Memorial Sloan-Kettering Cancer Center
IRB Protocol

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A Randomized Trial of Pharmacological Penile Rehabilitation in the Preservation of Erectile Function Following Bilateral Nerve-Sparing Radical Prostatectomy

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

The purpose of this study is to define if the use of nightly sildenafil after radical prostatectomy results in better erectile function outcomes than nightly placebo for men who have undergone this operation. The study is also designed to compare erectile function outcomes between men using regular sildenafil and those using regular penile injections. Patients undergoing either laparoscopic or open nerve-sparing radical prostatectomy, who meet the inclusion and exclusion criteria, will be asked to participate in the study. Patients will be randomized into one of the three arms:

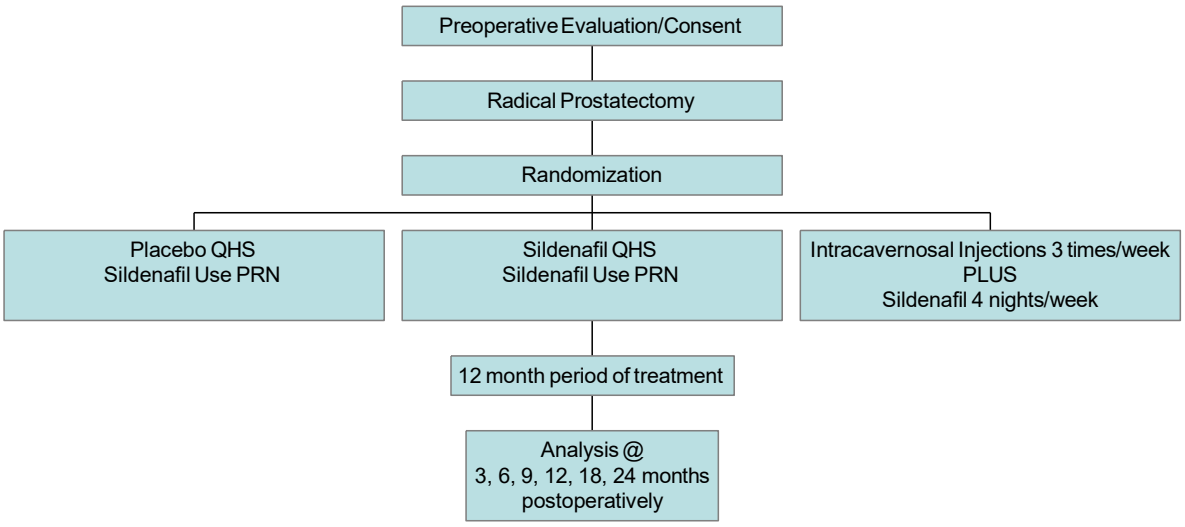
1. **PRN Sildenafil Arm**: Patients will use sildenafil 100 mg PRN for sexual relations. Patients will take placebo (blinded) at night regularly, except on nights when the sildenafil 100 mg pill is taken. There will be 40 patients in this group.

2. **Nightly Sildenafil Arm**: Patients will use sildenafil 100 mg PRN for sexual relations. Patients will take sildenafil 50 mg (blinded) at night regularly, except on nights when the sildenafil 100 mg pill is taken. There will be 80 patients in this group.

