)

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
DM	Diabetes mellitus
HIPAA	Health Insurance Portability and Accountability Act
PTT	Penile traction therapy
PD	Peyronie's Disease
RCT	Randomized controlled trial

Study Summary

Title	Penile Length Restoration in Men with Diabetes Mellitus, Type II
IRB Protocol Number	18-006696
Methodology	Controlled randomized study
Overall Study Duration	3 years
Subject Participation Duration	6 months
Objectives	Evaluate the efficacy of the RestoreX penile traction device in restoring length loss secondary to diabetes mellitus
Number of Subjects	120
Diagnosis and Main Inclusion Criteria	Men with diabetes mellitus, type II
Study Device	RestoreX®, penile traction therapy
Duration of Exposure	Subjects in Groups 1-3 will use device for 3 months for 30 minutes, twice daily. Subjects in Group 4 will be control and will not use the device. After the randomized period, subjects using the device will switch to not using the device (Group 1), using the device once weekly x 30 minutes (Group 2), or continuing to use the device twice daily x 3 months (Group 3).
Reference therapy	The use of the device will be compared against a control group using no traction therapy. Individuals will also be compared to themselves to evaluate changes from baseline.
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 penile length prior to and following therapy. Comparisons of subjective questionnaire responses will also be made between groups and at the various time points captured.

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 diabetes mellitus experience sexual dysfunctions at an earlier age and higher rate compared to men without diabetes. One of these sexual dysfunctions includes diminished penile length. It is currently unknown if the decreased length is due to earlier erectile dysfunction or secondary to diabetes itself. Penile traction therapy is one of several treatments which have been used historically to treat decreased penile length, however, to date, no studies have evaluated the role of traction therapy in men with diabetes. The objective of the current study is to evaluate the efficacy of the RestoreX penile traction device (developed by Mayo Clinic and licensed to PathRight Medical) in restoring penile length in men with established diabetes mellitus.

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.

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.

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). Preliminary data have demonstrated efficacy of the device with all end points (improvement in length, curvature, satisfaction, and standardized questionnaires). Detailed information is also captured on adverse events. Among men in the treatment group, the most common adverse events were erythema (31%), cold glans (4%), and minor discomfort (52%). All symptoms resolved within 5 minutes of discontinuing use, with the exception of one patient (4%) who experienced minor discomfort for 15 minutes. Findings are consistent with other traction device studies.

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 PD. To date, no studies have evaluated the role of PTT in restoring penile length in men with diabetes mellitus (DM), a condition known to result in decreased penile length. 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. As loss of penile length results in several issues including loss of sexual function, cosmetic concerns, and difficulty in maintaining hygiene (incontinence resulting in yeast infections), the ability to maintain or restore length may mitigate these issues. Additionally, men with DM have an increased rate of development of penile curvature (PD), which can be both functionally and psychologically distressing. PTT has previously been demonstrated to limit the extent of penile curvature that men experience among those with early PD, and therefore, the use of PTT in men with DM may reduce the likelihood of either developing the condition or in lessening the extent of the condition. It is unclear if PTT will impact (improve or worsen) erectile rigidity in men with DM, although preliminary data from the current PTT study in men with PD (IRB 17-001283) has demonstrated improvements in erectile function.

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 6 months of randomized treatment (for the treatment arm).

2 Study Objectives

2.1 Primary Objective

1. The primary objective is to assess penile length pre and post completion of RestoreX® traction therapy compared to control groups (no treatment) of DM subjects.

2.2 Secondary Objectives

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 the rate of Peyronie's disease development among groups
5. Compare patient satisfaction scores including satisfaction with overall penile length.
6. Evaluate and compare patient erectile function among groups
7. Review associations between DM factors and standardized questionnaires and outcomes

3 Study Design

3.1 Subject Selection

3.1.1 Inclusion Criteria

- Men with DM, type 2
- ≥18 years old

3.1.2 Exclusion Criteria

- Any evidence of end-organ failure attributed to DM (assessed based on medical history / patient history alone)
    - Loss of fingers / toes
    - CKD Stage IV or greater
    - Retinopathy
    - Myocardial infarction
    - Cerebrovascular accident
    - Indwelling penile prosthesis or prior history of penile prosthesis
- Peyronie's disease at baseline

3.2 Setting

The current study will be conducted at the Mayo Clinic in Rochester, MN Department of Urology. All patients will be recruited from mailers to Mayo Clinic patients with a known history of DM.

3.3 Recruitment

Patients with a known history of DM, type II will be sent a mailer and offered participation if meeting inclusion / exclusion criteria. Those interested in proceeding with the trial will be invited to meet with a study coordinator. At that time, the details of the study itself will be reviewed with the potential participant. Financial incentives will be provided, to include $100 for the first visit and $250 for each follow-up visit if meeting inclusion / exclusion criteria. Participants will also be given a RestoreX® device at no charge. Patients will not be charged for any visits related to the study, and no labs or other testing will be obtained which require payment.

Patients may also be recruited directly from the DM clinical practice, however, it is not anticipated that this will be the primary source of recruitment.

