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Evaluation of immediate and short-term efficacy of DualStim therapy with and without intracavernosal umbilical cord-derived Wharton's jelly in patients with erectile dysfunction: Study protocol for a randomized controlled trial

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ABSTRACT

Introduction: Erectile dysfunction (ED) affects a significant portion of the United States population and causes negative psychological burdens that affects men and their partner's quality of life and satisfaction. Extracorporeal shock therapy (ESWT) utilizing focused ESWT and radial ESWT in Low-intensity shock wave therapy has been used to treat ED with some success. Wharton's Jelly (WJ) is a biologic substance with large amounts of stem cells, growth factors, cytokines and extracellular components. The use of combined focused and radial ESWT (DualStim therapy) with injected WJ have potential uses in ED that may have advantages over current treatments.

Materials: A randomized, single-blinded, controlled clinical trial will be conducted to evaluate the efficacy and safety of DualStim therapy and intracavernosal injection of WJ in moderate to severe ED. A total of 60 patients with moderate to severe ED will be enrolled and treated with DualStim therapy with intracavernosal injection of WJ or saline for a period of 7 weeks. The International Index of Erectile Function – Erectile Function score will be used to gauge the treatment related changes in relation to the subject's baseline. The scores will be recorded at baseline and compared to follow-ups 1,3 and 6 months post-treatment. Any adverse events or severe adverse events will be recorded in the corresponding case report forms. Sexual Encounter Profile, as well as the Global Assessment Questionnaire and the Erection Hardness Score will be used to determine the sexual activity improvement from baseline leading to optimal penetration at follow-ups 1,3 and 6 months post-treatment.

Discussion: This clinical trial is one of the first studies to determine the immediate and short-term efficacy of DualStim therapy, with and without intracavernosal injection of formulated umbilical cord-derived WJ to improve and/or restore erectile function in patients with moderate to severe ED. This study will also provide insight into the safety and efficacy of WJ. We anticipate clinically significant improvement in patients suffering from moderate and severe ED treated with DualStim therapy with WJ compared to their baseline and DualStim with saline.

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Abbreviations

AEs	Adverse Events
CRFs	Case report forms
ED	Erectile dysfunction
EFD	Energy flux density
EHS	Erectile Hardness Score
ESWT	Extracorporeal shock wave therapy
fESWT	Focused extracorporeal shock wave therapy
GAQ	Global Assessment Questionnaire
IIEF-EF	International Index of Erectile Function
ICIs	Intracavernosal injections
IRB	Institutional review board
LISWT	Low-intensity shock wave therapy
PDE5i	Phosphodiesterase type 5 inhibitors
rESWT	Radial extracorporeal shock wave therapy
SEP	Sexual encounter profile
SAEs	Serious adverse events
SPIRIT	Standard protocol items: recommendations for interventional trials
WJ	Wharton's Jelly

1. Introduction

Erectile dysfunction (ED) is one of the most frequently reported medical condition in men, defined as the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance [1]. In the United States, ED has been reported to affect 52% of men aged 40–70 years and more than 70% of men aged over 70 years, affecting at least 12 million men [1,2]. In the past, ED was considered a psychogenic disorder, but current data indicates that pathogenesis of ED is multifactorial. These include comorbidities and risk factors such as, age, obesity, smoking, alcohol, diabetes, depression, cardiovascular diseases, prior pelvic surgery, spinal cord surgery, and other psychological variables [3]. ED has a severe negative impact on the patient and relationship with their partner [4]. Rates of depression in men with ED are as high as 56% [4]. ED is also associated with increased anxiety in sexual situations which can lead to loss of sexual confidence. These psychological burdens negatively affect a man's quality of life and satisfaction within their relationships, as well as their partners sexual function and satisfaction [4].

Currently, several non-invasive and invasive treatments are available to improve ED. The American Urological Association guidelines acknowledge that any treatment choice can be used as a first-line therapy [5]. Phosphodiesterase type 5 inhibitors (PDE5i) have become the most frequently used first-line treatment choice. Despite excellent efficacy and safety of PDE5i's, a significant number of ED patients do not respond to them due to underlying comorbidities or previous surgeries [6]. In these cases, more invasive treatment options such as intracavernosal injections (ICIs) of vaso-active substances, intraurethral suppository of prostaglandins E1, vacuum assisted erectile devices, and penile prosthesis are used [6,7]. However, these treatment modalities do not follow a curative approach, have a high prevalence of non- or less-responders, and do not modify the underlying pathophysiology of the erectile function [8]. To overcome the limitations of current treatment modalities, new alternative approaches such as extracorporeal shock wave therapy (ESWT) and/or regenerative therapies are being utilized.