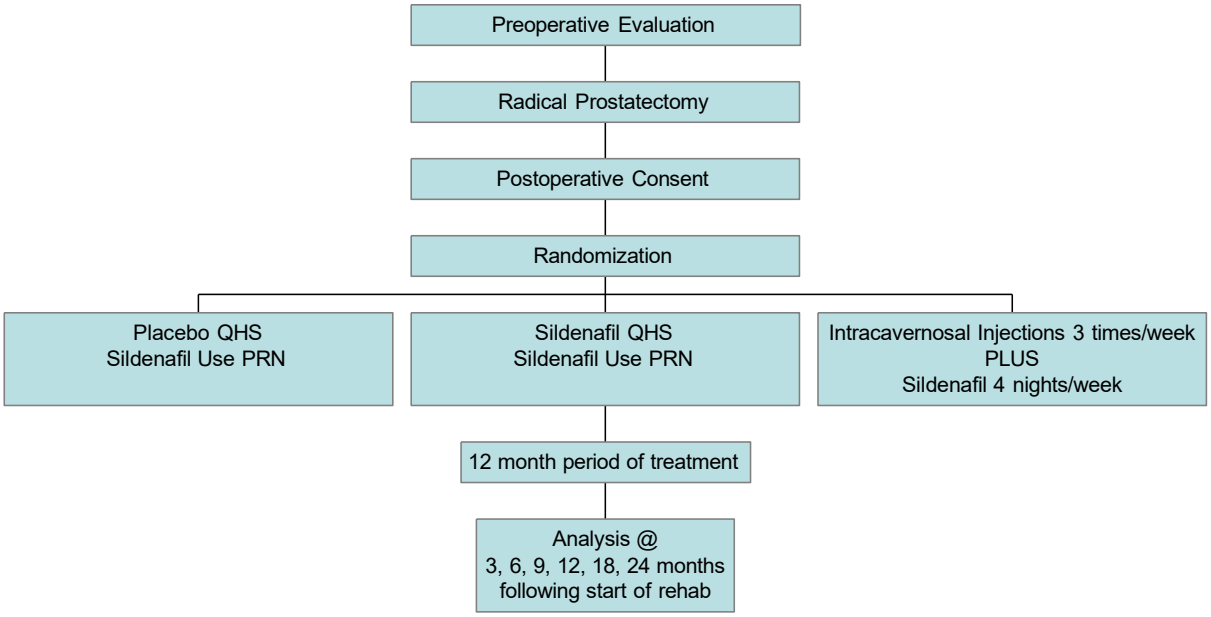
3. **Combination Therapy Arm**: Intracavernous injections of a trimix combination (Papaverine 30 mg/mL, Phentholamine 1 mg/mL, Prostaglandin E1 10 mcg/mL) will be injected three times a week and sildenafil 50 mg taken on the other four (non-injection) nights. Injection therapy can be used for the purposes of sexual relations. There will be 80 patients in this group.

Patients have the option of consenting either preoperatively or up to 6 weeks postoperatively.

Preoperative consent: Patients will be evaluated in the clinic and will complete the questionnaires at baseline (before surgery) and 3, 6, 9, 12, 18, and 24 months postoperatively. At 12 months postoperatively, all patients will stop treatment.



Postoperative consent: Patients will be evaluated in the clinic and will complete the questionnaires retrospectively (after surgery) and 3, 6, 9, 12, 18, and 24 months after starting rehab. At 12 months after starting rehab, all patients will stop treatment.



The estimated time to completion of enrollment is 18-24 months. Patients will be monitored for a total of 24 months. Visits 3, 6, 9, 12, 18, and 24 months will have ±2 week window.

	Baseline	3 Months (±2 weeks)	6 Months (±2 weeks)	9 Months (±2 weeks)	12 Months (±2 weeks)	18 Months (±2 weeks)	24 Months (±2 weeks)
Routine Blood Test	X						
Liver Function Blood Test		X	X	X	X	X	X
Sitting and Standing Blood Pressure and Pulse	X	X	X	X	X	X	X
International Index of Erectile Function Questionnaire (IIEF)	X	X	X	X	X	X	X
Pill Diary/Sexual Encounter Diary		X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X

2.1 OBJECTIVES AND SCIENTIFIC AIMS

The objective of this study is to analyze the ability of 3 different pharmacological strategies to preserve the ability of men to achieve spontaneous (non-medication assisted) functioning erections after bilateral nerve-sparing radical prostatectomy.

Primary End-Point: Difference in the erectile function (EF) domain score of the International Index of Erectile Function (IIEF) between the 3 groups at 24 months.

Secondary End-Points:

- The time to return of spontaneous functional erections
- The time for patients to respond to oral erectogenic therapy
- The proportion of patients who have normalization of their erectile function (normalization of the EF domain of the IIEF)

3.0 BACKGROUND AND RATIONALE

It is estimated that 10% of all men presenting with erectile dysfunction (ED) suffer the condition, as a result of surgical procedure, typically, radical pelvic surgery. ED is associated with a significant decrease in self-esteem, loss of productivity and relationship discord. Many treatments that restore erectile function have been demonstrated to increase quality of life for both patient and partner. Over the past 10 years there has been a recrudescence in interest in clinical and basic scientific research in post-radical prostatectomy erectile dysfunction. Major discrepancy exists in the literature regarding postoperative potency rates with spontaneous erectile function occurring in 30-80% of patients. Thus, despite the advent of nerve sparing techniques a significant percentage of men continue to suffer from erectile impairment following this operation. It is estimated that 50,000 men undergo radical prostatectomy in the USA alone each year. It has been postulated lately, that the development of transient ED following nerve-sparing surgery due to trauma to the cavernous nerve might trigger a process of damage to the endothelial and smooth muscle cavernous tissue that in turn can induce permanent veno-occlusive ED. Furthermore, preliminary data suggest that the regular erectile activity induced by pharmacological agents may translate into improved preservation of spontaneous erections following bilateral nerve sparing surgery.

