Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Martin Kathrins, M.D.
Project Title:	A single-centre, open-label, non-randomized, home use, clinical investigation in the use of MED3000 Topical Gel for On-Demand Treatment of Post-Radical Prostatectomy Erectile Dysfunction
Version:	Version 5.1 dated 2 November 2023
Phase:	Exploratory
Device:	MED3000 gel

Revision History:

Version 1.0	New Version
Version 2.0	Changes include: • Inclusion criterion related to IIEF-EF pre-radical prostatectomy changed to the use of IIEF-5 assessment • Removal of treatment for pelvic hematoma from Male exclusion criterion 2 • Current use of androgen deprivation therapy added to exclusion criterion 7 • Removal of severe phimosis as an exclusion criterion • Wording changed from "Prior surgical history for Peyronies disease" to "Prior surgery or intralesional treatment for Peyronies disease" in exclusion criteria • Inclusion of a question asking which party (male or female) predominantly applied MED3000 gel prior to intercourse • Other administrative changes.
Version 3.0	• Change in inclusion criterion 4 from "Normal pre-radical prostatectomy erectile function (IIEF-5 >21)" to "Normal pre-radical prostatectomy erectile function (EPIC-CP question 8 score of 0 [firm enough for intercourse])". • Details of manufacturer updated. • Recruitment criteria changed
Version 3.1	• Version 3.1 not prepared. Version 3.2 was created directly from 3.0 in error.
Version 3.2	• Section 5: Additional paragraph relating to the review of patient suitability for the study included
Version 3.3	• Altered pathologic inclusion criteria • Details for changes for versions 3.1 and 3.2 have been added to the Revision History section • Amended inclusion criteria 18 to 48 months of bilateral nerve-sparing radical

	prostatectomy, from 36 months • Removed "robotic-assisted laparoscopic only" from inclusion criterion 1 o PCa stage =< T3a • Included "or IIEF > 26" to inclusion criterion 4 • Appendix 3 [Onset of Action questionnaire] removed as not relevant in this study.
Version 4.0	• Administrative change- Eligibility criteria have been numbered for ease of referencing • Versioning corrected so that final versions are denoted using an integer • Version number has been corrected on the Approval Signature page • Massachusetts General Hospital included in Section 5.0 as a source of potential patients.
Version 5.0	• Clarification that the female may sign the informed consent on a date either before or after the patient, but both must have consented prior to any study related activity being performed.. • Alteration of protocol that an appropriate PSA and serum testosterone result within 4 months of V1 is acceptable and that a new set of lab work may not be necessary. • Alternation of protocol that serum assays for PSA and testosterone may be performed at any point between Visit 1 and Visit 2. • Removed requirement for repeat PSA assay after treatment and patient will instead be instructed to proceed with standard of care assays with his primary urologist
Version 5.1	• Clarification in ***Stopping/Discontinuation Rules*** that the end of the study is after Visit 6 (week 13). This is consistent with the ***End of Study*** section.

Approval Signature

Version 5.0

This clinical investigation plan has been approved by Dr Martin Kathrins MD

Sponsor's Signature:

Sponsor and Principal Investigator: Dr Martin Kathrins MD

Signature: _____ **Date:** _____

Sub-Investigator's Signature:

Sub-Investigator: Dr Alexandra Berger Eberhardt MD

Signature: _____ **Date:** _____

1. Background and Significance

Erectile dysfunction (ED) is a common side-effect after radical prostatectomy (RP), even with nerve-sparing techniques. Cavernosal nerve damage may be due to direct trauma, stretching, heating, ischemia and local inflammation. This damage may be temporary, and nerve transmission may be regained to some extent 1-3 years after surgery. As functioning nerves are necessary for erections, this means that the penile tissue is in a constant state of low oxygen supply during the time with nerve dysfunction. This may, in turn, lead to cavernosal smooth muscle apoptosis and fibrosis, which manifests as loss in penile length, and causes long-term ED. The anatomic nerve-sparing technique for radical prostatectomy has been employed for decades with the goal to preserve post-postoperative erectile function the results are still imperfect in regard to sexual function recovery.[2]

Penile rehabilitation post-RP with PDE5-inhibitors (PDE5i) have been postulated to improve cavernosal perfusion and maintain smooth muscle viability. Although the REACTT trial did not meet its primary end point of improved IIEF-ED over placebo at 10.5 months after RP, there was significantly less penile shortening in the tadalafil once daily group (-2.2mm) over placebo (-6.3mm).[3] Patients refractory to oral therapies may proceed to more invasive medical therapies such as penile injection therapy and even penile prosthesis insertion. Despite recent advancements in surgical technique and penile rehabilitation programs, less than 30% of men recover erectile function at one year post-operatively.[4]

MED3000 has been shown to improve erectile dysfunction when used as needed (unpublished data).[5] MED3000 topical gel utilizes a novel evaporative mode of action with a rapid onset of action within 10 minutes for most users. MED3000's combination of volatile solvent components creates a novel evaporative mode of action that stimulates nerve sensors in the highly innervated glans penis through temperature, touch and pressure. It is believed that this leads to smooth muscle relaxation, tumescence and erection. MED3000 is non-invasive and as such does not achieve its intended purpose through penetration of cutaneous or mucous membranes. Patients are treated with topical MED3000 just prior to intercourse. MED3000 was originally studied in a 12-week Phase III, dose-ranging, multi-centre, randomized, double-blind, placebo-controlled, home use, parallel group trial. Treatment involves self- or partner-administered gel to the glans penis for 15 seconds prior to attempting sexual intercourse. Adverse events were rare and mild including headache and penile burning. There were no serious adverse events. (unpublished data).[5]

It is postulated that on demand treatment with MED3000 may improve erectile function among men status-post radical prostatectomy, allowing for some endogenous cavernosal nerve function recovery for 1.5 to 3 years post-surgery among men with normal baseline pre-surgical erectile function. To verify that bilateral nerve sparing was indeed performed, nerve sparing status for each nerve (left and right) will be assessed by the attending surgeon documentation. This pilot study aims to explore the feasibility, safety and effectiveness of MED3000 topical gel for on demand therapy of erectile dysfunction 1.5 to 3 years status-post bilateral nerve sparing radical prostatectomy.

