Comparison of Collagenase Clostridium Histolyticum to Surgery for the Management of Peyronie's Disease: A Randomized Trial

Principal Investigator Landon Trost, MD

[Co-Investigator(s)] Tim Jenkins

Funding Sponsor: Endo Pharmaceuticals

Protocol Number: (IRBe) CUREPD101

Initial version: February 11, 2020 Version **(1.0)**

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CCH	Collagenase clostridium histolyticum
HIPAA	Health Insurance Portability and Accountability Act
I&G	Incision and grafting
IIEF	International Index of Erectile Function
PDE5s	Phosphodiesterase-5 inhibitors
PTT	Penile traction therapy
PD	Peyronie's Disease
RCT	Randomized clinical trial

Study Summary

Title	Comparison of Collagenase Clostridium Histolyticum to Surgery for the Management of Peyronie's Disease: A Randomized-Controlled Trial
IRB Protocol Number	***
Methodology	Randomized, prospective study
Overall Study Duration	7 years
Subject Participation Duration	60 months
Objectives	Compare key clinical outcomes between collagenase clostridium histolyticum and surgery for the management of Peyronie's Disease
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Men >18 years of age with Peyronie's Disease and without prior CCH or surgery for PD
Randomization	Patients will be randomized to either CCH + PTT (8 total injections) or penile surgery + PTT (plication or I&G). Randomization tables will be created and pre-stratified based on baseline penile curvature.
Follow-up Period and Assessments	Men will have objective assessments of curvature and length obtained at baseline, 3 months, 1 year, and 5 years. Subjective questionnaires will also be administered at baseline, 3, 6, 12, 24, 36, 48, and 60 months.
Statistical Methodology	Stratification of subjects prior to randomization to assure an equal representation based on baseline penile curvature (30-44, 45-59, 60-74, 75-89, 90 or above). Statistical comparisons between groups and to baseline will be made of responses to subjective questionnaires and objective measures.
Plan for Publication	It is anticipated that the primary study will be published following accumulation of data out to 1 year. A second manuscript would then be published using the long-term follow-up data. Pending novelty of findings, additional studies may also be published if felt to be warranted.

1 Introduction

This document is a protocol for a randomized, prospective clinical trial. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Western International Review Board policies and procedures.

1.1 Background and Clinical Need for the Current Study

Collagenase Clostridium histolyticum (CCH) is the first FDA approved medication for the treatment of Peyronie's Disease and demonstrated significant improvements in penile curvature and bother in two phase III trials.[1] Since its release, CCH has become increasingly utilized as a first-line agent, with recent abstract data presented at the SMSNA (by our team and Endo) demonstrating a provider preference of 2:1 over surgery as a first-line treatment for PD. However, despite this provider trend, there is ongoing debate as to whether CCH or surgery is the optimal treatment for PD.

Although multiple post-FDA release studies have been published on clinical outcomes of CCH, none have directly compared outcomes between CCH and surgery. Long-term data are even more lacking, with one CCH 5-year study demonstrating stability of outcomes and preserved satisfaction, while one 5-year surgical grafting paper suggested high rates of dissatisfaction (65%) and recurrence of curvature, length loss, and de-novo erectile dysfunction in an increasingly high rate of patients.[2, 3] In my own clinical practice, I had similarly observed higher satisfaction rates among men who chose CCH compared to surgery, which resulted in a strong shift away from surgery as a first-line agent in favor of CCH.

In addition to these clinical observations and published studies, there are ongoing, active debates at the AUA and SMSNA questioning superiority of CCH or surgery, with some arguing for CCH as a first-line agent (Hellstrom, Mills, Trost) and others arguing for superiority of surgery (Levine, Morey, Milam). Similarly, I currently sit on the AUA guideline panel for PD, and one of the key questions we recently evaluated was whether there were sufficient data to suggest that CCH should be considered as a first-line agent and used preferentially over surgery. Following a robust discussion, it was concluded that while the majority of the panel felt that it exhibited properties appropriate for first line, since there were no comparative studies available directly evaluating CCH and surgery, no specific statements could be made in that regard.