Shock waves are defined as a sequence of single, highly energetic, biphasic acoustic impulses described by rapid propagation of rapidly increased pressure in three-dimensional space applied directly into the tissues without influencing their global destruction [9]. There are two types of ESWT generators, focused (fESWT) and radial (rESWT) and with low or high energy [10,11]. The fESWT is generated by electromagnetic, piezoelectric and electrohydraulic sources [10]. In this method, the pressure increases quickly to a peak intensity and back downward with a beam that has a concentrated shape with a focal point with the highest energy density [11]. In contrast, rESWT is generated by pneumatic methods and the pressure increases slightly, slower, to a lesser intensity and with a dispersed beam shape [10,11]. ESWT also differs according to the energy flux density (EFD). LISWT with low EFD is used for various minimally invasive techniques and High-intensity with higher EFD is mainly used for lithotripsy [11]. Both fESWT and rESWT have been used with low EFD in LISWT and studied in regard to erectile dysfunction [12–14].

LISWT is a minimally invasive technique that has been successfully used to treat urinary tract stones, ischemic heart disease and musculoskeletal diseases [15–18]. The complete mechanism of action of LISWT has not been elucidated, but it is attributed to stimulation of expression of angiogenesis-related growth factors, recruitment of endothelial progenitor cells, improvement in penile blood flow, and activation of Schwann cells, known for the ability to regenerate nerves [17–20]. Recently, LISWT to the corpora cavernosa has been adopted as a treatment modality for ED [20]. Among several studies, Yee at al., Kitrey et al., and Kalyvianakis et al. [22–24], included patients with moderate to severe ED; other studies did not classify ED by severity [21]. A study by Kitrey et al., demonstrated that LISWT was effective in patients with severe vasculogenic ED who were PDE5i non-responders and half of them were able to achieve erection hard enough for penetration with PDE5i [20]. The study by Kalyvianakis et al., demonstrated beneficial effects of LISWT on penile hemodynamics in patients with vasculogenic ED [24] In contrast, the study by Yee et al., showed no significant difference between LISWT and sham group in baseline International Index of Erectile Function - ED domain score and Erection Hardness Score [22]. Similarly, Fojecki et al. [25] reported no clinically relevant effect of LISWT. More robust evidence from additional randomized clinical trials is needed.

In addition to ESWT, new approaches to treat ED have also centered around regenerative therapies to offer a cure to this disorder by restoring the structure and function of damaged erectile tissue, rather than only treating the symptoms [26]. A regenerative approach will allow for long-term maintenance of erectile function via downstream regulation of growth factors along with both muscle and nerve regeneration [26]. Recently, there has been an increased interest in the use of biologics for regenerative medicine applications [27,28]. Currently used biologics include platelet-rich plasma, bone marrow aspirate, amniotic fluid, amniotic membrane, umbilical cord-derived Wharton's Jelly (WJ) and cord blood [27–29]. Some of these are presently being studied for treatment of ED [30,31]. The healing capabilities of these products are attributed to presence of stem cells, growth factors, cytokines, hyaluronic acid and/or exosomes [32,33]. BMA is one of the most studied sources with limitations associated with increased pain and morbidity due to the bone marrow aspiration procedure involved in obtaining bone marrow aspirate [34]. Bone marrow aspirate also has been shown to have a limited number of bone marrow mesenchymal cells with about 0.001–0.01% of mesenchymal stem cells within the bone marrow [34]. Results using platelet-rich plasma, have been shown to be biased due to poorly designed studies [35]. WJ offers many advantages over most other biologic options. The expansion properties of umbilical-derived stem cells and clinically significant amounts of regenerative substances and its ease of harvest make it a promising biologic source [36,37].

