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Safety and Efficacy of Low Intensity Shockwaves for the Treatment of Erectile Dysfunction – Comparison of Two Treatment Schedules

IRB: 20160335 NCT03067987

IRB: SITE00000524

Safety and Efficacy of Low Intensity Shockwaves for the Treatment of Erectile Dysfunction – Comparison of Two Treatment Schedules

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SPONSER:	Direx System Corp
VERSION #:	1
VERSION DATE	May 27, 2016

TABLE OF CONTENTS

Investigator's Statement

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)
- Ethical principles that have their origins in the Declaration of Helsinki
- Food and Drug Administration (FDA) Code of Federal Regulation (CFR):
  - Title 21CFR Part 50 and 45 CFR Part 46, Protection of Human Patients
  - Title 21CFR Part 54, Financial Disclosure by Clinical Investigators
  - Title 21CFR Part 56, Institutional Review Boards
  - Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)

As the Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior

agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

I understand that my signature constitutes agreement and understanding of acceptance of the defined responsibilities of a Sponsor-Investigator as defined by the protocol, applicable FDA Regulations, and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor-Investigator. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol shall be implemented timely with my review and approval prior to implementation.

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Instructions for Use (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also

(first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

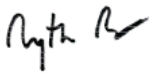
I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

RANJITH RAMASAMY

Print Name of Physician



Physician's Signature

April 13, 2016

Date

1. BACKGROUND

1.1 Study Disease

Erectile Dysfunction(ED) is a condition with an inability to develop or maintain an erection of the penis upon sexual stimulation. It occurs in association with aging, chronic illnesses and various modifiable risk factors. Amongst the modifiable risk factors, ED shares the most common risk factors with Coronary Artery Disease(CAD) which are smoking, hypertension and hyperlipidemia[1]. Even though

it is not a part of normal aging, it is seen in 52% men in the age group 40 to 70 years, with a higher rate in the men more than 70 years[2].

Penile erections are as a result of an interaction of the normal physiologic processes involving the central and peripheral nervous system, endocrine and vascular systems. Any imbalances in these processes will lead to the development of ED.

The phases of erection are,

- Dilation of the arterioles and arteries as a result of increased blood flow.
- Trapping of incoming blood by the expanding sinusoids.
- Compression of the venous plexuses reducing venous outflow.

- Stretching of the tunica to its maximum capacity, occluding the emissary veins and decreasing the venous outflow to a minimum.
- Erections occurs

ED can be classified in to two groups, Organic and Psychogenic.

Vasculogenic ED which belongs to the Organic group, can be either due to arteriogenic, or venogenic or mixed[2].

Arteriogenic ED is caused due to a narrowed lumen due to increased resistance of the arteries, enhanced basal and myogenic tone leading to vasoconstriction, and endothelial dysfunction resulting in impaired endothelium dependent vasodilation.

Venogenic ED occurs mainly due to failure of adequate venous occlusion.

The inadequate venous occlusion can be due to

- Development of large venous channels draining the corpora cavernosa.
- Degenerative disease (old age, Diabetes) or penile fracture (traumatic injury to the tunica albuginea) resulting in the inadequate compression of the veins.
- Alteration in the structure of the fibroelastic components resulting in venous leak.
- Acquired venous shunts.

1.2 Study Interventions

Renova-ED is a Linear Shockwaves (LISW) device which incorporates a unique shockwave transducer operable to deliver shockwaves to a treated region confined to a narrow rectangle. Shockwaves generation follows the electromagnetic principle.

Linear Shockwaves (LISW), as a treatment for ED has been in evaluation in contemporary medicine (see section 1.4). It has been in use for the last three years.

The present study is about a device called “Renova-ED”, in which shockwaves are focused onto line segments for improved organ coverage. Shockwaves produced by "Renova-ED" are aimed at the left and right corpora cavernosa and the crura. The study is aimed at determining the safety and effectiveness of this new type LISW in the relief of ED.

1.3 Rationale

LISW has been known to bolster angiogenesis by increasing the levels of vascular endothelial growth factor.

