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IRB Minimal Risk Protocol Template

General Study Information

Principal Investigator: Gregory Broderick, MD

Study Title: **Immediate and Short Term Efficacy of Low Intensity Shock Wave Therapy in the Management of Erectile Dysfunction Due to Mild – Moderate Cavernous Arterial Insufficiency**

Protocol version number and date: September 10, 2019 V 2.2

Research Question and Aims

The objective of this study is to evaluate the efficacy of low intensity shockwave therapy (LiSWT) via MoreNova in the treatment of erectile dysfunction (ED).

Aim 1: To assess the efficacy of the use of MoreNova shockwave therapy in individuals diagnosed with ED by a change in evidence based imagining via Color Duplex Doppler Ultrasound (CDDU)

Aim 2: To evaluate the efficacy of the use of MoreNova shockwave therapy based on patient reports erectile charges through the IIEF-EF, EHS, SEP 2+3, and GAQ questionnaires (1, 3).

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

ED is broadly defined as the inability to achieve or maintain an erection sufficient for penetration (NIH Consensus Statement 1992). Treatment for ED consists of oral medications, intracavernosal injections and surgically placed penile prosthetics. In the literature this has been described as a Stepwise Approach, empirically offering therapy beginning with the least invasive treatment option. Our approach at Mayo Clinic Florida has been to investigate the complaint of ED in men who fail the first step in ED management which is a trial of oral phosphodiesterase type-5 inhibitors (PDE5I). Using evidence-based technology we rule out psychologic ED and characterize vascular erectile function. Color Duplex Doppler Ultrasound (CDDU) in combination with an age specific dosage of intracavernous vasoactive medication (alprostadil, PGE1) stimulates erection for office testing. We have been able to categorize the severity of ED and identify the etiology of ED as arteriogenic ED, veno-occlusive ED or psychogenic ED. CDDU has become the standard of care in the evaluation of vascular erectile dysfunction (2). Penile injection therapy is often taught to men who have failed oral PDE-Type 5 Inhibitors (sildenafil, vardenafil, tadalafil). These therapies do not cure ED; they manage ED with escalating dosages of vasoactive drugs. The goal of LISWT is to restore natural erections and / or improve responses to oral medications (first line therapy).

LISWT for ED is under evaluation in the USA. The European Association of Urology Guidelines on ED were recently updated to include LISWT for men with mild to moderate ED. The energy/pulse used in this application is approximately 10% of the energy used for disintegrating kidney stones; no serious side effects have been reported. Shock wave therapy for diabetic ulcers has recently been approved by the FDA.

The present study proposal uses a device called MoreNova, in which shockwaves are focused onto linear

segments for improved organ coverage. Shockwaves produced by MoreNova are aimed at the penile shaft targeting the left and right corpora cavernosa and the crura. Our study is designed to identify immediate effects and short term durability of

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LISWT as a non-pharmacologic, non-surgical means of treating erectile dysfunction secondary to mild ED.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

APPROACH

This is prospective, pilot clinical study of 10 men aimed to evaluate the efficacy of MoreNova Shockwave therapy for men diagnosed with ED. We will restrict our target population to include men only between and including the ages of 40 and 55 who have been diagnosed with ED for over a year, but less than 5 years.

Efficacy is to be assessed by CDDU imaging during and from treatment up to follow-ups.

Efficacy is to be assessed by patient reported questionnaires data via IIEF-EF, SEP 2+3, GAQ and EHS that catalog the frequency of successful erections and side effects during treatment.

RECRUITMENT

Review of clinic patient records within the MCF Department of Urology to identify potential research participants (patients with ED who have already presented to MCF and had initial evaluation and CDDU diagnosis). Participants will first be identified through the treating physician and the PI on this proposal, Dr. Gregory Broderick. The study coordinator will then be notified of the potentially eligible patient who will further screen for eligibility. Once the patient has been determined eligible, the study coordinator will contact the potential study participant to schedule a research appointment to discuss the study in detail. The study coordinator will meet with the patient, describe the goals of the study, and ask if they would like to participate. If the patient agrees to participate at this time, a signed Patient Informed Consent is obtained before the patient leaves. The patient can decide at a later date to sign Informed Consent. If so, the study coordinator will schedule an appointment at a time when the patient will return for an appointment with a consultant. Recruitment will take place in quiet room where the study will be explained fully and the patient will have adequate time to decide. If a patient declines consent, the study coordinator will express that this in no way affects their current or future medical care.

Given the paperless initiative put forth by the clinical studies units, this study will utilize the Research Participant Tracking (PTrax) digital signature capture feature.

PARTICIPATION

Once consented, the participants' medical history will be reported and a physical examination will be performed as part of standard of care. Participants will be asked to stop all PDE-5 inhibitors or injectable vascular stimulants for 1 week prior to first treatment (washout period) and throughout the treatments. The participant will then be scheduled to receive their first shock wave therapy via the MoreNova device. Participants will receive a total of 6 treatments lasting approximately 20 minutes each, two treatments weekly for 3 weeks. A CDDU diagnostic will

be reviewed in clinical records (within 12 months prior to study enrollment). CDDU will be repeated as part of the study at the final treatment and at the 3-4-month follow-up. Below is test schedule for study participants.