WJ is a mucous connective tissue of umbilical cord present between the umbilical vessels and the amniotic epithelium [38]. Its key role is to provide cushion, protection and structural support to umbilical vessels by avoiding their bending, torsion and/or compression [38]. Our recently published study reported presence of numerous growth factors, cytokines, hyaluronic acid and extracellular vesicles including exosomes in the WJ, and the amount of these factors was higher compared to other

biologics [36]. WJ is also known to contain high amounts of extracellular components such as collagen and sulfated proteoglycans [39]. In addition, it is known to contain primitive mesenchymal stem cells and yields the highest concentration of mesenchymal stem cells per milliliter compared to other allogenic tissues [38,40]. WJ derived mesenchymal stem cells may also be more effective than mesenchymal stem cells from adult tissues for treatment of several conditions, however, more studies are necessary to support their routine clinical use [41].

The purpose of this study is to determine the immediate and short-term efficacy of the methodological application of DualStim therapy-LISWT using fESWT and rESWT, with and without intracavernosal administration of formulated umbilical cord-derived WJ to improve and/or restore erectile function in patients with ED. A recent pre-clinical study also suggested that the combination of low-intensity ESWT and stem cell therapy may have synergistic effects and would provide new research directions for the treatment of ED [42]. We hypothesize that patients in the active treatment group (DualStim + Wharton's Jelly) will show an improvement of at least 4 points for moderate ED and at least 7 points for severe ED on International Index of Erectile Function (IIEF-EF) questionnaire, and this difference will be significantly different from their baseline. In addition, patients in the DualStim + saline group will be significantly different from their baseline, however, will show less improvement compared to the active treatment group. Our null hypothesis is that there is no difference between DualStim with saline and DualStim with WJ groups and no difference between the baseline and after-treatment within the treatment groups for alleviating ED measured using IIEF-EF questionnaire.

2. Materials and methods

This study protocol is reported in accordance with the Standard Protocol Items- Recommendations for Intervention Trials (SPIRIT) criteria [43]. The complete SPIRIT checklist can be found in Supplementary data.

2.1. Study setting

This study is multicentered involving 6 sites consisting of healthcare centers, community clinics and academic hospitals in the United States of America.

2.2. Participants

Participation will be discussed to patients that meet the inclusion criteria. The patients will be given the opportunity to read an informed consent form and get answers to all questions before considering participation at the enrollment/baseline visit. Trial participants will be men from ages 40–80 years old with moderate ED for at least 1 year and less than 10 years.

The other inclusion criteria are:

- A body mass index of <35 kg/m^2
- ED (vasculogenic only) for at least 1 year but less than 10 years and be unresponsive to PDE5i (phosphodiesterase type 5 inhibitors)
- Have a minimum International Index Erectile Function (IIEF-EF) domain score of 11–16 classifying them as moderate ED
- An IIEF-ED score of 11 or greater and 25 or less if taking PDE5i or in ICI (injection therapy)
- Be willing and capable of giving written informed consent to participate in the clinical study and comply with study-related requirements, procedures and visits

The exclusion criteria are:

- History of radical prostatectomy or extensive pelvic surgery
- Hypogonadism (serum testosterone <300 ng/dL)
- Subjects with values outside normal range on serum testing for LH, FSH, Prolactin, total and free testosterone
- Subjects with neurogenic, psychogenic, traumatic, anatomic and endocrinologic ED
- Recovering from cancer or radiation therapy of the pelvic region within 12 months prior of enrollment
- Taking blood thinners
- History of diabetes mellitus, untreated hypogonadism or thyroid disease
- Penis deformity on physical exam
- Recent participation in another clinical trial or treatment with any investigational product within 30 days prior to inclusion in the study
- Serious neurological, psychological or psychiatric disorder which may affect erectile function
- Medical conditions determined by site principal investigator as interfering with the study
- Injury or disability claim under current litigation or pending or approved workers' compensation claim.

Participants may voluntarily withdraw from the study at any time. Withdrawal from the study will not affect the patient's access to other treatments nor will the patient be subjected to any sanctions.

Participation in the study may be terminated if continued participation in the study is not in the subject's best interest, according to the principal investigator's opinion or if the subject withdrawals participation. Determination of therapy cessation and need of explanation will be done by the principal investigator based on standard medical practice. Any patient who suffers an adverse event whether or not related to treatment may withdraw voluntarily.