3.4 Consent and Enrollment

Patients wishing to enroll in the study will be given the opportunity to meet with the study coordinator to further review study details and formal consent.

Patients that would like additional time to consider their participation will be given other opportunities to meet with the study coordinator if desired. If the patient expresses interest in participating at any of these times, a formal consent will be reviewed (see **Attachment – Consent Form**).

At enrollment, all participants will be assigned a study identifier, with a master list maintained in a password protected database (Mayo server – RAVE database) linking the patient to the identifier. A total of 30 patients will be enrolled into each arm of the study for a total of 120 patients enrolled overall. It is estimated that up to 360 patients will need to be screened to enroll the 120 patients.

3.5 Study Schema

All patients will have been previously seen at Mayo Clinic for a condition of DM. Following enrollment, key factors relating to their underlying condition will be abstracted from the chart by a study coordinator, including age, duration of disease (if known), number of DM medications, use of insulin, most recent fasting glucose and HbA1c, creatinine, and testosterone, HOMA1-IR, HOMA2-IR, and BMI. If any of these variables are not available, no additional attempts will be made to retrieve the information.

At the initial appointment, patients will also undergo a penile length assessment by a urology provider and Men's Health Nurse and receive questionnaires (IIEF-15 and disease specific history)

Once consent and study assessments are completed, the patients will be randomized into one of four groups:

1. PTT for 30 min 2x/day x 3 months, followed by no treatment x 3 months
2. PTT for 30 min 2x/day x 3 months, followed by once weekly (30 minutes) x 3 months
3. PTT for 30 min 2x/day x 6 months
4. Control (no treatment)

Patients in the treatment arm will record a daily journal of their usage of the device. Patients will then begin using the device as instructed for the times appropriate to their group.

After 3 months of using the device (+1.5 months permitted), patients will return for subsequent assessments (see below) and a follow-up questionnaire. At this time, patients will be encouraged to report any adverse events. They will also be requested to bring their device back to the clinic to review proper usage and any questions on the device. After completion of the subsequent assessments, patients will begin the second phase of the trial.

After 6 months (+ 1.5 months permitted) patients will return to the clinic to undergo final assessments, which are identical to the 3-month assessments.

Since participants are being asked to travel to Mayo Clinic for subsequent assessments, we will provide a remuneration amount of up to $600. The purpose is to assist participants in their travel to and from Mayo Clinic. Those that provide consent will be provided $100 after their baseline assessment. After their second and third visits (3 and 6-months, respectively), they will receive $250 for a possible total of $600.

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 as <10 cm, 10cm-13cm, 13.1cm-16cm, >16cm stretched length. Each stratum will have a separate randomization table provided such that one of three 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.

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 Baseline Assessments

- Participant consented
- Abstracted from chart
    - Age
    - Duration of DM
    - DM medications including use of insulin
    - Fasting glucose, HbA1c, HOMA1-IR, HOMA2-IR, creatinine, testosterone
    - BMI
- Objective assessments
    - Penile length – pubic symphysis to glanular corona
- Subjective questionnaires
    - Disease specific history
    - IIEF-15
- Device usage diary provided for treatment group

4.2 3 Month Visit

- Penile length assessment
- Questionnaires
    - 3 month
    - IIEF-15
- Device usage diary retrieved from treatment group
- Device usage diary given to all participants

4.3 6 Month Visit

- Penile length assessment
- Questionnaires
- **month**
    - IIEF-15
- Retrieve device usage diary

4.4 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 at baseline and at the 3 and 6 month follow-ups.

See **Attachments – Device Usage Diary, Disease Specific History, IIEF-15, Questionnaire 3 Month and 6 Month**

4.5 Schedule of Events

Table 1: Schedule of Events

Study Activity	Baseline Assessment	3 Month	6 Month
Consent	X		
IIEF-15	X	X	X
Disease Specific History	X		
Length Assessment	X	X	X
Patient Diary Provided	X	X	
Questionnaire 3 Month		X	
Questionnaire 6 Month			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 penile length between traction and no traction will be made, as well as reviewing historical records to increase statistical power. Comparison of length from baseline to post-traction for individual participants will also be reviewed.

The data will also be analyzed in three ways: 1- with all patients included, regardless of their compliance to utilize the device for the recommended treatment time, 2- with patients excluded if they failed to achieve 90% compliance with the recommended duration of treatment, 3- with patients excluded if they failed to achieve 75% compliance with the recommended duration of treatment. Factors which will also be included to determine compliance will include frequency and duration of use and whether or not the device was used correctly (black rods buried, amount of time white line showing).

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. All data will be normalized by baseline 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 adverse event reporting period is the 6 month study duration. Participants will also be encouraged to contact the study team to report any additional adverse events during the 6 months following study completion.

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 6 months following study completion.

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 follow-up visits. 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"

   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 (IRB17-001283).

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. Trost, L. W., Munarriz, R., Wang, R. et al.: External Mechanical Devices and Vascular Surgery for Erectile Dysfunction. J Sex Med, **13:** 1579, 2016