Principal mode of action used in other disease:

Coronary Artery Disease: Kikuchi et al.[3] showed significantly improved symptoms and decreased nitroglycerin use in patient who had a coronary artery bypass grafting and were suffering from stable angina.

Bone Healing: Haupt et al.[4] showed that Low intensity shock waves treated group showed radiological signs of faster healing.

Calcifying tendinitis: Rompe et al.[5] showed that shock wave to patient suffering from calcifying tendinitis showed a 62.5% partial and complete disintegration of the the deposits. Moreover, 85% of the patients reported improvement at 24-week follow up period.

Diabetic Foot Ulcers: Wang et al.[6] showed that Extracoproral Shock Wave Therapy (ESWT) to patients with diabetic foot ulcer showed complete improvement in 31%

and partial improvement in 58%. Moreover, ESWT showed significantly better clinical results and local blood flow perfusion, higher cell concentration, and activity than the Hyperbaric Oxygen group.

1.4 Preliminary Studies

Contemporary literature shows two important studies in this field both conducted by Vardi et al[7,8].

The efficacy trial study published in 2010 recruited 20 men with vasculogenic ED and were given serial 2 sessions of treatment for about 3 weeks followed by 3 – week no intervention period. At 1-month duration there was a significant improvement in their erectile function measured by International Index of Erectile Function ED (IIEF-ED) domain scores (20.9 5.8 vs 13.5 4.1, p < 0.001). This significant result was consistent at 6-month follow up. Moreover, no pain or adverse event was noted during the follow-up period.

The second randomized, double-blind, sham controlled study by showed that treatment group showed better outcome than control group measured using International Index of Erectile Function-Erectile Function domain (mean SEM 6.7 0.9 vs 3.0 1.4, p 0.0322) at the first follow-up. Additionally, penile hemodynamics improve significantly in the treatment group in comparison to control group (maximal post-ischemic penile blood flow 8.2 vs 0.1 ml per minute per dl, p 0.0001).

2. HYPOTHESIS

2.1 Alternate Hypothesis (H_A):

Active Treatment groups will show a >2-point increase in the IIEF-EF score from baseline for mild erectile dysfunction, and >5 points for moderate erectile dysfunction and will show significant change.

2.2 Null Hypothesis (H_O):

There is no difference from baseline and after-treatment in Treatment groups for alleviating ED measured using IIEF-EF score.

3. OBJECTIVES

3.1 Primary Efficacy Objective

To evaluate change of IIEF-EF score[9] from baseline to follow-ups 1, 3 and 6 months' post treatment (appendix I).

3.2 Secondary Objectives

To study sexual activity improvement leading to optimal penetration at follow-ups according to:

SEP- Sexual Encounter Profile: Questions 2 and 3 (appendix II)
GAQ- Global Assessment Questions (appendix III)
EHS- Erection Hardness Score (appendix IV)

4. STUDY DESIGN

4.1 Accrual goal

A total of 80 patients with Vasculogenic ED meeting the eligibility criteria will be recruited from the Department of Urology clinic.

4.2 Duration of Study Participation

The total duration of the study will be for 7 months– including 1-month pretreatment (washout) followed by a period of 6 months' follow-up after the treatment.

5. STUDY ENTRY AND ENROLLMENT AND WITHDRAWAL

5.1 Study Entry

Study entry, as used in this protocol, will be defined as a subject signing informed consent. Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist. As per University of Miami policy, each study participant, including participants who have screened failed, who signs an informed consent form should be entered into the study database.

5.2 Enrollment Procedure

Completed and signed protocol-specific eligibility checklist;
All pages of the original signed informed consent forms (ICFs), including HIPAA Form B;
Relevant source documents or medical records such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.
Documentation from the Investigator that he/she has determined the subject meets eligibility criteria.

5.3 Cancellation Guidelines

The following are reasons for withdrawal of subjects from the study:

- A subject does not meet the eligibility criteria; (the subject will be considered a screen failure).
- A subject withdraws consent,
- A subject die's during protocol participation from causes other than the study treatment (not due to adverse events) or
- A study investigator decides the subject should be withdrawn from the study (e.g. subject non-compliance)

Regardless of reason for withdrawal, once a patient has been randomized to an arm, an intention to treat analysis will be performed.