Abbreviation	**Explanation**
PSA	Prostate specific antigen

ADE	Adverse Device Effect
AE	Adverse event
ED	Erectile dysfunction
EPIC	Expanded Prostate Cancer Index Composite
FDA	United States Food and Drug Administration
FMD	Futura Medical Developments, Ltd
HCV	Hepatitis C
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
IIEF	International Index Erectile Function
IIEF-EF	Erectile Function Domain of the International Index Erectile Function
IRB	Institutional Review Board
MCID	Minimally clinically important difference
PI	Principal Investigator
PHRC	Partners Human Research Committee
SAE	Serious Adverse Event
SEAR	Self-esteem and Relationship
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others

2. Specific Aims and Objectives

Primary Objective:

1. To investigate the effect of MED3000 topical gel for treatment of erectile dysfunction after nerve sparing prostatectomy (based on the Erectile Function domain of the International Index Erectile Function [IIEF-EF] assessed at treatment completion after 12 weeks compared to post-washout baseline).
2. To observe a mean change from baseline of the IIEF-EF domain in patients after nerve sparing prostatectomy treated with MED3000, assessed at treatment completion after 12 weeks, greater than or equal to the minimally clinically important difference (MCID) of 4, as published by Rosen et al 2011.[1]

Secondary Objectives:

To investigate the following in patients after nerve sparing prostatectomy treated with MED3000 for 12 weeks:

1. The efficacy of MED3000 in patients at weeks 4, 8 and 12 using:
   a. The change from baseline in Self-Esteem and Relationship (SEAR) questionnaire for men
   b. The change from baseline in Urinary incontinence using the Expanded Prostate Cancer Index Composite (EPIC) - (climacturia question added to EPIC)
   c. Change from baseline in all domains of the IIEF.
2. The change from baseline in 24 hour pad weight and usage number per day at 12 weeks.
3. The change from baseline of the stretched flaccid penile length following 12-weeks of treatment
4. Treatment-related adverse events in male patients and female partners occurring during treatment with MED3000.

3. General Description of Study Design

This is an open-label, non-randomized, single-arm trial. Patients with no evidence of prostate cancer biochemical recurrence (Prostate specific antigen [PSA] undetectable) with mild to severe post-radical prostatectomy erectile dysfunction based on IIEF-EF criteria will be enrolled. Patients will washout from use of prior erectogenic regimens for at least four weeks in order to standardize the cohort and establish a symptomatic baseline. By the 1.5 to 4 year point after surgery, many men may have pursued other erectogenic aids. Patients will be instructed to cease all erectogenic aids for at least 4 consecutive weeks prior to commencing intervention. Aids may include phosphodiesterase 5 inhibitors, vacuum erection device, intraurethral suppository, or intracavernosal injection therapy. During the 4-week Screening Period, patients will be advised to attempt at least 4 sexual intercourse attempts. IIEF-EF will be assessed at the end of this period to assess candidacy for trial and assess baseline status.

All eligible enrolled patients will receive treatment with MED3000 topical gel and use on demand for up to 12-weeks. Patients will be assessed at 4 weeks, 8 weeks, and 12 weeks (treatment cessation) after the baseline visit (Visit 2). No other erectogenic aids are allowed during the 12-week (±1 week) treatment period. Patients will be managed using standard of care but will attend the site for follow-up evaluation at 12-weeks (±1 week). Study assessments will include: IIEF, SEAR, EPIC and climacturia questionnaires, stretched flaccid penile length, urinary incontinence analysis, prostate-specific antigen (PSA) assessments, and use of other erectogenic aids specifically penile prosthesis placement.

Intervention

Patients will be instructed to make at least 4 intercourse attempts in each of the three 4-weekly periods during treatment (Weeks 1-4, 5-8, 9-12). Patients will apply a single dose (approximately 300 mg) to the glans penis and rub in for at least 15 seconds (to ensure a thorough distribution of gel) prior to each sexual intercourse attempt. Patients may have telehealth visits at Weeks 4 (Visit 3), 8 (Visit 4) and the 13-week follow-up visit (Visit 6). The patient will be expected to attend the site for the Screening (Visit 1), Baseline (Visit 2), and 12 week (Visit 5) assessments The patient reported outcome questionnaires (IIEF, SEAR, EPIC and climacturia) will be completed at Screening (Visit 1), Baseline (Visit 2), and the end of each of the 4-weekly periods (Weeks 4, 8, and 12). At study visits where it is not necessary for the patients to attend the site in person (Visits 3, 4, and 6), the questionnaires will be completed by the patients at home using paper copies of the respective questionnaires. Site staff will phone the patient to prompt them to complete the questionnaires and ask how many device assisted sexual intercourse attempts the patient had. The patients will be expected to bring the completed questionnaires and used and unused MED3000 tubes to site at their next on-site visit where a compliance assessment will be performed.

The site will encourage patient retention in the study by following up with the patients periodically between study visits if there any questions or concerns from patients. Additionally,

the site will send reminders to the patients of upcoming on-site study visit.

On June 6, 2022 the Food and Drug Administration determined the proposed investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under 21 CFR 812.3 (m) of the investigational device exemptions (IDE) regulation (21 CFR 812).

Safety will be evaluated throughout the study, whilst patients are on treatment by evaluating all reported adverse events (AEs) and the use of concomitant treatments. Additionally, standard assessments including physical examinations and visual examination of the penis, vital signs (BP, heart rate [HR], body temperature) will be conducted at the screening and baseline visits (Visits 1 and 2), and Week 12 (Visit 5). Details relating to AEs and concomitant medication will be collected during the patient's study contact with the site.

International Index for Erectile Function (IIEF) questionnaire

The IIEF was developed and validated in 1996–1997 as part of the sildenafil clinical study program and in 1999, the IIEF was recommended by the first International Consultation on Erectile Dysfunction as the primary effectiveness endpoint of choice for clinical studies in ED.6,7 After years of use, the IIEF is considered the gold standard self-report questionnaire for measuring EF. The IIEF has been validated, is widely used in numerous countries, and has demonstrated specificity for detecting treatment-related changes in EF.8 The IIEF consists of 15 questions divided into five domains of sexual function: EF (6 questions), orgasmic function (2 questions), sexual desire, (2 questions), intercourse satisfaction (3 questions) and overall satisfaction (2 questions). A score of 0 to 5 is awarded to each of the 15 question.6 Higher scores indicate better sexual function. The IIEF-EF domain, a subset of the IIEF measuring erection function, is commonly used as the primary endpoint in clinical trials and comprises Questions 1–5 and 15 of the IIEF. The questionnaire is completed by a patient's recollection of the effects that his erection problems have had on his sex life over the previous 4 weeks.