2.3. Study design

The study is a randomized, prospective, single-blinded study. The short-term efficacy of DualStim therapy with intracavernosal WJ injection will be assessed in patients with ED. The treatment arm will have subjects receive DualStim therapy – fESWT and rESWT with ICI of Umbilical cord derived WJ (1 ml GeneXSTEM, BioIntegrate Inc., Lawrenceville, GA, USA; dilute to q.s. 5 ml with sterile normal saline). The control arm will have subjects receiving DualStim therapy with 5 ml ICI of sterile normal saline. Patients will be followed for 6 months after last treatment visit with optional follow-up visits up to 18 months (Fig. 1 and Table 1). Table 1 represents an overview of the schedule for enrolment, intervention and assessment according to the SPIRIT guidelines.

2.4. Randomization

Patients will be assigned to treatment groups using sealed opaque enveloped coded with an alphanumeric identifier to ensure consecutive allocation of envelopes. Block randomization across sites will be used to ensure even distribution to each group with a 1:1 allocation.

2.5. Ethics

This study will be conducted in accordance with Good Clinical Practice guidelines and recommendations guiding physicians in biomedical research involving humans. This study has been granted ethical approval by GARM International Foundation IRB (IRB unique identifier: GXS-ED; Study number: GARM04132020-1). Written, informed consent will be obtained from all participants. All participants will be given sufficient time to reach a decision to sign the consent form prior to the study. The protocol has been registered on ClinicalTrials.gov (ID: NCT04424394).

2.6. Assessment points

Assessments for the study period will occur at week 0 (baseline visit)