All of the above findings (clinical observations, published data, ongoing debates among specialists, and AUA PD guideline discussions) led me to seek to perform a clinical trial directly comparing CCH to the historical gold-standard surgical therapies (plication / I&G). A trial of this nature would provide answers to several key clinical questions:

1 – Which therapy are patients more satisfied with overall (CCH or surgery)?
2 – How do long term outcomes compare between groups?
3 – What percentage of men in either group go on to do subsequent therapies?

Additionally, results from the current study would provide a basis of evidence to suggest that CCH should be used as a preferred first-line agent prior to considering penile surgery (for the AUA guidelines) and would confirm clinical observations that outcomes of penile surgery are generally not

long-lasting. Each of these would have a significant impact on clinical practice, improve outcomes for patients, and would likely aid Endo Pharmaceuticals from a business perspective.

1.2 Investigational Treatments

The current study would randomize men into one of two treatment cohorts: CCH + PTT or surgery + PTT.

CCH + PTT – Men in this cohort would receive the full series of 8 Xiaflex injections using a protocol similar to the one used during the IMPRESS I and II trials: 2 injections separated by 1-3 days, repeated 3 additional times with 6 week breaks between treatments.[1] A total of 0.58 mg of collagenase Clostridium histolyticum would be administered with each injection. Men would also be treated with RestoreX PTT based on our prior clinical findings at Mayo which demonstrated nearly 2x greater improvements when RestoreX was used in combination with CCH compared to CCH alone.[4] Traction would begin on the day of injection and continue until the 3-month post-treatment time point. RestoreX is a Class I PTT device developed by PathRight Medical, is registered with the FDA, and has randomized controlled data demonstrating efficacy when used for the treatment of PD.[5]

Surgery + PTT – Men in this cohort would undergo surgery using either penile plication or incision and grafting. The specific surgery would be selected based on commonly used criteria: plication for curvatures <70 degrees; I&G used for ≥70 degrees or severe hourglass / hinge deformities.[6-8] I&G would not be performed in men with any degree of erectile dysfunction (as measured on the IIEF). Men who required penile prostheses (those with erectile dysfunction unresponsive to PDE5 inhibitors or intracavernosal injections) would have been previously excluded from the study, and therefore, this treatment is not applicable. Traction using RestoreX would be combined with surgery post-operatively based off of limited published data which suggest improvements in subjective and objective penile lengths post-operatively.[9] Additionally, the inclusion of traction in both cohorts would eliminate it as a potential confounder, and PTT is increasingly being seen as an adjunctive standard treatment in the management of PD.

1.3 Preliminary Data

As noted previously, there are currently numerous studies demonstrating safety and efficacy of CCH, PTT, and surgery.[1, 10, 11] However, there are no true prospective studies directly comparing outcomes between CCH and surgery. Although indirect comparisons of different treatment cohorts have been performed, studies such as these lack any ability to directly compare outcomes and are of little utility.[12] Limited long-term data on outcomes have been published for CCH and I&G and have demonstrated preserved outcomes at 5 years with CCH and significantly worsened outcomes and satisfaction among I&G men.[2, 3]

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

1.4.1 Study Rationale

There is currently an ongoing, active debate as to whether CCH or surgery should be considered as first-line or gold-standard therapies for PD. As noted previously, there are published and non-published data suggesting that CCH is increasingly being used as a first-line agent, and long-term outcomes may be superior with CCH. However, there are currently no direct, head-to-head studies comparing CCH and surgery. As such, there are no data to directly suggest that CCH should be used preferentially or as a first-line agent for PD compared to surgery. It is the expectation that the current study would provide these data and the rationale necessary to suggest that CCH should be considered first line therapy for the treatment of PD.