Objective Performance Criteria and Clinically Meaningful Differences

Objective performance criteria (OPC) are standardized numerical target values derived from

historical data taken from clinical studies and/or registries that may be useful for the review and comparison of safety or effectiveness endpoints in novel trials. OPC serve as additional evidence for the effectiveness of MED3000.

In 2011 Rosen et al. published a paper titled 'Minimally clinically important differences in the erectile function domain of the International Index of Erectile Function scale'.1 In this paper, the EF domain of the IIEF questionnaire were questions 1 to 5, inclusive, and question 15. The study used anchor-based minimal clinically important differences (MCIDs) estimated using data from 17 randomized, double-blind, placebo-controlled, parallel-group clinical trials of the PDE-5 inhibitor tadalafil (Cialis®) for 3,345 men with ED who received treatment for 12 weeks (meta-analysis). An overall MCID for IIEF-EF change from baseline of 4 was established across all ED

severities. MCIDs for IIEF-EF changes from baseline were also established for different ED severities as follows: mild, 2; moderate, 5; and severe, 7. These 'Rosen' criteria have now been widely accepted and used for responder definitions by academia and leading experts in the field of ED, and are cited by the US FDA in a recent strategic review as an acceptable patient reported outcome.

Self-Esteem And Relationship (SEAR) questionnaire

The Self-Esteem And Relationship (SEAR) questionnaire has strong psychometric properties that support its validity and reliability for measuring sexual relationship satisfaction, overall relationship satisfaction, confidence and particularly self-esteem in men with ED.9

It consists of 14 items investigating two dimensions: sexual relationship satisfaction (8 items) and confidence (6 items; subdivided into self-esteem and overall relationship satisfaction). All items are scored on a 5-point Likert-type scale. A higher score signifies a more favorable response for all 14 items. The questionnaire is completed by a patient's recollection over the previous 4 weeks.

EPIC: The Expanded Prostate Cancer Index Composite

The Expanded Prostate Cancer Index Composite is a validated patient related outcome mean to monitor quality of life in prostate cancer survivors. The evaluated data points include urinary incontinence, lower urinary tract symptoms, sexual, gastrointestinal, and hormonal on a scale of 0 to 100. The 26 question form is referred to as the Short Form. 10,11 The questionnaire is completed by a patient's recollection over the previous 4 weeks. We have added a question specifically regarding climacturia, which is the occurrence of urinary incontinence during sexual activity.

Minimally Important Differences have been studied for the various sub-categories of EPIC Short Form. (Skolarus et al 2015).

Identification and Description of the Investigation Device

Details of the manufacturer:
BCM LTD
(BOOTS CONTRACT MANUFACTURER)
D10 THANE ROAD
BEESTON
NOTTINGHAM
NG902PR
UNITED KINGDOM

Name/Number of model to permit full identification:
Not applicable.

Device traceability:

MED3000 gel will be supplied to the site in single-dose tubes contained within an outer carton (each carton contains 4 tubes). Both carton and tubes will display details of the investigational device's batch number and unique kit identification number. The labels applied to the MED3000 will comply with the requirements of 21 CRF 812.5.

After a patient is deemed eligible to participate (Visit 2), each patient will be provided with sufficient medication for the entirety of their participation in the study (9 carton [36 tubes]). It is assumed that each patient will make no more than 12 intercourse attempts using MED3000 gel within each 4-week treatment period.

Traceability of dispensed and returned investigational product (i.e. MED3000 gel) will be managed using site maintained dispensing/return logs.

Details of device components:

MED3000 is a clear to turbid gel free from particulate matter and is composed of the following ingredients: water, ethanol, propylene glycol, glycerine, carbomer, and potassium hydroxide (Table 1). All ingredients are commonly used in topical formulations.

Table 1. MED3000 Qualitative Formula

Component	Specification	Function
Alcohol	USP	Volatile component
Purified water	USP	Volatile component
Glycerin	USP	Non-volatile vehicle
Propylene glycol	USP	Non-volatile vehicle
Carbomer interpolymer type A (Carbopol Ultrez-10)	NF	Viscosity modifier
Potassium hydroxide solution (18% w/w) [a]	NF	pH modifier

NF=National Formulary; USP=United States Pharmacopoeia; w/w=weight for weight
[a] Potassium hydroxide is added to adjust to a pH of 5.5.

Summary of required training: The device is applied to the glans penis immediately prior to sexual intercourse. The site staff will provide training to eligible patients with or without their partner how MED3000 gel should be applied to the glans penis prior to dispensing the product. Further training may be provided to the participants as required. Previous studies have demonstrated that MED3000 gel is a safe product with an extremely favorable safety profile.

4. Subject Selection

All patients who underwent bilateral nerve sparing radical prostatectomy through Brigham and Women's Hospital / Brigham and Women's Faulkner Hospital may be considered for this study. Men who have undergone radical prostatectomy have obstructive azoospermia/anejaculation and are infertile in regard to any potential for natural conception through intercourse.

Patients will be recruited through the active patient cohort of the Brigham and Women's urologic men's health clinic which has a large patient volume of men with erection dysfunction following radical prostatectomy. Approximately 20 patients will enter the treatment phase of this study.