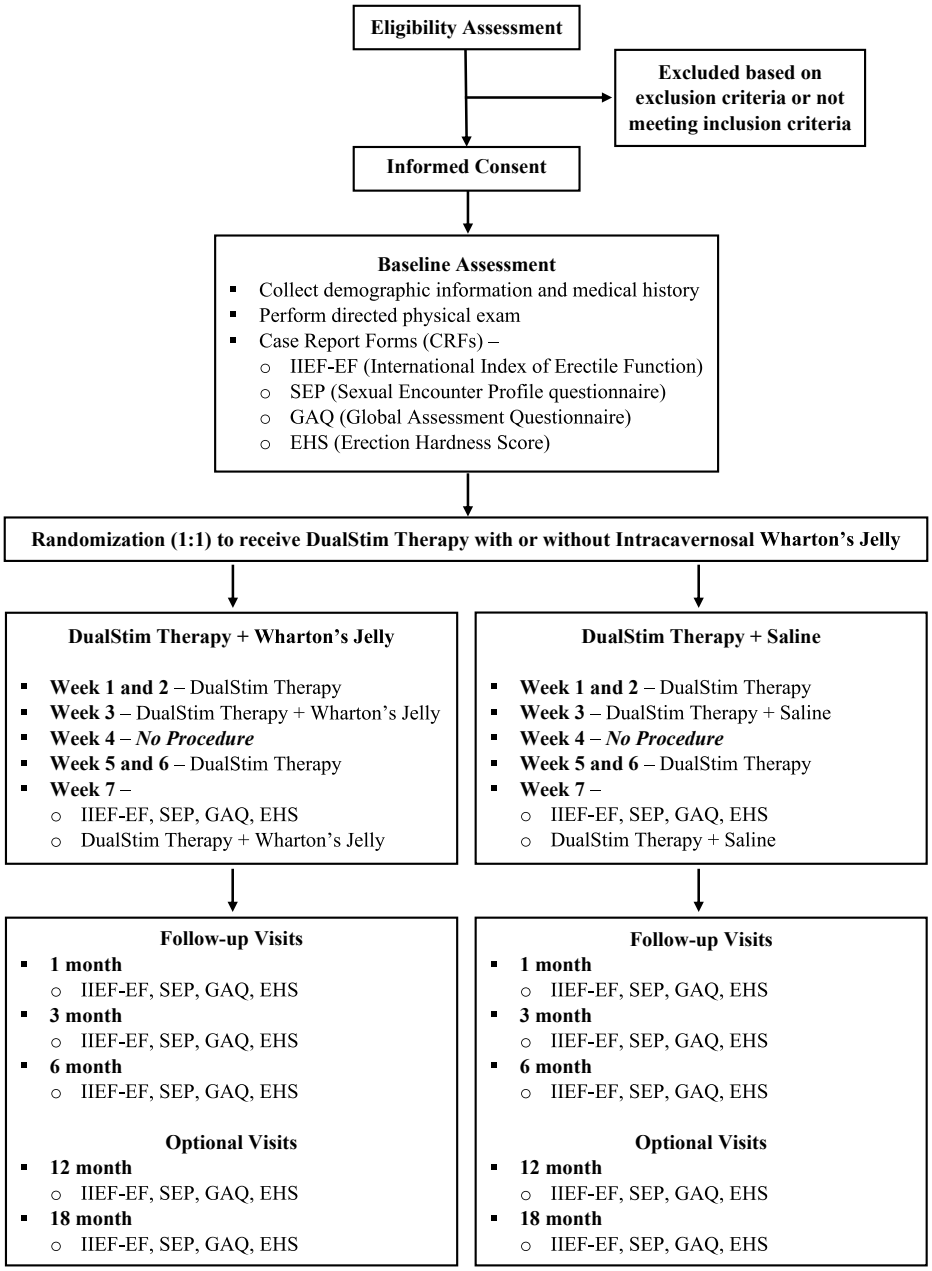

Fig. 1. Summary of the trial design.

with collection of data using the Case report forms (CRFs) that include IIEF-EF domain score, Sexual Encounter Profile Questionnaire (SEP), Global Assessment Questionnaire (GAQ) and Erection Hardness Score (EHS) forms. There will be 6 procedure visits with Dual Stim therapy and injection of WJ or saline. The second assessment will be at week 4 (1-month follow-up) with collection of data using the same CRFs. The next assessments will be at week 12 (3-month follow-up) and week 24 (6-month follow-up) with data collection using the CRFs. There will be two optional follow up visits at weeks 48 (12-month follow-up) and 72 (18-month follow-up) with data collection with the same CRFs.

2.7. Interventions

After completion of the week 0 baseline visit, and determination of patient's eligibility to be enrolled in the study, patient will be scheduled for 6 procedure visits. The procedure visits will involve all interventions over a period of 7 weeks. During the first procedure visit, patient will be randomized and enrolled into either the treatment arm or the control arm. Once randomized the subject will receive DualStim therapy using both rESWT and fESWT without an ICI on week 1 and 2. On the third procedure visit (week 3) both the treatment arm and the control arm will receive DualStim therapy. The treatment arm will receive 2.5 ml ICIs of GeneXSTEM (Wharton's Jelly) in each corpus cavernosum. The control arm will receive 2.5 ml ICIs of sterile saline in the same manner. No visit or procedure will be scheduled for week 4. Patients from both the treatment and control arms will both receive DualStim therapy on procedure visits 5 and 6 (week 5 and 6). On visit 7 (week 7) before any intervention the subject will be required to fill the necessary CRFs. After the CRFs are completed, both arms will receive DualStim therapy with the treatment arm receiving 2.5 ml ICIs of WJ in each corpus cavernosum. The control arm will again receive 2.5 ml ICIs of sterile saline in each corpus cavernosum (Table 2).

Table 1
Standard protocol items: recommendations for interventional trials (SPIRIT) flowchart.

	STUDY PERIOD											
	Enrolment (Weeks)	Allocation (Weeks)	Post-allocation									
			Treatment (Weeks)							Follow-up Visits (Months)			Optional Visits (Months)	
TIMEPOINT	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**3**	**6**	**12**	**18**
ENROLMENT:														
Eligibility screen	X													
Informed consent	X													
Baseline Data Collection (*Demographic Information, Medical History, Physical Exam*)	X													
Randomization		X												
Allocation		X												
INTERVENTIONS:														
DualStim Therapy			X	X	X		X	X	X					
ASSESSMENTS:														
International Index of Erectile Function (IIEF-EF)	X								X	X	X	X	X	X
Sexual Encounter Profile (SEP)	X								X	X	X	X	X	X
Global Assessment Questionnaire (GAQ)	X								X	X	X	X	X	X
Erection Hardness Score (EHS)	X								X	X	X	X	X	X
Adverse and Severe Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X

Table 2
Summary of the intervention visits.