1.5 Anticipated Duration of the Clinical Investigation

The overall study will be scheduled for 7 years, although the first set of key outcomes and publication would be expected within 2-3 years. It is expected that it will take 12-24 months to receive at least 3 month data back on 50 men in the trial (given its randomized nature). This is anticipated to require screening of up to 80 men to achieve the 3-month outcomes data on at least 50 men. Once enrolled, the first set of key endpoints will be reached at 1 year (objective and subjective assessments), and a publication will be planned based off of those data. Men will then be followed longer-term to determine the durability of satisfaction and other outcomes out to 5 years. As such, the total study duration would be set for 7 years.

2 Study Objectives

2.1 Primary Objective

1. Compare the response to SAPS question #1 (below) between cohorts to determine overall satisfaction at all time points
2. Compare complication rates between cohorts at all time points: erectile dysfunction, changes in penile sensation, perceived changes in penile length

SAPS Question #1
- How satisfied are you with the effect of your treatment?
    - Very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied

2.2 Secondary Objectives

Compare the following between cohorts and against baseline within cohorts at all time points
1. PDQ scores

2. IIEF scores (all domains except erectile function – erectile function domain assessed as a primary endpoint)
3. BDI scores (depression)
4. Penile curvature
5. Penile length
6. Number and type of subsequent interventions required – surgeries or CCH injections in particular
7. Number of hospitalizations or ER visits resulting from treatment
8. Non-standardized questionnaire responses (See Attachments)

3 Study Design

3.1 Subject Selection

3.1.1 Inclusion Criteria

- Men with PD
- >18 years old
- Curvature ≥30 degrees
- Ability to achieve an erection satisfactory for intercourse with or without PDE5 inhibitors

3.1.2 Exclusion Criteria

- Prior treatment with CCH or surgery
- Moderate (shadowing) or severe (>1 cm) penile calcification
- Any contraindications to CCH, PTT, or surgery – as determined by the PI

3.2 Setting and Investigator

The current study will be conducted at the Male Fertility and Peyronie's Clinic in Orem, UT. The Male Fertility and Peyronie's Clinic was established by Landon Trost to specialize specifically in Peyronie's Disease and vasectomy reversal. The clinic currently sees up to 15 new Peyronie's patients weekly. The clinic also has a formal academic association with Brigham Young University.

Dr. Landon Trost is the former head of male infertility and Andrology at the Mayo Clinic in Rochester, MN. During his time at Mayo, he completed more investigator-initiated randomized controlled trials than any other urologist in the department's history.

The Male Fertility and Peyronie's Clinic also has several advantages over a traditional academic center. Since the clinic is owned and operated by Landon Trost, there are significant cost savings, including no mandatory overhead fee, ability to control surgical prices, and ability to utilize clinical resources indirectly and without reimbursement.

The possibility of a multicenter study was initially considered. However, because of the significant costs that would be associated with a multicenter trial (surgical costs at Mayo Clinic for example would be 4-5x higher, in addition to a 35% automatic overhead and significantly higher study coordinator costs), this idea was abandoned (cost would likely reach 1 million or more).

3.3 Recruitment

Men who are seen in the Male Fertility and Peyronie's Clinic for Peyronie's Disease will be offered entry into the trial at the time of their clinical visit.

If the study fails to recruit at least 10 men within 6 months, the study will be changed to an open label (rather than randomized allocation) format. This would be expected to greatly facilitate enrollment.

3.4 Consent and Enrollment

Patients attending the Male Fertility and Peyronie's Clinic will receive a description of the study. Those interested in participating, 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 another opportunity to meet with the study coordinator at a later time. If the patient expresses interest in participating at any time, a formal consent will be reviewed.

At enrollment, all participants will be assigned a study identifier, with a master list maintained in a password protected database linking the patient to the identifier. A total of up to 25 patients will be enrolled into each arm of the study to achieve 3-month outcomes on a minimum of 15 patients in each arm. Thus, the total enrollment may be up to 50 men depending on the number of dropouts.

3.5 Study Schema

Patients meeting criteria who have consented will be randomized to either CCH + PTT or surgery + PTT using previously created random allocation tables. The allocation tables will assure equal representation within both cohorts of various baseline penile curvatures to prevent the possibility of one cohort having a more severe disease presence than another.