All subjects who either screen fails, is withdrawn from the study or has completed all visits should be de-enrolled from the research database within 48 hours.

6. PATIENT SELECTION/ELIGIBILITY CRITERIA

6.1 Inclusion (Eligibility) Criteria

- The patient must be able willing and able to provide informed consent.
- The patient is a male between ≥30 and ≤80 years of age.
- The patient has ED of Vasculogenic origin determined by penile duplex ultrasound.
- The patient is PDE5i responsive, meaning he is able to achieve and maintain an erection under the effect of the maximal dosage of PDE5i.
- The patient has been in a stable heterosexual relationship for over 3 months prior to enrollment.
- A minimum of 2 sexual attempts per month for at least one month prior to enrollment – as documented by the Sexual Health Questionnaire (SHIM).
- The patient is suffering from erectile dysfunction lasting for over 6 months and not more than 5 years as per history provided by patient.
- IIEF-EF score between 11 and 25.
- Testosterone level 300-1000 ng/dL within 1 month prior to enrollment.
- A1C level ≤ 7% within 1 month prior to enrollment.
- Patients have at least a natural tumescence during sexual stimulation (EHS score ≥ 1).

6.2 Exclusion (Eligibility) Criteria

- The patient is currently or has participated in another study within the past three months, that may interfere with the results or conclusions of this study.
- The patient is under judicial protection (prison or custody).
- The patient is an adult under guardianship.
- The patient refuses to sign the consent.
- History of radical prostatectomy or extensive pelvic surgery ever.
- Venous leak.
- Past radiation therapy of the pelvic region within 12 months prior to enrollment.
- Recovering from any cancer within 12 months prior to enrollment.
- Neurological disease such as Alzheimers or Parkinsons disease which affects erectile function at the discretion of the investigator.

- Psychiatric diagnosis or medications such as antidepressants which affects erectile function or any other medications at the discretion of the investigator.
- Anatomical malformation of the penis, including Peyronie's disease.
- Testosterone level <300 or >1000 ng/dL within 1 month prior to enrollment.
- A1C level > 7% within 1 month prior to enrollment.
- The patient is taking blood thinners and has an international normalized ratio >3.

6.3 Study Population

80 heterosexual males suffering from Vasculogenic ED.

7. STUDY DESIGN, CLINICAL, RADIOLOGICAL, LABORATORY AND SURGICAL EVALUATIONS

7.1 Study Design

This is a prospective, randomized, clinical study aimed to evaluate the safety and efficacy of the two treatment schedules on symptomatic ED patients. The patients are randomized in a 1:1 ratio into two active treatment groups. (Refer section 18)

7.2 Screening Evaluations and Procedures

The first visit of the patients will be for screening and medical evaluation. Patient's medical co-medication history will be collected and documented and a physical examination will be performed.

Previous month's blood test results will be reviewed including a general chemistry panel, a lipid profile, A1C and Testosterone levels during chart review.

Patients will sign an informed consent and will answer the IIEF-EF questionnaire to see if they fit the criteria for enrollment. In case they meet all inclusion criteria (and do not meet any exclusion criteria), they will be recruited to the study.