Mechanisms of Post-Prostatectomy Erectile Dysfunction

Mechanistically, post-RP ED may be neurogenic, arteriogenic, venogenic, or mixed vascular (arteriovenogenic) in nature. Neurogenic impotence, while obviously occurring after cavernous nerve interruption, may also occur transiently following cavernous nerve traction and/or dissection. Even in the hands of expert nerve sparing surgeons, temporary neural trauma may occur. It is believed that the primary mechanism of development of arteriogenic erectile dysfunction results from transection of the accessory pudendal arteries, and venogenic impotence is based upon corporal smooth muscle collagenization and fibrosis and this is most probably the result of either apoptosis associated with neural injury and/or disuse atrophy. The

venocclusive mechanism is a major determinant of success with vasoactive therapies, indeed, most of the patients failing to respond to erectogenic pharmacologic therapy have venous leak contributing to their ED. The venocclusive mechanism is dependent upon appropriate corporal smooth muscle expansion with resultant occlusion of the subtunical venules. Failure to expand the corporal smooth muscle adequately because of structural alterations in the tissue results in failure to compress the subtunical venules present between the corporal smooth muscle and the tunica albuginea resulting in venous leak. Corporal smooth muscle integrity is believed to be dependent upon 2 factors, cavernosal tissue oxygenation (as occurs during penile erection) and neural integrity (neural injury has been shown to lead to apoptosis and corporal smooth muscle fibrosis).

In previous work, Mulhall et al have examined the chronology of venous leak development post-radical prostatectomy in patients with excellent preoperative erectile function who developed postoperative erectile dysfunction. The incidence of venous leak, (suggestive of permanent, irreversible structural damage to the erectile tissue) was 8% less than four months postoperatively, 22% four to eight months postoperatively and 50% eight to twelve months postoperatively. In this analysis no patient was treated with postoperative pharmacotherapy in any regimented fashion. More recent data, from our clinical database, has indicated that the post-RP penile vascular status is predictive of return of spontaneous erections, degree of erectile rigidity, and response to sildenafil citrate (unpublished to date). The data also indicate that the prognosis is poor for the return of functional erections in the presence of abnormal end diastolic velocity values.

Rationale for the Use of Nightly Viagra Postoperatively

Sildenafil is a PDE5 inhibitor, which has been shown to be effective in men with erectile dysfunction of various etiologies including post-RP. It has also been demonstrated to increase the recovery of erectile function after cavernous nerve injury in human and animal models.

Sildenafil citrate (Viagra) enhances the effects of nitric oxide (NO), a signaling molecule that has a diverse range of physiological effects in many tissues, including promoting relaxation of smooth muscle in the walls of blood vessels and the erectile tissue within the corpora cavernosa of penis. The effect of NO on smooth muscle is mediated by cyclic guanosine monophosphate (cGMP); sildenafil works by inhibiting the enzyme, cGMP-specific phosphodiesterase type 5 (PDE5), that degrades cGMP. Experience has established the role of sildenafil citrate in the treatment of erectile dysfunction (ED). The efficacy of sildenafil for ED post-radical prostatectomy has been studied. In the seminal publication by Goldstein et al, subpopulation analysis suggested a 43% responder rate (GAQ positivity) for this population. Since then in numerous prostatectomy specific studies, sildenafil has been identified as a useful management strategy to facilitate men resuming sexual relations.

A recent Pfizer sponsored study assessed the utility of daily sildenafil citrate administration on the recovery of spontaneous erectile function after radical prostatectomy. In a randomized fashion, 25 men were treated with 50 mg daily, 25 with 100 mg daily and 25 were treated with

placebo. Therapy was instituted at 4 weeks postoperatively and lasted 38 weeks. Analysis was conducted at 48 weeks following RP. The criteria for inclusion were rigorous, patients requiring a combined score of 8 from questions 3 and 4 on the IIEF questionnaire as well as at least one 55% erection on nocturnal penile tumescence and rigidity analysis. Success was defined as preservation of the score of 8 on questions 3 and 4 of the IIEF. No difference was seen in the success rate between the 50 mg and 100 mg arm of the study. However, 27% of men in the treatment arm compared to 4% of men in the placebo arm had preservation of preoperative erectile function. While cavernosal oxygenation may be a contributor to these results, most of these patients did not obtain an erection in response to sildenafil early postoperatively, thus other factors must be at play.