Male subject inclusion criteria

1. Men who underwent bilateral nerve-sparing radical prostatectomy between 18 and 48 months prior to study commencement
2. Age 40 – 70 at the time of screening.
3. Diagnosed with prostate cancer:
    a. PSA < 20 ng/ml
    b. Gleason score =< 8
    c. PCa stage =< T3a
4. Normal pre-radical prostatectomy erectile function (EPIC-CP question 8 score of 0 [firm enough for intercourse] or IIEF > 26)
5. Baseline erectile dysfunction at time of screening (despite use of erectogenic aids of any kind) and at enrolment following washout (IIEF-EF domain <=25)
6. Sexually active, in a stable heterosexual relationship for at least 6 months prior to screening
7. Female partner meets their respective inclusion and exclusion criteria
8. Able to understand and complete patient questionnaires
9. Serum PSA undetectable (no evidence of disease recurrence)
10. Willing and able to provide written consent to participate in the study (note: both the patient and his female partner must provide written consent to participate before any study related procedure is undertaken)
11. Willing to refrain from the use of other erectogenic devices and pharmaceutical interventions during the washout and 12-week treatment periods.

Male subject exclusion criteria

1. Anatomical abnormalities in the genitalia or pelvic region such as severe phimosis
2. Post-RP complications that could impact safety or effectiveness of medical therapy for

erectile function (urinary or intestinal fistula, unresolved anastomotic leak)
3. Tumor upstaging beyond T3a
4. Incomplete / sub-total nerve sparing on either side
5. Previous or scheduled treatment with pelvic salvage radiotherapy and/or androgen deprivation therapy
6. Prior receipt of androgen deprivation therapy
7. Unwillingness of the patient to make the required attempts at sexual intercourse during the screening period (at least 2 sexual intercourse attempts) and during the 4-weekly assessment periods (at least 4 sexual intercourse attempts per period) in the treatment phase.
8. Patient cannot communicate reliably with the Investigator
9. Any significant or serious cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrinological, metabolic, neurological or psychiatric disease which, in the opinion of the Principal Investigator, renders the male patient unfit to take part in the investigation
10. Patient has any history of an unstable medical or psychiatric condition or using any medication that, in the opinion of the PI, is likely to affect the patient's ability to complete the investigation or precludes the patient's participation in the investigation
11. Hypersensitivity to any of the excipients
12. Any clinically significant abnormal laboratory, vital signs or other safety findings as determined by medical history, physical examination or other evaluations conducted at screening or on admission
13. History of severe uncontrolled diabetes
14. Patients with nursing partners, known pregnant partners or partners who wish to become pregnant
15. Clinical evidence of alcohol or drug abuse (including marijuana) (in last 12 months)
16. Patients receiving testosterone pellets
17. History of hypogonadism
18. Prior surgical or intralesional treatment for Peyronie's disease
19. Any other condition that would prevent the patient from completing the study, as judged by the Investigator

Female partner inclusion criteria

1. Willing and able to provide written consent to participate in the study (note: both the patient and his female partner must provide written consent to participate before any study related procedure is undertaken)
2. Documented written informed consent

Female partner exclusion criteria

1. Unwillingness of the partner to make the required attempts at sexual intercourse during the screening period (4 requested sexual intercourse attempts) and during the 4-weekly assessment periods (4 requested sexual intercourse attempts per period) in the treatment phase.
2. Unwilling to disclose any experienced adverse events to the site study team.
3. Partner cannot communicate reliably with the Investigator
4. Any other condition that would prevent the patient from completing the study, as judged by the Investigator

5. Subject Enrollment

Patients will be recruited through the active patient cohort of the Brigham and Women's urologic men's health clinic and Massachusetts General Hospital. Approximately 20 patients will enter the treatment phase of this study.

The recruitment of patients will primarily be undertaken by research assistant(s) and/or Investigator(s) through the men's health clinic patient cohort, with a research assistant and/or investigator available to support any eligible and interested patients. Patients will initially be approached by his/her healthcare provider who is known to the potential patient and has first-hand knowledge of the patient's medical history. The healthcare provider may be one of the investigators. We will mitigate the possibility of undue influence when subjects are enrolled from among the Investigators' own patients. We plan to employ the following approaches as appropriate separately or in combination:

- Contact the patient in writing initially (via Research Invitation) and allow a patient to make the first contact if they're interested
- Ask a physician colleague, research nurse, or clinical research coordinator to initially explain the study or to re-contact the potential subject after the Investigator has presented the study at a routine in-person or telehealth visit
- Offer patients the opportunity to take home the Consent Form, and call or message back if they wish to participate

We will also review operative records at Brigham and Women's Hospital, and Faulkner Hospital for those patients who have undergone radical prostatectomy surgery during the enrolment period. These patients may not have recently seen a Brigham-affiliated clinician. We will access the operative reports and patient medical records through the electronic medical record. We will screen the medical records for relevant enrolment and exclusion criteria such as nerve sparing status, pathology for stage and margin status, PSA status, presence of erectile dysfunction. If patients are deemed to be potential subjects and have not opted out of receiving research invitations, we will send either a targeted research announcement or personalized research announcement to advise them of the study. If the patient is not enrolled in Patient Gateway we may mail the personalized research announcement. If we have not heard back from the patient after a week we will call them. If patients respond favorably they will complete pre-screening over the phone.

Once the provider gives approval to the research team to continue with contacting the patient, with the patient's verbal permission, during the course of providing medical care, the research assistant or investigator will be introduced to the patient and will be available to support any eligible and interested patients. The subjects will not be paid for their participation in the study. The consenting procedure for the trial will be administered by the members of the investigator site study team.

The female partner of the patient will accompany the male patient to his appointment and be informed about the study and asked to participate at the initial visit. The female partner will review and sign her own version of the informed consent form. Both patient and partner must sign their respective informed consent forms before any study related procedure is carried out on either party.

It is not anticipated that advertising will be needed to recruit patients and their partners. Instead, other clinics within Brigham and Women's Hospital/Dana Farber Cancer Institute may cross-refer any suitable patients as necessary.

All potential patients will have the medication risks and possible benefits explained to them and given sufficient time to ask questions and consider whether they wish to participate. Only patients and female partners who have signed the IRB approved informed consent forms may be enrolled into the study.

Non-English speakers, children and those lacking capacity will not be offered participation in the study. Following the Partners Human Research Committee (PHRC) policy on Obtaining and Documenting Informed Consent of Subjects who do not Speak English, non-English speaking patients will not be recruited as a full-translation consent is not available.

Patients will be allowed to withdraw consent at any time without compromising their future clinical care.