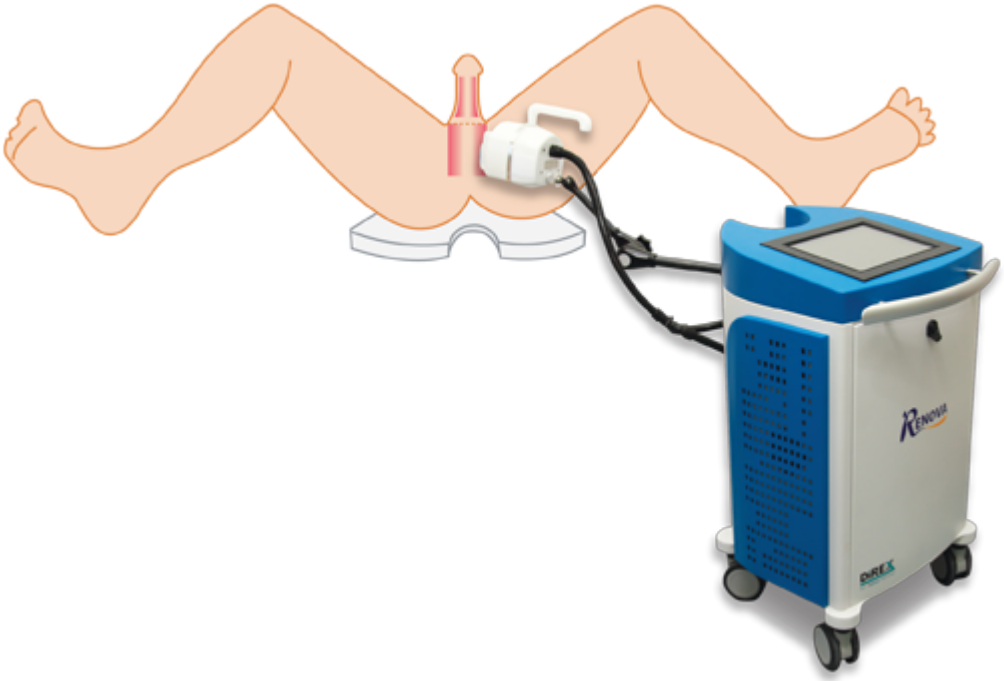
Patients who have been using PDE5-i in the last 4 weeks will report on their medicine type and dosage, and this data will be recorded in their files (reported prior to consent and gathered from chart review).

7.3 Pre-Treatment Procedures and Evaluations

Upon evaluating the inclusion/exclusion criteria, patients will be recruited to the study and randomized into one of the two groups in a 1:1 ratio (randomization will be performed by a computer software maintained by the Department of Urology). Patients randomized to the treatment groups will be instructed to stop any use of PDE5i for 4 weeks prior to first treatment session and refrain from using any other ED therapy option during the study. They will be instructed to undergo a PDE5i washout period of 4 weeks prior to treatment and to avoid using PDE5i or any other ED treatment during the entire study duration (shockwave treatment and follow-ups). After the washout period and before the first treatment session, patients will answer the IIEF-EF, SEP and EHS questionnaires for baseline evaluation.

7.4 Treatment Procedures

The treatment session lasts approximately 20 minutes and may be performed in an office environment. Treatment is applied in the physician's office. For session and treatment details (see below)



During the treatment, the same total number of shocks will be delivered according to the two treatment schedules as follows:

Group A:

5 daily sessions within a week (MTWThF), in which 720 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura).

Group B:

Three sessions per week (MWF) for 2 consecutive weeks, in which 600 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura)

Following the last treatment session, each patient will resume his baseline consumption of PDE5i, in terms of type and dose of drug, for the remainder of study duration.

7.5 Follow-Up Procedures and Evaluations:

Follow-up visits will be conducted at month 1, month 3 and month 6 after the last treatment session and shall include:

Measuring IIEF-EF, GAQ, SEP, and EHS scores of patients at the clinic at every follow-up visit

Reporting and recording adverse events at every follow-up visit.

8. ADVERSE EVENTS

8.1 Expected Adverse Events

In known studies where LISW was used for treatment of ED, there have been no reported adverse events (Ref. 2, Ref. 3). However minimal side effects like Transitory reddening of the skin, pain small bruising and swelling can be expected.

8.2 Serious Adverse Events

Serious injury or death

Any adverse event (penile hematoma or penile fracture) and eventual complication must be recorded at any time during the treatments and the follow up visits, and throughout the entire study duration. Patients will be instructed to alert the study investigator by telephone of any side effects occurring in the period after the treatment and until the study end.