WEEK	VISIT	PROCEDURE
1	2.1	DualStim Therapy
2	2.2	DualStim Therapy
3	2.3	DualStim Therapy and inject Wharton's Jelly or saline (**5 ml total – 2.5 ml in each corpus cavernosum**)
4	***NO VISIT***	***NO PROCEDURE***
5	2.4	DualStim Therapy
6	2.5	DualStim Therapy
7	2.6	**CRFs - IIEF-EF, SEP, GAQ, EHS** DualStim Therapy and inject Wharton's Jelly or saline (**5 ml *total* – 2.5 ml *in each corpus cavernosum***)

2.8. Outcome measures

2.8.1. Primary outcome measurements

The IIEF-EF questionnaire score is a multidimensional scale that addresses the relevant domains of male sexual function [44]. It demonstrates the sensitivity and specificity for detecting treatment related changes in ED [44]. Evaluating the immediate and short-term efficacy of DualStim therapy with WJ post intervention is one of the main primary outcomes of this study. The IIEF-EF score will be used to gauge the treatment related changes in this study in relation to the subject's baseline. The score will be recorded at baseline and compared to follow-ups 1,3 and 6 months post treatment. The second primary outcome measurement is determining the safety of intracavernosal umbilical cord derived WJ injection. The patients will be monitored for adverse events (AEs) and safety outcomes. Any AEs will be recorded in the corresponding CRFs and the principal investigators will determine if it is a serious adverse event (SAEs) or an AE.

2.8.2. Secondary outcome measurements

Sexual Encounter Profile Questionnaire (SEP) is widely used to quantify the number of intercourse attempts and sexual events and is favored due to its decreased susceptibility to recall bias (45). SEP has been used in over 100 publications and has been recommended by the International Consolation of Sexual Dysfunction for clinical trials in ED [45]. The SEP, as well as the Global Assessment Questionnaire (GAQ) and the Erection Hardness Score (EHS) will be used to evaluate the improvement in sexual activity from baseline leading to optimal penetration at follow-ups 1,3 and 6 months post treatment. Lastly the IIEF-EF score will be used to evaluate the immediate and short-term efficacy of DualStim therapy with WJ compared to DualStim therapy with saline are each time-point throughout the study.

2.9. Adverse events (AEs)

The following is a list of potential adverse events expected:

a. Related to DualStim therapy:
   i. Bruising (unlikely)
   ii. Excoriation of skin surface (highly unlikely)
   iii. Worsening of condition (highly unlikely)
b. Related to Wharton's Jelly injection:
   i. Injection site pain (possible)
   ii. Inflammation (possible)
   iii. Swelling (possible)
   iv. Infection (unlikely)
   v. Allergic reaction (highly unlikely)
   vi. Death (highly unlikely)

2.10. Serious adverse events (SAEs)

The following is a list of potential severe adverse events expected:

a. Leads to death
b. Leads to a serious deterioration of the health of the patient that results in:
   i. Life-threatening illness or injury
   ii. Permanent impairment of a body structure or body function
   iii. Inpatient hospitalization or prolongation of existent hospitalization
   iv. Medical or surgical intervention to prevent permanent impairment to body structure or body function

All SAEs will be reported to the sponsor within 24 h after the principal investigator first learns of the event and to the IRB within 5 days after.

2.11. Sample size

For this study, we propose an estimated group size of 30 patients per group, a total of 60 patients overall. Considering dropout rate and possible loss to follow up the goal is to have complete information on 25

patients per arm to achieve >80% power. An interim analysis will be performed, and group size will be adjusted, if necessary.

2.12. Statistical analysis

All statistical analysis will be performed by an independent statistician. Descriptive statistics will be computed for all study variables. Continuous variables will be described with central tendency measures (mean, median) and dispersion (range, standard deviation). Categorical variables will be summarized as frequencies and percentages. Chi-Square or Fisher's Exact test will be used to compare categorical variables. The Student's t-test/ANOVA or nonparametric equivalent, depending on distribution, will be used to compare continuous variables. Paired data will be assessed with paired *t*-test or Wilcoxon Rank sum test. Logistic regression will be used to assess predictors of improvement. Odds ratios with 95% confidence intervals will be reported. A mixed model repeated measures analysis with appropriate post hoc tests will be used to analyze score over time. P-values less than 0.05 will be considered statistically significant.