While much of the attention has been focused on corporal smooth muscle in the study of post prostatectomy ED, it is appreciated that the endothelium plays a major role in erection and thus maintaining endothelial health following RP may improve long-term spontaneous erectile function outcome. Desouza et al utilized flow-mediated dilation (FMD) of a transiently occluded brachial arteries as a model assessing nitric oxide dependent endothelial function. In their study, 14 patients with both type II diabetes and erectile dysfunction were enrolled. Following the baseline measurement of brachial artery width patients received 25 mg sildenafil, and an hour later the acute phase FMD was measured. Patients continued sildenafil 25 mg once daily for 14 weeks. 24 hours after the last sildenafil dose chronic phase FMD was measured. In both the acute and chronic phase of treatment patients in the treatment arm had a significantly greater FMD than the placebo-controlled group, thus indicating that sildenafil enhanced endothelial function. The positive effects of sildenafil on endothelium has been confirmed in men with cardiovascular disease. In the laboratory of Dr. Mulhall, daily administration of sildenafil in the rat model of cavernous nerve crush injury has resulted in better preservation of endothelial staining (using CD31 immunohistochemistry) and reduction in apoptotic indices (on TUNEL assay). Unpublished data from Pfizer indicates that sildenafil has a positive impact on the PI3/AKT/eNOS pathway.

Rationale for the Use of Regular Intracavernosal Injections Postoperatively

The relationship between hypoxia and cavernosal fibrosis has been documented in several studies (11), it is thought that hypoxia induces TGF-beta1 that in turn accelerates collagenization of the corpus cavernosum smooth muscle, while at the same time, decreasing the level of PGE1 that help protect from fibrosis (12). Since, hypoxia of cavernous tissue is related to the blood supply and the greatest blood supply occur at time of erection any neural damage that results in ED may expose the cavernous tissues to longer periods of hypoxia. Leungwattanakij et al (13) demonstrated in a cavernous neurotomy rat model that sharp neural injury resulted in an increase in hypoxia inducible factor-1 (HIF-1alpha) and TGF-beta1 as well as increase in cavernous tissue collagen synthesis. In a landmark study, Montorsi et al (5) based a study on the assumption that the events of nocturnal erection supply the cavernous bodies with oxygenation that might protect them from developing fibrotic changes during the transient period of erectile dysfunction following nerve sparing radical prostatectomy. In their study they treated patients with 3 weekly intracavernousal injections of Alprostadil. This in

turn would ensure that when the erectile function would resume the secondary fibrotic changes to the penile tissue would not be sever enough to cause erectile dysfunction on their own. In this prospective study 30 patients were enrolled, all potent, all had nerve-sparing RP. 15 received 3 weekly injections for 15 weeks. 12 completed the treatment. Although the trial was small, the difference between treatment and control group was statistically significant. (Treatment group - 67% had erections sufficient for intercourse versus. 20% in the Control group - $p < 0.01$) However, to date this is the only randomized evidence supporting the role of penile rehabilitation with intracavernosal injections after radical prostatectomy. There is a need for a larger confirmatory study particularly using a modality that avoids intracavernosal injections. Intracavernosal injection therapy was originally discovered in 1983. In 1985, trimix, in the form of papaverine/phentolamine/prostaglandin E1 was introduced. It is efficacious in approximately 90% of patients with ED.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Patients undergoing either laparoscopic or open nerve-sparing radical prostatectomy, who meet the inclusion and exclusion criteria described in section 6.0, will be asked to participate in the study. Patients will be randomized into one of three arms and assigned a study number from CRDB (unrelated to their medical record number):

1. **PRN Sildenafil Arm**: Patients will be instructed to try and resume their sexual life according to their ability; patients interested in using medication for sexual activity, will be offered sildenafil 100 mg to be used before intercourse on an as-required basis. They will be given six 100 mg doses, per month, for a 12 month duration. Each patient in this group will use a placebo pill (blinded) each night, except on a night that 100 mg is taken for the purpose of sexual relations. This group can be considered to constitute "usual care" as it represents the current approach to penile rehabilitation in the community. We estimate, in the first 3 months, most people will not use sildenafil at all, after this, probably no more than once per week on average. The total expected dose in the PRN group is about 4000 mg over the course of the year. There will be 40 patients in this group.