For Reporting of adverse events see section 9

9. DATA AND SAFETY MONITORING PLAN

The study investigators will report to a surgeon monitor Dr. Murugesan Manoharan in the department of urology (who is not involved in the study) to ensure data quality and subject safety. The investigators will conduct continuous reviews of the data and subject safety, keeping track of the number of subjects, significant toxicities in accordance with the protocol and observed responses, which will be discussed at research committee meetings. All grade 3-5 adverse events (CTCAE v4.0), regardless of association with the LISW, will be entered into study database and reviewed at research committee meetings. In addition, all adverse reactions considered "serious" will be entered into research database and reviewed by the Surgeon monitor on an ongoing basis. If a death occurs within 30 days of LISW treatment and is determined to be related to the study, the investigators will notify the Department Chair Dr. Dipen Parekh within 1 business day. If an increase in the frequency of grade 3 or 4 adverse events is noted in the study, a report will be submitted to the Department Chair Dr. Dipen Parekh at the time the increased rate is identified. If at any time the principal investigator stops enrollment or stops the study due to safety issues, the Department Chair (Dr. Dipen Parekh) will be notified within 1 business day and a formal letter will be sent to the Department Chair (Dr. Dipen Parekh) to be received within 10 business days.

10. STATISTICAL CONSIDERATIONS

10.1 Primary Study Endpoints

The IIEF-EF questionnaire (appendix I) was chosen as the primary clinical efficacy assessment tool in this study. The total score (range 0-30) will be used for statistical analysis.

10.2 Secondary Endpoints

Sexual activity improvement leading to optimal penetration at follow-ups will be done according to:

SEP 2 & 3 at follow-ups
GAQ at follow-ups
EHS at follow-ups.

Endpoint Measurements: using CRF/questionnaire analysis

10.3 Endpoint definitions

IIEF-EF Questionnaire see appendix I
SEP 2 & 3 Questionnaire see appendix II
GAQ Questionnaire see appendix III
EHS Questionnaire see appendix IV

10.4 Sample size, accrual and study duration

TOTAL SAMPLE SIZE: 80
TOTAL ACCRUAL: 80
ACCURAL DURATION: 12 MONTHS
STUDY DURATION: 7 months

10.5 Statistical Analysis and Power calculation

The average and standard deviation of all relevant variables, including demographic and baseline characteristics, primary and secondary outcomes will be calculated.

IIEF-EF and EHS scores will be analyzed using ANOVA with repeated measures throughout the study, in order to compare the trends of groups A and B.

GAQ, SEP and success rates will be analyzed and compared between the groups according to Fisher's exact test in each of the endpoints. The statistical significance will be set at $P<0.05$.

Demographic characteristics such as age and ED duration will be compared between groups A and B using student's test. Other demographic characteristics, such as medical background and risk factors will be compared between these groups using Fisher's exact test.

A sample of 80 men with failing scores on the IIEF SEP2 question will be randomized 1:1 into one of two arms (low intensity or high intensity treatment) using a permuted random block algorithm. We hypothesize that following placebo treatment between 0 and 5% of men will pass the SEP2 question and at least 35% of men treated at either intensity level will pass. We have two co-primary

endpoints, the percentage of men passing after low intensity and high intensity relative to placebo, which will be assessed by two independent Fisher's exact tests. Each of these tests will be conducted with a 0.025 alpha error level to allow for a 0.05 experiment wide type I error rate. Power calculations done in SAS 9.4 suggest that with 40 men randomized into each group we will have at least 85% power to detect the difference between a 5% and 35% response rate. So long as our non-compliance/drop-out rate remains above 10% will will have at least 80% power (see Figure 1).

Computed N per Group			
Index	Nominal Power	Actual Power	N per Group
1	0.80	0.813	37
2	0.85	0.852	40
3	0.90	0.900	45

Figure 1. Sample size needed for 80% 85% and 90% nominal power for a Fisher's exact test with alpha = 0.025 (using an exact conditional distribution with the Walters normal approximation method).

10.6 Randomization:

80 patients will be randomized 1:1 to treatment groups with 40 patients each. An online based randomization tool called randomized.org will be used. This will be prepared beforehand, with treatment option printed on the paper and then sealed in an envelope (80 envelopes). Each would have Patients ID number printed out side and randomization information inside. This would be opened after a patient has signed the informed consent and is ready to receive treatment. The PI nor the study coordinator will not have the knowledge of patient's treatment group beforehand.