Most patients with post-radical prostatectomy erectile dysfunction treated at Brigham and Women's Hospital/Dana Farber Cancer Institute are internally referred to PI or sub-investigator for management. Thus, recruitment from the patient cohort treated by PI or sub-investigator reflects the general population of post-prostatectomy men treated at the institution. Trial information will be disseminated to medical oncology, radiation oncology, and urologic oncology at / Brigham and Women's Hospital / Dana Farber Cancer Institute/ Massachusetts General Hospital. Before patients are approached by the investigation site staff regarding study participation, a health care provider, usually a physician, known to the potential subject and has first-hand knowledge of the patient's medical history will (1) give approval for his/her patient to be contacted for research purposes, (2) initially introduce the study to the patient and (3) obtain the patient's permission to be contacted by study staff. The healthcare provider can introduce the study and obtain the patient's permission to be contacted by study staff verbally during the course of providing medical care.

Data on patient enrolment including race and ethnicity and plan to perform sub-group analyses for efficacy will be recorded. The investigation site staff will reach out to providers in medical oncology, radiation oncology, and urologic oncology to inform them of the study and encourage them to contact research group with potential research subjects, irrespective of whether the patient is met in clinic or via telehealth visit by the primary health care provider. It is planned that visits performed during the study will be via Telehealth, thus limiting the burden of travel for in-person visits.

6. STUDY PROCEDURES

Patients will be screened by the research assistant and/or investigator according to the specific inclusion/exclusion criteria.

Schedule of Assessments (Core Investigation)

	Screening (5 or 4 weeks before Day 1)[1]	**Treatment Period (12 Weeks)**				**Follow-up Visit**
	Visit 1	**Visit 2** (Day 1)	**Visit 3**[2] (Week 4 ± 1 week)	**Visit 4**[2] (Week 8 ± 1 week)	**Visit 5**[7] (Week 12 ±1 week)	**Visit 6**[2] (Week 13 ±1 week)
Eligibility assessment of male & female	X	X[3]				
Informed consent (male and female)[9]	X					
PSA Serum[8]	X					

	Screening (5 or 4 weeks before Day 1)[1]	**Treatment Period (12 Weeks)**				**Follow-up Visit**
Hormonal assays (testosterone)[8]	X					
Genital examination	X				X	
BMI	X					
IIEF	X	X[4]	X	X	X	
EPIC + climacturia	X	X	X	X	X	
SEAR	X	X[4]	X	X	X	
Heart rate and blood pressure	X	X			X	
Penile length measurement	X				X	
24 hour pad weight and number of pads used	X				X	
Treatment		←	—	→		
MED3000 dispensing		X[5]				
Adverse events reporting (including device deficiencies)[6]	←	—	—	—	—	→
Concomitant treatment	←	—	—	—	—	→

[1] Patients using ED treatment (device or medication), a 5-week screening period will be observed (including 1 week washout). Patients not using any form of ED treatment only need to observe a 4-week screening period).
[2] Assessments at this Visit may be performed via Telehealth. The site will phone the patients to prompt them to complete the IIEF, SEAR, EPIC and climacturia questionnaires, if required in the

protocol schedule of assessments. The completed questionnaires will be brought to the site at the next scheduled on-site visit.
[3] Eligibility assessment at Visit 2 will consider whether the patient has had the 4 requested sexual intercourse attempts during the screening period and has a score of <= 25 on the IIEF-EF questionnaire at Visit 2.
[4] IIEF, EPIC, climacturia, and SEAR Baseline scores will be obtained at Visit 2
[5] At Visit 2, sufficient MED3000 will be dispensed to meet the needs of each patient's entire participation in the study (36 tubes)
[6] Adverse Events will be recorded from the point that patient and partner sign their respective informed consent forms.
[7] Visit 5 assessments will be undertaken for patients who withdraw from the treatment period prematurely
[8] PSA and testosterone samples do not need to be drawn if the patient has had these completed within 4 months of the Visit 1 visit. Samples may also be drawn at a timepoint between Visits 1 and 2 as long as they are available to assess eligibility at Visit 2.
[9] The female may sign the consent form at a date either prior to or after the patient provides consent. However, both patient and partner must sign their respective consent forms before any study related activity begins such as male lab draws and avoidance of erectogenic aids.

Study Visits

Screening Visit (Visit 1- on site): Patients and their respective partners will visit the site to be consented and have their eligibility assessed. If more convenient for the patient's partner, she may complete her in-person Visit 1on a date prior to or after the patient provides his consent. However, both patient and partner must have given consent before any study related activity is undertaken. PSA serum and hormonal assay samples will be taken. PSA and hormonal (testosterone) assay results are acceptable for review if completed within 4 months of Visit 1, completed on the day of Visit 1, or completed between V1 and V2 (e.g., during the screening period). Patients will complete the IIEF, EPIC, climacturia and SEAR questionnaires. The patient's penile length will be measured, 24-hour urine pad weight and number of pads used will be assessed, and concomitant treatment and AE information collected. The patient's BMI, heart rate and blood pressure will be measured, and a genital assessment of the patient performed.

Commented [AG1]: I have modified the requirement her because the female, in effect, is a participant in the study and the IRB may believe that their not being allowed a voice in the consenting process is unethical. Also, if the female refuses to participate then the assessments undertaken a V1 will have been unnecessary.

Baseline Visit (Visit 2- on site): Men will have their eligibility reaffirmed at the site. Patients will complete the IIEF, EPIC, climacturia and SEAR questionnaires and have their heart rate and blood pressure taken. If the patient continues to be eligible, MED3000 treatment will be dispensed and training on the use of the treatment provided to both the patient and, if present, their partner. The site will record any new or changes to existing AEs. Additionally, the site will record any new or changes to concomitant mediation being taken. Patients will be given paper copies of the IIEF, EPIC, climacturia and SEAR questionnaires to allow them to complete these assessments at TeleHealth Visits 3, and 4.

Visit 3 (phone -Week 4 (± 1 week): Patients will be asked to complete the paper IIEF, EPIC, climacturia and SEAR questionnaires. The patient will bring the completed questionnaires to the

site at Visit 5 Adverse events. Protocol compliance will be assessed by questioning the patient about their use of MED3000 and the number of unused tubes of MED3000 available. Patients will be asked about any changes to their concomitant medication and any new or changes to AEs (including their partner). Additionally, patients will be asked whether the patient or partner predominantly applied the gel to the glans penis prior to sexual intercourse.