A baseline visit will be performed, at which point the patient will receive an initial set of questionnaires (demographics, IIEF-15, PDQ, BDI, and non-standardized questions). A baseline penile length and curvature will also be performed with erectogenic medication administered as well as a penile ultrasound.

Patients will then undergo one of two treatments:
1 – CCH + PTT: Men will have two injections of CCH administered, 1-3 days apart, followed by manual modeling and PTT 30-60 min/day as outlined in our prior publication.[4] Each injection consists

of 0.58 mg of collagenase Clostridium histolyticum. Approximately 6 weeks later, the next round of injections will be performed until a maximum of 8 injections in total has been administered. PTT will be continued until the 3-month post-treatment visit.

2 – Surgery + PTT: Men will undergo either penile plication or I&G. Men with curvatures <70 degrees will undergo a penile plication, while those >70 degrees may undergo an incision and grafting procedure or penile plication. Incision and grafting will be performed in those who are <60 years old and have normal erectile function without need for phosphodiesterase-5 inhibitors (Viagra, Levitra, Cialis, Stendra). Penile plication involves the placement of stitches on the opposite side of the curvature to result in straightening of the penis. Incision and grafting involves cutting into the point of maximal curvature and placement of a graft in the resulting gap. 2-4 weeks post-operatively (depending on tolerability), the patients will be asked to perform PTT 30-60 minutes daily until the 3-month post-treatment visit.

At 3, 12, and 60 months post-treatment, men will undergo repeat physical assessments for penile length and curvature using an erectogenic medication administered (alprostadil) and a goniometer.

At 3, 6, 12, 24, 36, 48, and 60 months post-treatment, men will receive a set of questionnaires that they can complete online. These questionnaires include SAPS #1, IIEF-15, PDQ, BDI, interval history (including AEs), and other non-standardized questions.

3.6 Randomization Protocol

Following enrollment and completion of the consent, a length and curvature assessment will be performed as well as baseline questionnaires. Men will then be randomized based on a previously created randomization table that takes into account baseline curvatures. Groupings are divided based on initial curvature of 30-44, 45-59, 60-74, 75-89, 90 or above. Men will then undergo treatment with either CCH + PTT or surgery + PTT.

4 Study Procedures

4.1 Screening Assessments

- Potential patient questioned to assure that they meet all inclusion / exclusion criteria
- Participant consented
- Penile ultrasound obtained to assess for calcification

4.2 Baseline Assessment

- Objective measurements
    - Penile length obtained (pubic symphysis to corona and tip) – obtained by two separate providers with experience in PD therapies
    - Erection induced with alprostadil

    - Curvature assessed in two planes as well as with photography (obtained in two planes)
- Questionnaires
    - Demographics questionnaire (if not previously obtained)
    - IIEF-15
    - PDQ
    - BDI
    - Non-standardized baseline assessment
    - Disease specific history (if not previously obtained)
- Device usage diary provided

4.3 3, 12, 60 Month Visits

- Objective assessments
    - Penile length and curvature as described above
- Questionnaires
    - IIEF-15
    - PDQ
    - BDI
    - Interval treatment history
    - Adverse events
    - Non-standardized assessments and SAPS #1
- Device usage diary retrieved from treatment groups

4.4 6, 24, 36, 48 Month Time Points

- Questionnaires administered online
    - IIEF-15
    - PDQ
    - BDI
    - Interval treatment history
    - Adverse events
    - Non-standardized assessments and SAPS #1

4.5 Schedule of Events

Table 1: Schedule of Events

Study Activity	Screening / Baseline Visit	3, 12, 60 Month Visit	6, 24, 36, 48 Month
Penile U/S	X		
Consent	X		
Objective Assessments	X	X	
Demographics	X		
Disease Specific history	X		
IIEF, PDQ, BDI	X	X	X
SAPS #1		X	X
Non-standardized Subjective Questions	X	X	X
Interval Treatment History		X	X
Adverse Events	X (baseline)	X	X
Treatment Diary (given or retrieved)	X (given)	X (retrieved at 3 mo)	

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. Information will remain de-identified throughout the remainder of the study period and will remain on password protected, Male Fertility and Peyronie's Clinic servers.