	Baseline	Treatment 1-5	Treatment 6	Follow-Up 1 month	Follow-up 3-4 month
Level 4 Evaluation/Consult H&E	X[a]				
Return Physical (Level 2 Return)		X	X		
Washout period		X[b]	X	X	
MoreNova Therapy		X	X		
Color Duplex Doppler Ultrasound (CDDU) Exam	X[a]		X		X
Questionnaires[c]	X[a]		X[a]	X[a]	X[a]
Adverse Events		X	X	X	X
Concomitant Medications	X	X	X	X	X

[a]standard of care
[b]Begin one-week **prior** to treatment 1
[c]IIEF-EF, EHS, SEP 2+3, and GAQ

DATA COLLECTION

Clinical data will be collected begin at time of consent from the patients' medical record as well as the administered questionnaires. All data obtained for this investigation will be entered and maintained into electronic case report forms via REDCap database. Clinical data collection will include subject demographics (age, gender, race/ethnicity), current medications, and medical history relevant to cancer risk such as smoking history, body mass index, and family history of cancer. In addition, we will collect clinically variables resulting from the CDDU exam (see primary endpoint). The participant questionnaire responses will also be entered. Follow-up data collection for outcomes on all participants will be performed at 3-4 months after the last treatment was given.

All data will be entered by approved study staff. Continuous data queries will be performed to ensure data integrity and completion.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*: This proposal will require collaborative efforts between the Department of Urology and Clinical Studies Unit. For this proposal we will utilize the existing research infrastructure nestled within the Department of Urology. A clinical research coordinator will assist in screening, consenting, and enrollment and follow-up data and AE collection for all participating patients. Our Urology Senior Program Coordinator will

provide oversight and management to ensure timely and on budget study completion. Staff from the Urology Department will administer MoreNova shockwave therapy.

FUNDING

For this proposal we are requesting funding through the Florida Comprehensive Focus Research Team for a total of **$36,969.60**. Below is a breakdown of the approximated expected costs.

- Color Duplex Doppler Ultrasound (CDDU): ~$728.48 per exam x 2 research exams per participant= $1,456.92 per participant x 10 total enrolled= **$14,569.60**
- Return Level 3 Office Visit: ~$250 per visit x 6 visits= $750.00 per participant x 10 total enrollment= **$7,500**
- Clinical Research Coordinator (CCRC) .10 FTE for 1.5 years= ~ **$10,016**
- Clinical Research Assistant .10 FTE for 1.5 years= ~**$4,884**

To note, these are estimated costs and may not be reflective of true coordinator and data entry support.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 10

Subject population (children, adults, groups): Participants will be men only requiring treatment for ED and following the inclusion/exclusion criteria below.

Inclusion Criteria:

1. The patient must have given his informed and signed written consent
2. The patient is a male
3. Between 40 to and including 55 years of age
4. The patient has ED for longer than 1 year but less than 5 years.
5. The patient is PDE5i responsive, meaning he is able to achieve and maintain an erection under the effect of the maximal dosage of PDE5i
6. IIEF-EF Domain score of 17-20
7. Evidence Based Criteria: Doppler Clinical Exam

Exclusion Criteria:

1. The patient is participating in another study that may interfere with the results or conclusions of this study
2. History of radical prostatectomy or extensive pelvic surgery
3. Past radiation therapy of the pelvic region within 12 months prior to enrollment
4. Recovering from cancer within 12 months prior to enrollment
5. Neurological disease which effects erectile function
6. Psychiatric disease which effects erectile function

7. The patient is taking blood thinners
8. History of Diabetes Mellitus
9. History of Coronary Artery Disease
10. Evidence Based Criteria: Doppler Clinical Exam
11. Severe erectile dysfunction with IIEF-EF domain score $\leq$ 16

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: Prospective Pilot Investigation

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot, nor feasibility studies.

This investigation is a pilot study to determine the efficacy of the shockwave therapy MoreNova for patients with ED and as such, no previous formal power calculations were completed.

Primary Endpoint:

- To assess efficacy for patients receiving MoreNova therapy for treatment of ED via CDDU exam. To provide and evidence basis for improved of ED, we will closely monitor the 10 patients enrolled in the study. By including CDDU imaging done as part of patient's clinical assessment in PI's standard clinical practice, at time of last protocol treatment, and at 3-4 month follow-up, we will have evidence based data for improvement of erectile function. Specifically, we will measure cavernosal artery inflow, peak systolic velocity, end diastolic velocity, resistive index and erection hardness (EHS). CDDU is performed in privacy with Male Nurse provider recording Doppler data and PI performing ultrasound. Patients receive an intracavernous injection of alprostadil (10 mcg, standard of care). CDDU measurements are taken at 5-10 minutes and again after a period of privacy and visual sexual self-stimulation.

Secondary Endpoint:

- To assess efficacy for patients receiving MoreNova therapy for treatment of ED via IIEF-EF, Total IIEF-EF, EHS, SEP 2+3, and GAQ questionnaires. To provide clinical and participant self-reported date, we will administer questionnaires at baseline, after the last treatment, and at the 1 and 3-4 month follow-up. Specifically, these questionnaires target sexual and erectile function as well as quality of life.

References:

1. R. Rosen, A. Riley, G. Wagner, I. Osterloh, J. Kirkpatrick, A. Mishra, The International Index of Erectile Function (IIEF): A Multidimensional Scale for Assessment of Erectile Dysfunction. Urology 49: 822-830 (1997)
2. T. LeRoy, G. Broderick, Doppler Blood Flow Analysis of Erectile Function: Who, When, and How. Urol Clin N Am 38 (2011) 147-154
3. Mullhall JP, Levine LA, Junemann KP, Erection hardness: a unifying factor for defining response in the treatment of erectile dysfunction. Urology 2006 Sep; vol 68 (issue 3 suppl) : 17-25