2. **Nightly Sildenafil Arm**: Patients will be instructed to take sildenafil 50 mg (blinded) at night regularly, even when intercourse is not planned. These patients will be instructed to take 100 mg pill on occasions that they are interested in sexual relations. On these occasions, they will forego the usual nightly pill. They will be given six 100 mg doses, per month, for a 12-month duration. There will be 80 patients in this group.

3. **Combination Therapy Arm**: Intracavernous injections of a trimix combination (Papaverine 30 mg/mL, Phentholamine 1 mg/mL, Prostaglandin E1 10 mcg/mL) will be injected three times a week, and sildenafil 50 mg taken on the other four

(non-injection) nights. Injection therapy can be used for the purpose of sexual relations. There will be 80 patients in this group.

Preoperative consent: Patients will be evaluated in the clinic and will complete the questionnaires at baseline (before surgery) and 3, 6, 9, 12, 18 and 24 months after surgery. At 12 months postoperatively, all patients will stop treatment. Visits 3, 6, 9, 12, 18, and 24 months will have ±2 week window.

Postoperative consent: Patients will be evaluated in the clinic and will complete the questionnaires retrospectively (after surgery) and 3, 6, 9, 12, 18 and 24 months after starting rehab. At 12 months after starting rehab, all patients will stop treatment. Visits 3, 6, 9, 12, 18, and 24 months will have ±2 week window.

4.3 Blinding

Preoperative consent: Patients are to be consented and registered as pending prior to their surgery. Full registration and randomization will occur immediately following surgery, if nerve bundles have been spared.

Postoperative consent: Patients may also consent to the study up to 6 weeks postoperatively at which point they will be registered and randomized immediately following informed consent in clinic.

The blind 50 mg pills will be taken last thing at night, before the patient goes to bed without sexual stimulation (100 mg will be used for sexual relations). Thus, the chances of a man having an erection that would "unblind" him is remote. Furthermore, in the first 9 months after surgery, very few men will respond to any PDE5 inhibitor medication because of the intra-operative transient nerve injury. Finally, it takes on average, one hour before an erection can occur, and this must be in the setting of sexual stimulation. Thus, the patient will likely be asleep at this time. Hence, we believe that patients will remain blinded to whether they are on active or placebo sildenafil. Nonetheless, blinding will be assessed at the end of the study.

4.4 Intervention

Three interventions are to be used:

1. **PRN Sildenafil Arm**: Patients will be instructed to take placebo QHS (blinded) except on nights that they are interested in sexual relations, they will then be instructed to use sildenafil 100 mg (open-label) and skip the placebo dose. Placebo will start within 24-48 hours after registration. There will be 40 patients in this group.

2. **Nightly Sildenafil Arm**: Patients will be instructed to take sildenafil 50 mg QHS (blinded) except on nights that they are interested in sexual relations, they will then be instructed to use sildenafil 100 mg (open-label) and skip the 50 mg dose. Sildenafil treatment will start within 24-48 hours post-surgery. There will be 80 patients in this group.

3. **Combination Therapy Arm**: Trimix combination (Papavarine 30 mg/mL, Phentholamine 1 mg/mL, Prostaglandin E1 10 mcg/mL), at initial dose of 5 units (0.05 mL) will be given; the first 2 injections will be done in the MSKCC urology outpatient clinic (if needed, the investigator can determine appropriate amount of injections for patient training). The patients will be instructed, by the sexual medicine nurse practitioner, on the technique of injection and dose titration, as well as the limitations, contra-indications, side effects and alternatives. The dosing data will be entered into electronic medical record or patient medical record by the NP. The dose being used cannot be altered by a patient. For safety reasons all dose adjustments are conducted by phone with the NP.

   For the first 2 weeks after registration, patients will use nightly sildenafil 50 mg before commencing penile injections 2 weeks (+3 days) later. Sildenafil treatment will start within 24-48 hours after registration. Patients will inject three times per week and use sildenafil 50 mg on the other four nights. In this arm, patients will be instructed to obtain 3 penetration hardness (≥ 60% rigidity) erections per week. There will be 80 patients in this group.

4.5 Treatment Start Time

Preoperatively: Patients scheduled for Monday-Thursday surgery will begin treatment 24-48 hours after surgery. Patients scheduled for Monday-Thursday surgery that remain in the hospital longer than 24-48 hours for recovery will begin their treatment the night they return home. Patients scheduled for Friday and Saturday surgery may have their registration completed on Monday to begin treatment Tuesday night. Pharmacy will express deliver the medication to the patient's home if they have been discharged.