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

5.2 Statistical Analysis

The current study is considered exploratory in nature. Analyses will be performed using comparisons within and between patient cohorts. All captured data will be utilized as a point of comparison based on accepted standards (e.g. IIEF subdomains, PDQ subdomains, etc.). All data will be analyzed to determine if it is normative / non-normative and will be described and compared appropriately (mean, SD versus median, IQR).

Patients with partial missing data will have all available data included for analysis, with no attempts made to statistically replace missing variables. All data will be analyzed using an intent-to-treat analysis.

Adverse events will be reported as a total as well as compared between cohorts.

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, 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 the last administration of study treatment (for new symptoms). AE's will be followed out to 60 months to determine ongoing symptoms.

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 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.

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 appropriate 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 Western IRB

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

The study team will report to the Western IRB any UPIRTSOs and Non-UPIRTSOs.

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 treatment 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 Western 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 a period of 2 years after the investigation is terminated or completed.

8 Study Finances

8.1 Funding Source

This study is funded by Endo Pharmaceuticals.

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 clinical studies as a Primary Investigator (IRB17-001283).

8.3 Subject Stipends or Payments

Subjects will receive payment for their participation, including stipends for travel, and all treatments provided at no cost.

8.4 Regulatory Information

CCH is an FDA approved therapy for the treatment of PD.

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] Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *The Journal of urology*. 2013;**190**: 199-207.
[2] Goldstein I, Lipshultz LI, McLane M, et al. Long-Term Safety and Curvature Deformity Characterization in Patients Previously Treated With Collagenase Clostridium Histolyticum for Peyronie's Disease. *The Journal of urology*. 2020: 101097JU0000000000000743.
[3] Chung E, Clendinning E, Lessard L, Brock G. Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. *The journal of sexual medicine*. 2011;**8**: 594-600.
[4] Alom M, Sharma KL, Toussi A, Kohler T, Trost L. Efficacy of Combined Collagenase Clostridium histolyticum and RestoreX Penile Traction Therapy in Men with Peyronie's Disease. *The journal of sexual medicine*. 2019;**16**: 891-900.
[5] Ziegelmann M, Savage J, Toussi A, et al. Outcomes of a Novel Penile Traction Device (RestoreX) in Men with Peyronie's Disease: A Randomized, Single-blinded, Controlled Trial. Submitted J Urol Jan 2019: Mayo Clinic; 2019.
[6] Mulhall J, Anderson M, Parker M. A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. *The journal of sexual medicine*. 2005;**2**: 132-8.
[7] Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU guidelines on penile curvature. *European urology*. 2012;**62**: 543-52.
[8] Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. *The journal of sexual medicine*. 2010;**7**: 2359-74.
[9] Rybak J, Papagiannopoulos D, Levine L. A retrospective comparative study of traction therapy vs. no traction following tunica albuginea plication or partial excision and grafting for Peyronie's disease: measured lengths and patient perceptions. *The journal of sexual medicine*. 2012;**9**: 2396-403.

[10] Ziegelmann M, Savage J, Toussi A, et al. Outcomes Of A Novel Penile Traction Device (Restorex) In Men With Peyronie's Disease: A Randomized, Single-Blinded, Controlled Trial. *The Journal of urology*. 2019: 101097JU0000000000000245.
[11] Barbosa ARG, Takemura LS, Cha JD, et al. Surgical Treatment of Peyronie's Disease: Systematic Review of Techniques Involving or Not Tunica Albuginea Incision. *Sex Med Rev*. 2019.
[12] Yafi FA, Diao L, DeLay KJ, et al. Multi-institutional Prospective Analysis of Intralesional Injection of Collagenase Clostridium Histolyticum, Tunical Plication, and Partial Plaque Excision and Grafting for the Management of Peyronie's Disease. *Urology*. 2018;**120**: 138-42.