Visit 4 (phone -Week 8 (± 1 week): Patients will be asked to complete the IIEF, EPIC, climacturia and SEAR questionnaires. The patient will bring the completed questionnaires to the site at Visit 5. Protocol compliance will be assessed by questioning the patient about their use of MED3000 and the number of unused tubes of MED3000 available. Patients will be asked about any changes to their concomitant medication and any new or changes to AEs (including their partner). Additionally, patients will be asked whether the patient or partner predominantly applied the gel to the glans penis prior to sexual intercourse.

Visit 5 (on-site -Week 12 (± 1 week): Patients have PSA serum samples taken and have a genital examination. Patients will also complete the IIEF, EPIC, climacturia and SEAR questionnaires. An assessment of the stretched flaccid penile length will be performed, heart rate and blood pressure will be measured. AEs, changes in concomitant treatment, and protocol compliance and a genital assessment will be assessed. The patient will return all used MED3000 tubes and unused MED3000 treatment at this visit and full verification of MED3000 usage compliance determined. The site will also perform an assessment of the patient's 24 hour pad weight and the number of pads used. Additionally, patients will be asked whether the patient or partner predominantly applied the gel to the glans penis prior to sexual intercourse.

Follow-up Visit 6 (phone-7 day post-study treatment, (± 2 days)): Patients will provide details about ongoing or new adverse events and any new concomitant treatment. Usage of erectogenic aids will also be recorded. Patient will be instructed to continue with his primary urologist for PSA monitoring per standard of care.

End of Study Definition

The study ends once the last patient enrolled in the study has undergone Visit 6 or lost to follow-up.

Assessment of Safety

Safety monitoring will be performed in the following manner: The investigator will routinely monitor each subject and their partner for the occurrence of AEs or any unusual medical occurrence. This will include a genital examination of the patient before and after MED3000

topical gel treatment, as well as interviews with each subject during each treatment visit and the Follow-up Visit. In addition, all subjects will be provided with a telephone number to call in case of medical emergencies, or to report AEs at any time.

The Principal Investigator will follow IRB policy that any Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) or Unanticipated Adverse Device Effects (UADE) are reported to the IRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. Additionally, the PI will maintain an Adverse Event Log for the duration of the study.

A description of each AE will be recorded including the date of onset, time course, severity, relatedness to study treatment, action taken regarding the study treatment, outcome, and any treatment administered. The investigator will list the specific diagnosis, disease, or syndrome rather than associated signs and symptoms.

All serious adverse events ("SAEs") will be followed by the investigator until resolution or stabilization and reported to the IRB as per the local requirements. Any SAE that is related to MED3000 treatment, or is a not expected occurrence, will be reported within 24 hours of knowledge of the event to the device provider (Futura Medical Developments Limited).

Occurrence of an SAE during the treatment period may result in termination of study treatment.

A subject may be withdrawn by the investigator, regardless of consent, if the investigator determines health and/or safety concerns preclude continuation of investigational product treatment.

Adverse Events

AEs will be monitored and assessed throughout a patient's involvement in the study (from the point of signing the ICF to the follow up visit (Visit 6). At each study visit, the site staff will ask the patient about any AEs the patient and their partner may have experienced. The site study staff will also ask the patient about any device deficiencies that they experienced.

Adverse Event Grading Scheme

Causality/relationship and intensity of an AE to the device, or affected site will be determined by the investigator and will be classified as one of the following:

Unrelated	The event is clearly related to an event that may be due to environmental or accidental occurrence or other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Possibly related	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and/or follows a known response pattern to the study drug or device, but could have been produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Probably related	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and follows a known response pattern to the study drug or device, and cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Related	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and follows a known response pattern to the study drug or device, and cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, and either occurs immediately following study drug administration or use of device or improves on stopping the study drug or device, or reappears on repeat exposure.

Severity: events will be classified as outlined in the below table, which reflects the Common Terminology for Adverse Events ("CTCAE") scale.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

A Serious Adverse Event ("SAE") is an AE that meets one or more of the following criteria:

- Fatal;
- Life threatening;
- Results in an unanticipated or prolonged hospitalization;
- Results in a significant and persistent disability/incapacity;
- Results in a congenital anomaly or birth defect.

Adverse Device Effect (ADE)

An AE related to the use of the investigational medical device. This

definition includes:

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device (malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with this protocol)
- Any event resulting from use error or from intentional misuse of the investigational medical device (user error is user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user)

Device Deficiencies

Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is any AE that leads to any of the following:

- Death
- A serious deterioration in the health of the patient or the patient's partner by one or more of the following:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function including chronic diseases, or
    - In-patient or prolongation of hospitalization, or
    - Medical or surgical intervention to prevent a life-threatening illness or injury, or permanent impairment to a body structure or body function
- Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: In this study, planned hospitalization for a pre-existing condition, or procedure required by the protocol without serious deterioration in health will not be considered an SAE. SAEs will be reported to the Institutional Review Board and other required authorities within the required timeframe.

Serious Adverse Device Effect (SADE)

An ADE which results in any of the consequences as characterized in an SAE.

Serious Health Threat

Signal from any AE or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in patients, users or other persons, and that requires prompt remedial action for other patients, users or other persons. A device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Unanticipated Serious Adverse Device Effect (USADE)

A SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. In some regions, this may be referred to as an Unanticipated Adverse Device Effect.

AEs/ADEs will be collected from the signing of the ICF at screening (Visit 1) until the end of the investigation. Any AEs that are unresolved at the patient's last AE assessment during the

investigation (i.e. at the patient's final investigation visit) are to be followed up by the PI for as long as medically indicated, but without further recording in the eCRF. FMD retains the right to request additional information for any patient and/or their female partner with ongoing AE(s)/SAE(s) at the end of the investigation, if judged necessary.