Postoperatively: Patients that consent in clinic up to 6 weeks postoperatively will begin taking their medication 24-48 hours after being registered and randomized in clinic.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Sildenafil citrate is a PDE5 inhibitor manufactured by Pfizer, who will supply the medication as well as its placebo. This medication will be maintained by the MSK pharmacy.

Each site will receive a stipend for the purchase of the intracavernosal vasoactive agent trimix combination. This agent is composed of 3 medications: Papaverine 30 mg/mL, Phentholamine

1 mg/mL, Prostaglandin E1 10 mcg/mL. The pharmacy will maintain the supply of injection medication in a refrigerated state.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Male, must be ≥ 18 years of age, with histologically confirmed prostate adenocarcinoma, that is clinically localized to the prostate gland
- Stable sexual relationship for ≥ 6 months
- Open or laparoscopic bilateral nerve-sparing radical prostatectomy
- Baseline score of ≥ 22 on the International Index of Erectile Function Domain (Appendix A)
- Able to speak, read and write in the English language
- Calculated creatinine clearance (using the 4 variable MDRD equation based on serum creatinine, age, race, and gender) of > 60 cc/min
- Patient is able to walk up two flights of stairs briskly without chest pain
- Patient needs to have their baseline sitting AND standing blood pressure and pulse done at the time of consent

6.3 Subject Exclusion Criteria

- Preoperative or planned postoperative pelvic radiation therapy
- Preoperative or planned postoperative androgen deprivation
- Presence of Peyronie's disease at baseline
- Presence of a penile prosthesis at baseline
- Resection of one or both nerve bundles at surgery
- Any contraindications to sildenafil:
    - Patient is currently using nitrates;
    - Presence of retinitis pigmentosa;
    - Presence macular degeneration;
    - MI or CVA within 3 months;
    - Patient is currently using MAOI medications
- Patient is taking using alpha blockers
- Patient is taking potent inhibitor of cytochrome P450 CYP3A4 (e.g., Ketoconozole)
- Patient has hepatic impairment
- Patient has history of substance or alcohol abuse
- Patient is currently using penile self injection medication (Trimix, Bimix, or PGE-1)
- Patient requiring sildenafil for penetration
- Use of sildenafil within 30 days of consent

7.1 RECRUITMENT PLAN (WITH LIMITED WAIVER OF AUTHORIZATION)

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

A total of 200 patients will be enrolled. Given that MSK does approximately 850 radical prostatectomies annually, we estimate that it will take approximately 18 months to 24 months to complete enrollment. Given the baseline erectile function of the general radical prostatectomy population, it is likely that approximately 50% of patients will be eligible.

Patients scheduled for nerve-sparing open or laparoscopic RP will be advised of the study. Those expressing interest will be screened. If eligible, they will be randomized (see Section 14.0) to one of the three arms in a 1:2:2 ratio.

8.0 PRETREATMENT EVALUATION

After subjects are assessed for baseline inclusion and exclusion criteria, eligible patients will be approached. Only patients meeting all pre and post-operative criteria will be included. Patients will complete the IIEF (Appendix A) preoperatively if they consent before surgery or retrospectively if they consent after surgery, and must have a score of ≥ 22 on the Erectile Function Domain. Patients will have standard blood and urine tests to check the function of their organs (e.g. kidney, liver). Patients will also have a sitting and standing blood pressure and pulse done.

Preoperative consent: Patients will be registered as pending on the day of consent.

Postoperative consent: Patients will be registered if they consent within 6 weeks after surgery.

After registration, subjects will be randomized into one of the three previously described study groups and instructed accordingly. Patients will be given a pill diary/sexual encounter diary (Appendix B), drug accountability (Appendix E), and patient instructions sheet (Appendix F). Patients will be given enough diaries to capture all study medication use and at least 18 sexual attempts.