2.13. Data collection and handling

The principal investigator will maintain all source documents and data will be transcribed on to paper study CRFs. The original data will be secured by the principal investigator and be made available to the sponsor and study monitors. The principal investigator will also be required to maintain records for a period of five years. All CRFs pages will be subject to initial inspection for omitted data, data inconsistencies, illegible data and deviations b stud monitors. All hard copies of CRFs and media will be stored in a secure location.

The principal investigator will be responsible for submitting data and reports as follows:

a. AEs: In an ongoing basis. This will be reported in the proper section of the CRFs.
b. SAEs: Report within 24 h of knowledge of event to sponsor and report to IRB within five days as per their regulations.
c. Deviations, exceptions, violations of protocol: Report to sponsor within 5 days and report to IRB per their regulations.
d. Protocol progress report: Provide a copy to sponsor and IRB as per regulations.
e. Study closure report: Provide a copy to sponsor and IRB as per regulations.

2.14. Quality control and assurance

All documents and data will be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The sponsor, study monitors, and representatives of regulatory authorities are permitted to access study documents as needed. All attempts will be made to preserve patients' privacy and confidentiality.

3. Discussion

Erectile dysfunction is a common disease among men which can lead to negative psychological burdens that affects the quality of life of both men and their partners. This clinical trial will be one of the first study to determine the immediate and short-term efficacy of the application of DualStim therapy, with and without ICIs of formulated umbilical cord-derived WJ to improve and/or restore erectile function in patients with moderate to severe ED. This study will also determine the safety of ICI of WJ.

This study should demonstrate that a portion of the patients suffering from moderate and severe ED will achieve a clinically significant improvement of at least 4 points and 7 points respectively, on the IIEF-EF questionnaire. This may decrease the need for PDE5i's, reduce or completely eliminate the use of other medications treating ED, lead to more spontaneous erection, improve sensitivity, and increase the size due to increased blood flow. This in turn will add to better sense of wellness in the patients. This study will add to our understanding of treatment options for treating patients suffering from ED and will allow us to characterize responders and non-responders to the treatment more distinctly, which can facilitate the development of more tailored and targeted treatment strategies in the future.

3.1. Trial status

The study is registered on ClinicalTrials.gov; Identifier: NCT04424394; URL: https://clinicaltrials.gov/ct2/show/NCT04424394?term=NCT04424394&draw=2&rank=1.

The study was registered on 11 June 2020. The Global Alliance for Regenerative Medicine (GARM) International Foundation IRB approved the study on 13 April 2020 (IRB unique identifier: GXS-ED; Study number: GARM04132020-1). This protocol is version 1.0, dated 5 March 2020. The recruitment is expected to begin in June 2020. Expected date when recruitment will be completed is 31 July 2022.

Ethics approval and consent to participate

This study has been granted ethical approval by GARM International Foundation IRB (IRB unique identifier: GXS-ED; Study number: GARM04132020-1). Written, informed consent will be obtained from all participants.

Consent for publication.

Not applicable.

Availability of data and materials

The full study protocol, statistical codes and participant-level dataset for the current study can be made available upon reasonable request from the corresponding author once the final results of the trial have been published.

Funding

This study is funded by BioIntegrate Inc. BioIntegrate has contributed to the design of study, and will contribute to the collection, management, and interpretation of data, and preparation, review and/or approval of the manuscript(s). Data analysis will be conducted by an independent statistician (KD) not employed by the funder. The decision to publish findings will not be influenced by the funder or sponsor.

Trial registration

Registered on ClinicalTrials.gov; the trial number is NCT04424394.

CRediT authorship contribution statement

Ashim Gupta: Conceptualization, Project administration, Methodology, Writing – original draft, preparation, Writing – review & editing. **Hugo C. Rodriguez:** Writing – original draft, preparation, Writing – review & editing. **Kristin Delfino:** Writing – review & editing, Formal analysis. **Howard J. Levy:** Writing – review & editing, Data curation. **Saadiq F. El-Amin:** Writing – review & editing, Visualization. **Richard Gaines:** Conceptualization, Supervision, Investigation, Writing – review & editing, Visualization.

Declaration of competing interest

AG is a consultant for BioIntegrate. HJL and SFE owns equity in BioIntegrate. The remaining authors declare that they have no

competing interests.

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Not applicable.

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