11. INVESTIGATORS RESPONSIBLITIES

11.1 Investigator Responsibility/Performance

The investigator (or a person designated by the investigator) should inform the patient of all pertinent aspects of the study, including the written information.

The investigator should provide the patient ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient. Neither the investigator, nor the study staff, should coerce or unduly influence a patient to participate or to continue to participate in a study.

11.2 Confidentiality

The identity of the patients in this study will be treated as confidential. Patients eligible to participate in the study following the pre-treatment visit will be assigned a unique patient code. The results of the study, including any other data, may be published for scientific purposes but will not give the patients' name or include any identifiable references to them.

However, any records or data obtained as a result of the patient participation in this study may be inspected by the sponsor, by any relevant governmental agency, by the Hospital Ethics Committee, or by the persons conducting this study, provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private in so far as permitted by law.

11.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate).

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information

obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.4 Source Documentation and Investigator Files

The investigator will maintain adequate and accurate records to document the conduct of the study and to ensure that study data can be subsequently verified. These documents will be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and special assessment reports; QOL forms, signed informed consent forms. When the CRF or any form is used as the source document, this will be clearly stated in the investigator study file.

At a minimum, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria.
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit.
- Laboratory test results.
- Condition and response of subject upon completion of or early termination from the study.
- Quality of Life Surveys.

11.5 Recording and Processing of Data

Data for this study will be entered into electronic CRFs in research database (a web-based clinical research management application). A CRF is required for every patient who received any study intervention. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring

it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.**

11.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

11.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics

11.8 Essential Documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The following documents will be on file:

- CV's and license of all investigators.
- IRB documentation/correspondence.
- Documentation of IRB certification.

12. Appendix I International Index of Erectile Function (IIEF – EF) Questionnaire. [9]

Name:	**Date:**
Write the number that best describes your erectile function <u>for the past 4 weeks</u> in the spaces provided	
Over the past four weeks: 1. How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the

	time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
4. During intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
15. How would you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate

	4 = High 5 = Very high

13. Appendix II Sexual Encounter Profile (SEP- Questions 2 and 3)[10]

SEP-Q2: Over the past 4 weeks, were you able to insert your penis into your partner's vagina?

Yes…… **No……**

SEP-Q3: Over the past 4 weeks, did your erection last long enough for you to have successful intercourse?

Yes…… **No……**

14. Appendix III Global Assessment Question (GAQ)[10]

GAQ-Q1: Over the past 4 weeks, has the treatment you have been taking improved your erectile function?

Yes…… **No……**

GAQ-Q2: If yes, has the treatment improved your ability to engage in sexual activity over the past 4 weeks?

Yes…… **No……**

15. Appendix IV EHS- Erection Hardness Score.[11]

How would you rate the hardness of your erection?

- 0: Penis does not enlarge
- 1: Penis is larger but not hard
- 2: Penis is hard but not hard enough for penetration
- 3: Penis is hard enough for penetration but not completely hard
- 4: Penis is completely hard and fully rigid