All AEs/ADEs will be recorded in the patient's paper diary and entered into the eCRF after review by the PI or suitable qualified designee (e.g. sub-investigators) at the next investigation visit. The details to be recorded are:

- The date of the AE/ADE onset and its resolution
- Treatment (if any)
- Seriousness
- Relationship to the investigational device or control and the related procedure

Any SAE/SADE/USADE will be notified by the PI or designee to the IRB and other authorities as per local regulations and requirements.

Concomitant Treatment

The use of any concomitant treatment will be monitored throughout the study from the point of signing the ICF at Screening Visit (Visit 1) until the final study visit. The site will ask the patient about any concomitant treatment the patient is taking or any changes in concomitant treatment at each of the study visits.

Patients are not permitted to take other forms of erectogenic treatment during their participation in the study. Erectogenic treatments may include PDE5i inhibitors such as sildenafil citrate, vardenafil and tadalafil or mechanical devices used to treat erectile dysfunction.

Central/Local Laboratories

Analysis of serum PSA and hormonal (testosterone) assessment will be performed by Mass General Brigham central clinical laboratory or another certified laboratory (if the patient prefers).

7. Risks and Discomforts

Anticipated Adverse Events Associated with MED3000 topical gel:

- Penile pain/discomfort
- Headache

Adverse Events Associated with Blood Draws

- Infection at blood sampling site
- Pain at blood sampling site
- Hematoma or thrombus
- Extensive bleeding
- Nerve Damage
- Vasovagal reaction Syncope, fainting
- Allergic Reaction

Of note, in regard to patients status-post radical prostatectomy for prostate cancer, approximately 20-40% of patients with clinically localized prostate cancer may present tumor biochemical recurrence after radical prostatectomy. There is no anticipated risk of biochemical recurrence with MED3000 topical gel.

All SAEs will be recorded and reported to IRB as required by their regulations.

8. Benefits

Patients may not directly benefit from taking part in this research study. Other men with post-radical prostatectomy erectile dysfunction and their female partners may benefit in the future from what we learn in this study.

Patients may benefit from improvements in erectile function and quality of life.

9. Statistical Analysis

Sample size calculation

It is planned to enrol and treat approximately 20 patients for a 12-week treatment duration. There is no formal sample size calculation performed. This is an exploratory study for treatment of novel patient population without precedent.

Statistical analysis

Baseline characteristics of the trial participants will be summarized using the following baseline data. Mean, median, minimum, maximum and standard deviation or proportion (as appropriate) will be reported.

- Age
- Baseline comorbidities
- BMI
- Baseline IIEF/ SEAR/EPIC (+climacturia question) (following 4 week screening period)
- 24 hour pad weight
- 24 hour pad number usage
- Stretched penile length
- Prostate cancer stage (surgically-verified)

Full Analysis Set: Patients who received at least one dose MED3000 topical gel treatment.

Per-protocol Analysis Set: Patients who meet the inclusion/exclusion criteria and who have completed all the treatment and follow-up sessions up to the 12-week visit.

Analysis of Primary Efficacy Endpoint

The primary efficacy assessment is the mean change in IIEF-EF from baseline (post 4-week washout) at 12 weeks. The observed primacy efficacy assessment will be compared to the MCID of 4.

Analysis of Secondary and Safety Endpoints

The secondary assessments are:

- Mean change from baseline in all domains of the IIEF at 4, 8 and 12 weeks, besides the IIEF-EF at 12 weeks.
- Mean change from baseline in SEAR, EPIC at 4, 8 and 12 weeks
- Mean change from baseline in stretched flaccid penile length at 12 weeks
- Proportion of patients on penile injection therapy or penile implant at 12 months follow-up
- Mean change in 24 hour pad weight and 24 hour pad number usage at 12 weeks
- Serum PSA indicative of biochemical recurrence
- Proportion of patients who experienced treatment-related adverse events

Continuous variables: Estimates of mean changes from baseline, along with 95% confidence intervals, will be produced. The change from baseline in endpoints within the group will be analysed by one-sample t-tests with a two-sided significance threshold of p=0.05, testing the null hypotheses of mean change from baseline equal to zero. Covariates / sub-groups may also be evaluated such as age and comorbidities.

Discrete variables: Estimates of proportions, along with 95% confidence intervals, will be produced.

Any missing, impossible (inconsistent with human life) or inconsistent recordings in the Case Report Forms will be referred back to the Principal Investigator and documented for each individual patient before clean file status is declared. Missing data will not be imputed.

Data will be analyzed with Microsoft Excel, Graphpad Prism 7, or equivalent statistics software. Efficacy endpoints will be analysed after the last patient has completed all follow up visits.

10. Monitoring and Quality Assurance

The principal investigator will provide monthly status updates to FMD in regard to any unanticipated AEs, SAEs etc. in addition to standard reporting of such events to IRB.

Withdrawal Criteria

- Occurrence of a serious adverse event during the treatment period will result in termination of MED3000 topical gel treatment.
- A subject may be withdrawn from MED3000 topical gel treatment by the investigator, regardless of consent, if the investigator determines health and/or safety concerns preclude continuation of investigational product treatment. If a subjective is not sufficiently cooperative may be grounds for dismissal from trial participation.
- A subject may be withdrawn from the study by the investigator in the event that a late inclusion/exclusion criteria violation is found to have occurred and there are corresponding health and/or safety concerns.
- Tumor recurrence (defined as biochemical recurrence: serum PSA ≥ 0.2 ng/ml) during the MED3000 treatment period will result in immediate withdrawal from the study such that adjuvant/salvage therapies for cancer control will be needed.
- A subject may withdraw from the study at any time, for personal reasons or otherwise.

Information regarding the timing and type of withdrawal (treatment and/or study) will be documented. Information collected for study purposes may be maintained and used by investigators after study withdrawal has occurred, but no new information will be collected after that time. Subject withdrawal due to an AE will be distinguished from withdrawal due to other reasons by appropriate documentation.

Stopping / discontinuation rules

Completion of trial is defined as the point at which the last patient enrolled in the study has completed the visit 6 (week 13) follow-up phone call visit or withdrawn from the study.

Although unlikely to occur, the study may also be terminated early if recurrent serious protocol deviations are reported, and/or the study team is unable to continue (e.g. manpower or financial issues). In this case, a report will be filed with the IRB within 1 month, and all treated patients

will continue to be followed up until follow-up visit (Visit 6) if possible and undertake the assessments scheduled for each visit.