9.0 TREATMENT/INTERVENTION PLAN

Patients will be randomized into one of 3 arms as described above, and will be followed up for 24 months. Patients will be encouraged to have sexual relations, when comfortable after RP. This is 'usual care'. The use of nightly sildenafil citrate and intracavernosal injection therapy is considered investigational, and this study is designed to define whether one, or the other, or a combination of these strategies, should become 'usual care'. Patients routinely complete questionnaires after surgery, the only additional requirement for patients will be the completion of a pill diary/sexual encounter diary, to delineate the exact utilization of medication for sexual relations as well as document all study medication use. Patients will be followed at 3, 6, 9, 12, 18, and 24 months. Intervention (placebo, sildenafil or injection) will be used for 12 months. Patients will have their sildenafil dose adjusted according to their erectile response and side effects (listed in section 11.0). For example, for men responding robustly to sildenafil 100 mg may be down-titrated to 50 mg or 25 mg. Likewise, men who have side effects (as outlined in Section 11.0) at sildenafil 100 mg will be down-titrated to 50 mg or 25 mg. If patients are experiencing side effects from daily 50 mg dose, they may down-titrated to 25mg, by halving the pill. Intra-cavernosal injection agent dose will be down-titrated for penetration hardness erection lasting for greater than 60 minutes or if any side effects are seen, as listed in section 11.0. Trimix and Bimix have a 1 month expiration date. Combination Therapy Arm patients will be prescribed a total of 3 vials of Trimix or Bimix at their 2nd injection training visit and 3, 6, and 9 month protocol visits. The patient will pick up 1 vial after their appointment and outpatient pharmacy will arrange to have the remaining 2 vials shipped to the patient at 1 month intervals to cover their treatment plan for a total of 3 months.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Before treatment (baseline) and 3, 6, 9, 12, 18, and 24 months visits, patients will be evaluated in clinic. Patients will be asked for any adverse events, since last visit, and will be given the International Index of Erectile Function (IIEF) validated questionnaire (Appendix A), pill diary/sexual encounter diary (Appendix B), and drug accountability (Appendix E). The pill diary/sexual encounter diary (Appendix B) and drug accountability (Appendix E) will be completed at home. Patients will be given enough diaries to capture at least 18 sexual attempts. At each study visit, the paperwork will be collected and the patient given new diaries. The assigned research professional will review paperwork for any mistakes or inconsistencies before patient leaves clinic. Patient's liver functions will be tested and sitting and standing blood pressure, and pulse will be completed at 3, 6, 9, 12, 18, and 24 months visits.

The IIEF is the gold standard questionnaire in erectile function assessment. It has been validated in numerous languages and has been used for more than a decade now in this field. It has 5 domains, one of which is erectile function (the others are libido, orgasm, intercourse satisfaction and overall satisfaction). Each question is scored on a 5 point scale, where '5' is 'always' and '1' is 'never' and '3' is 'half the time', in response to questions pertaining to obtaining and maintaining erection.. The pill diary/sexual encounter diary will ask patients to record sexual encounters, whether sildenafil or penile injections was used, at what dose, whether vaginal penetration occurred, and how they rate their erectile rigidity as well as all study medication use.

At 12 months, patients will be instructed to discontinue treatment (that is, either daily pill use or injection therapy). They will be permitted to use PRN sildenafil or injections for the purpose of sexual relations, prescribed through treating physician. Follow up will continue for 24 months in total. The administration of the study medications will be monitored by the research pharmacy staff to ensure compliance with the protocol, as well as maximizing patient safety.

11.1 TOXICITIES/SIDE EFFECTS

The side effects from each pharmacologic intervention are listed below. Side effects will be assessed at each follow-up visit by direct questioning of patients.

Sildenafil:

1. Headache 15%
2. Flushing of the face 10%
3. Gastrointestinal upset 7%
4. Temporary visual changes 2%
5. Nasal congestion 4%.

Trimix and Bimix:

1. PGE1 can induce pain (in up to 30% of patients taking PGE1)
2. Fibrotic reactions (i.e. subcutaneous nodules, intracavernosal fibrotic areas, have been reported). In most cases, penile nodules that occur with injection therapy disappear within a few months of stopping.
3. Ecchymosis
4. Priapism (0.5-5%). (If not treated right away, permanent damage to the penis could occur). Of note, the incidence of priapism in Dr. Mulhall's practice is less than 0.15%.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patient outcome will be assessed by the IIEF (International Index of Erectile Function). Therapeutic response will be evaluated by comparing the IIEF score for patients in each treatment arm at each time point.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Sildenafil will be stopped should any significant side effects occur or should the patient require the use of organic nitrate medications.

Intracavernosal injections will be stopped if the patient develops any fibrotic reactions on the penis (except Peyronie's disease).

The patient can also be removed from this study if they chose to withdraw or the study doctor decides it is in the patient's best interest to remove them from the study if these options are appropriate.