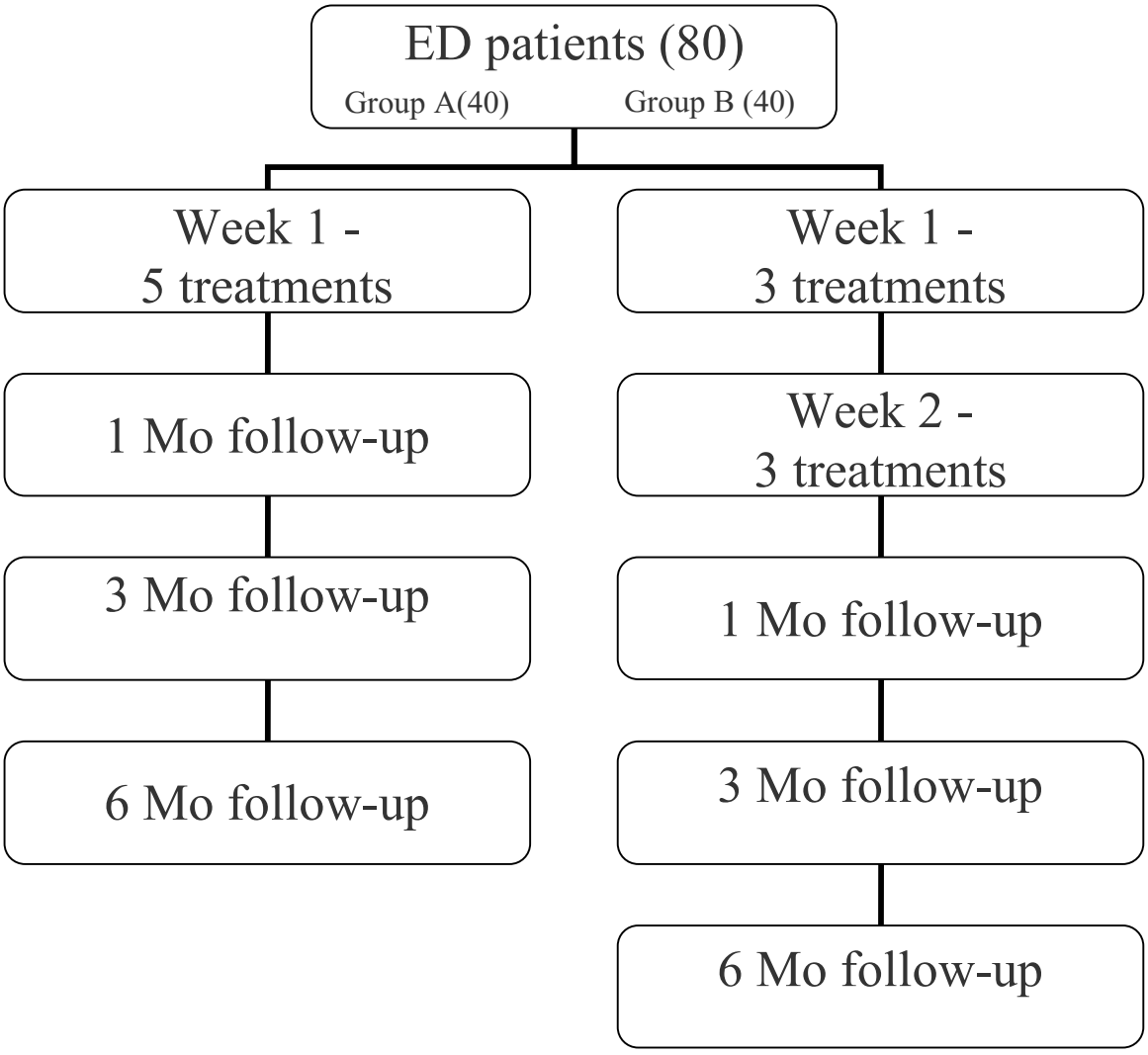
16. List of Abbreviations

ED	Erectile Dysfunction
AE	Adverse Event
EHS	Erection Hardness Score
GAQ	Global Assessment Questions
IIEF-EF	The International Index of Erectile Function – Erectile Function
LISW	Low Intensity Shock Wave
PDE5i	Phosphodiesterase type 5 inhibitor
SEP	Sexual Encounter Profile

17. Study Calendar

Visit #, Time / Activity	Visit 1 Screening	Visit 2 Pre-Treatment	Week 1 Visits 3-7 5 Treatment sessions	Week 1 Visits 3-5 3 Treatment sessions	Week 2 Visits 6-8 3 Treatment sessions	Visit 8/9 1 Mo FU	Visit 9/10 3 Mo FU	Visit 10/11 6 Mo FU
Medical & Urological History	•							
Physical Examination	•							
Informed Consent	•							
Inclusion & Exclusion Criteria	•							
IIEF-EF, GAQ, SEP, EHS	•					•	•	•
Study Recruitment & Group Randomization		•						
Record Treatment Parameters			Group A	Group B	Group B	•	•	•
Report Complications			•	•	•	•	•	•

18. Study Design Flowchart:



19. References:

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