The final clinical study report will document the reasons for trial discontinuation if it occurs.

Deviations from the Protocol

Emergencies excepting, under no circumstances will prospective deviations (waivers) from the approved Clinical Investigation Plan and subsequent amendments be permitted. Any changes to the approved protocol should be covered by an amendment which will be approved by the necessary Regulatory Authorities and/or IRB as necessary.

All deviations that are identified during the course of the study, be they major or minor in severity, will be recorded on a protocol deviations tracking log. This log will be reviewed by the site staff periodically for risk and trend evaluation purposes, and corrective and preventative actions taken as necessary. Futura will be notified of all protocol deviations as part of the PI's periodic update reports.

Monitoring, quality control and assurance

The study coordinator or designee is responsible for quality control of the data.

The manufacturer (Futura Medical Developments Ltd) or appointed party has the option to monitor the data and perform onsite monitoring visits to ensure the precision, quality, and integrity of the data collected. The investigator(s) agrees to permit access to study records, source data, and source documents for this purpose

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research

- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections

Each enrolled subject will have a study ID substituted for names and MRNs and no identifiers will be included on their paperwork or electronic study record. All electronic data will be stored on Partners built computers updated with the latest anti-virus software and stored in locked offices on the BWH campus.

12. References

1. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the international index of erectile function scale. *Eur Urol*. 2011;60(5):1010-1016. doi:10.1016/j.eururo.2011.07.053
2. PC W. Anatomic radical prostatectomy: evolution of the surgical technique. *J Urol*. 1998;160(6 Pt 2):2418-2424. doi:10.1097/00005392-199812020-00010
3. Montorsi F, Brock G, Stolzenburg J, et al. Effects of Tadalafil Treatment on Erectile Function Recovery Following Bilateral Nerve-sparing Radical Prostatectomy : A Randomised Placebo-controlled Study (REACTT). 2014;65:587-596. doi:10.1016/j.eururo.2013.09.051
4. Capogrosso P, Vertosick EA, Benfante NE, et al. Are We Improving Erectile Function Recovery After Radical Prostatectomy ? Analysis of Patients Treated over the Last Decade. *Eur Urol*. 2018;75(2):221-228. doi:10.1016/j.eururo.2018.08.039
5. Futura Medical Developments L. A phase III, dose-ranging, multi-centre, randomized, doubleblind, placebo-controlled, home use, parallel group clinical trial of topically-applied glyceryle trinitrate (GTN) for the treatment of erectile dysfunction (ED), with an open label extension. Fut. 2020.
6. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49(6):822-830. http://www.ncbi.nlm.nih.gov/pubmed/9187685. Accessed March 16, 2016.
7. Rosen RC, Cappelleri JC, Gendrano N. The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int J Impot Res*. 2002;14(4):226-244. doi:10.1038/sj.ijir.3900857
8. JC C, RC R, MD S, A M, IH O. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology*. 1999;54(2):346-351. doi:10.1016/S0090-4295(99)00099-0
9. Cappelleri JC, Althof SE, Siegel RL, Shpilsky A, Bell SS, Duttagupta S. Development and validation of the Self-Esteem and Relationship (SEAR) questionnaire in erectile dysfunction. *Int J Impot Res*. 2004;16(1):30-38. doi:10.1038/sj.ijir.3901095
10. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*. 2010;76(5):1245-1250. doi:10.1016/j.urology.2010.01.027
11. Ted A. Skolarus1, 2, 3, Rodney L. Dunn1, Martin G. Sanda4, Peter Chang5, Thomas K.

Greenfield6, Mark S. Litwin7, John T. Wei1 and the PC. Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology*. 2015;85(1):101-106. doi:10.1016/j.urology.2014.08.044.Minimally

12. Fisher WA, Gruenwald I, Jannini EA, et al. Standards for Clinical Trials in Male and Female Sexual Dysfunction: III. Unique Aspects of Clinical Trials in Male Sexual Dysfunction. *J Sex Med*. 2017;14(1):3-18. doi:10.1016/j.jsxm.2016.08.016

APPENDICES

APPENDIX 1

INTERNATIONAL INDEX
OF ERECTILE FUNCTION
(IIEF)

Subject Questionnaire

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. In answering the questions, the following definitions apply:

- sexual activity includes intercourse, caressing, foreplay & masturbation
- sexual intercourse is defined as sexual penetration of your partner
- sexual stimulation includes situation such as foreplay, erotic pictures etc.
- ejaculation is the ejection of semen from the penis (or the feeling of this)
- orgasm is the fulfilment or climax following sexual stimulation or intercourse

---

	Over the past 4 weeks:	*Please check **one** box only*
☐ Q1	How often were you able to get an erection during sexual activity?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	During sexual 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 or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	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

☐ Q6	How many times have you attempted sexual intercourse?	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	When you attempted sexual intercourse, how often was it satisfactory for you?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q8	How much have you enjoyed sexual intercourse?	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	When you had sexual stimulation or intercourse, how often did you ejaculate?	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	How often have you felt sexual desire?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	How would you rate your level of sexual desire?	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	How satisfied have you been with your overall sex life?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	How satisfied have you been with your sexual relationship with your partner?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	How do you rate your confidence that you could get and keep an erection?	1 Very low 2 Low 3 Moderate 4 High 5 Very high

APPENDIX 2

Self-Esteem And Relationship (SEAR) Questionnaire

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

1. I felt relaxed about initiating sex with my partner.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

2. I felt confident that during sex my erection would last long enough.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

3. I was satisfied with my sexual performance.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

Self-Esteem and Relationship Questionnaire
Version 2: 20FEB02 PPG Mens/Womens Health Team

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

4. I felt that sex could be spontaneous.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

5. I was likely to initiate sex.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

6. I felt confident about performing sexually.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

7. I was satisfied with our sex life.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

8. My partner was unhappy with the quality of our sexual relations.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

9. I had good self-esteem.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

10. I felt like a whole man.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

11. I was inclined to feel that I am a failure.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

12. I felt confident.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

13. My partner was satisfied with our relationship in general.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never

14. I was satisfied with our relationship in general.

- ☐ Almost always/always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never/never