14.1 BIOSTATISTICS

14.2 Sample Size

For each endpoint we will conduct three analysis:

1. A comparison of nightly sildenafil to PRN sildenafil with an alpha of 2.5%
2. A comparison of combination treatment to PRN sildenafil with an alpha of 2.5%
3. A non-inferiority comparison between nightly sildenafil and combination treatment: in this analysis, nightly sildenafil will be considered non-inferior to combination treatment if the upper bound of a 90% confidence interval for the difference between groups does not include combination treatment being at least three points superior to nightly sildenafil.

Our rationale is for the different comparisons is as follows. We want to know whether the two active arms (nightly sildenafil and combination treatment) are superior to control (PRN sildenafil). We will therefore test each against control using an alpha half of the conventional value to account for multiple testing. Furthermore, combination treatment, which involves penile injection, is less tolerable for patients than nightly sildenafil, which only involves oral medication. Therefore unless nightly sildenafil is demonstrably inferior to combination treatment, we will recommend that injections are not required. Hence we will conduct a non-inferiority comparison between the two active arms.

Our primary endpoint is the IIEF-EF at 24 months. Based on previous studies, we estimate that the SD for the IIEF-EF will be 9 points. Prior data at MSKCC suggest that the correlation between baseline and follow-up IIEF-EF will be small enough as to have a negligible effect on variance. The minimum, clinically significant difference between active and control arms is 6 points based on our clinical experience and discussion held with Raymond Rosen PhD the designer of the IIEF. If we obtain data from 80 patients on each of the two active arms (nightly sildenafil and combination therapy) and 40 patients on the control arm (PRN sildenafil), we will have 89% power for the comparison between active and control and 80% power for the non-inferiority comparison between active arms.

MSKCC surgeons do approximately 850 radical prostatectomies per year. We estimate that 50% of patients will be eligible for the study. Assuming that 25% - 33% of eligible patients enroll, we should complete accrual within 18-24 months.

14.3 Data Analysis

Summary statistics will be calculated, by group, for age, surgery (open or laparoscopic), tumor characteristics (stage, grade, PSA), baseline erectile function and quality of life scores. Compliance and off-study use of medications for erectile function will be described by group and follow-up time. Biochemical recurrences will be described separately by group using Kaplan-Meier methods.

The primary analysis will compare the erectile function domain score of the IIEF at 24 months. Secondary endpoints include:

1. EF scores at other time-points
2. The proportion of patients who have normalization of their erectile function, defined as a score of 26 or greater on the EF domain of the IIEF at any point during the study
3. Time for response to sildenafil (as defined by diary)
4. Time to return of spontaneous functional erections (as defined by diary)

The primary comparison and secondary comparison 1 will be made by analysis of co-variance with baseline score and randomization strata as the covariates. Secondary endpoint 2 will be compared by Fisher's exact test. Secondary endpoints 3 and 4 will be compared between groups by log rank. Three pairwise comparisons will be made: nightly sildenafil vs. PRN sildenafil; combination treatment vs. PRN sildenafil; nightly sildenafil vs. combination treatment.

As an additional analysis, we will model EF scores over time using Generalized Estimating Equations with time, treatment, time by treatment and baseline score as predictors. Treatment will be entered as two dummy variables: nightly sildenafil (coded 0 in the PRN group and 1 otherwise) and injection therapy (coded 1 in the combination group and 0 otherwise).
All analyses will be on the intention-to-treat principle with patients analyzed in their randomized groups regardless of the treatment actually received. All comparisons between combination and PRN sildenafail, and between nightly and PRN sildenafil, will use a 2.5% alpha; all comparisons between the two treatment arms will use a 90% non-inferiority bound.

The nature, severity and day of onset of adverse effects will be described along with assessment of causality.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

This is a randomized comparison of PRN sildenafil arm (Group 1), nightly sildenafil arm (Group 2), and Combination arm (Group 3). After eligibility has been established and immediately after consent has been obtained, patients will be registered to the study in the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted blocks with varying block size, stratified by surgeon. A total of 3 surgeons at MSKCC will perform the nerve sparing RP for a total of 3 strata.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.
The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g.,

protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

17.1 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)

- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A:	IIEF – International Index of Erectile Function
Appendix B:	Pill Diary/Sexual Encounter Diary
Appendix C:	Patient Handout
Appendix D:	Adverse Event Form
Appendix E:	Drug Accountability Form
Appendix F:	Patient Instruction Sheets