SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

# Miami Membrane for Potency (MMeP) Trial to Assess the Impact of Dehydrated Human Amnion Membrane Allograft Placement during Robotic Radical Prostatectomy on Early Return of Erectile Function


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# 1. BACKGROUND

## 1.1 Study Disease

Radical prostatectomy for localized prostate cancer provides excellent cancer control, but comes at a significant detriment to health related quality of life, primarily in the domains of sexual and urinary quality of life[1-3]. A recent population based study reported that 76% and 87% of men could not attain erections sufficient for intercourse at 5 and 15 years after surgery, respectively[4]. The greatest decline in erectile function occurs immediately after surgery, with some recovery in the next 1-2 years. However, potency never returns to baseline and there will always be some degree of permanent loss in erectile function. Even with the influx of minimally invasive surgery, we continue to see a significant proportion of men with post-surgical impotence.

Urinary incontinence following surgery have been as high as 50%[5]. This undesirable side effect of treatment can significantly interfere with quality of life. Although most men improve with time, up to 10% can have persistent leakage and may seek further surgery for moderate to severe urinary incontinence[6,7]. Even men with mild incontinence may still be bothered by having to wear even a pad, which may interfere with their quality of life and result in less satisfaction with treatment outcomes[8,9]. Men undergoing minimally invasive surgery have similar levels of bother related to incontinence post prostatectomy, suggesting that the minimally invasive nature of the procedure does not preclude them from the side effects of urinary incontinence[10].

These issues pose a significant burden to health related quality of life for men undergoing surgery for prostate cancer. Given the prevalence of prostate cancer, they also have a significant public health impact. Any treatments or techniques that can reduce the magnitude or improve the recovery of these functional outcomes would be a welcome addition.

## 1.2 Study Interventions

Placement of amnionic membranes over the neurovascular bundle after bilateral nerve sparing robotic radical prostatectomy

## 1.3 Rationale

A recent study reported that the use of dehydrated human amnionic membrane allograft placed over the neurovascular bundle during robotic assisted radical prostatectomy accelerated an early return to potency.[11] These findings have resulted in a wide adoption of this technique by many surgeons and patients. However, these findings are observational and have never been validated in a randomized trial.

## 1.4 Preliminary Studies

Patel et al[11] conducted an interventional trial wherein men with prostate cancer undergoing Robot Assisted Radical Prostatectomy (RARP) were implanted with a dehydrated human amnion chorion allograft (dHACM) around the neuro-vascular bundle. The subjects were previously continent (American Urological Association Symptom Score <10) as well as potent (Sexual History Inventory for Men Score >19).

This study showed that dHACM placement significantly facilitated early return to potency and continence. Continence at 8 week returned in 81.0% of the dHACM group and 74.1% of the no-dHACM group (p = 0.373). Mean time to continence was enhanced in dHACM patients (1.21 months) versus no-dHACM patients (1.83 months; p = 0.033). Potency at 8 weeks returned in 65.5% of the dHACM patients and 51.7% of the no-dHACM group (p = 0.132). Mean time to potency was enhanced in dHACM group, (1.34 months), compared to no-dHACM (3.39 months; p = 0.007). Graft placement enhanced mean time to continence and potency

As a result of this study many centers have begun using amnionic membranes with the hope that they will induce an earlier recovery of potency and urinary control. Furthermore, many patients have been requesting to have amniotic membranes placed at the time of surgery for similar beliefs regarding it's potential utility for functional recovery. However, a major limitation of this study is that it was conducted as an observational study with a computer matched cohort rather than a randomized trial, leaving a significant potential for bias. As a result, the findings should be considered hypothesis generating at best and further validation should be required in randomized studies before this technique can be considered in contemporary clinical practice.

## 2. HYPOTHESIS

The use of dehydrated human amnionic membrane allograft will reduce the decline in erectile function (as measured by SHIM score) at 12 months after robotic assisted radical prostatectomy (RARP).

## 3. OBJECTIVES

### 3.1 Primary Objective

To see if the use of dehydrated human amnionic membrane allograft improves erectile function recovery (as measured by SHIM score) at 12 months after robotic assisted radical prostatectomy (RARP) compared to a control group with no allograft.

### 3.2 Secondary Objectives

- Among men with a SHIM greater than or equal to 17 at baseline, to compare the proportion of men in each group with mild ED or better, defined by a SHIM greater than or equal to 17, at 3, 6, 9 and 12 months post RARP
- Among men with a SHIM greater than or equal to 17 at baseline, to compare the proportion of men in each group who are able to achieve an erection sufficient for intercourse more than 50% of the time at 3, 6, 9 and 12 months post RARP.
- Among men with a SHIM greater than or equal to 17 at baseline, to evaluate the proportion of men in each group who require the use of more invasive erectile aids (intra-cavernosal injection, vacuum pump, or penile prosthesis) at 3, 6, 9, and 12 months post RARP
- Rates of urinary control as measured by no pads per day at 3, 6, 9, and 12 months
- To compare 5 year rates of prostate cancer recurrence between the two groups

## 4. STUDY DESIGN

This is a phase 2 prospective randomized trial investigating the impact of amniotic membrane placement over the neurovascular bundles after bilateral nerve sparing robot assisted radical prostatectomy on potency. The study will have a control arm that will follow standard of care surgery, without placement of any membranes.

### 4.1 Accrual goal

70 men will be allocated to each arm. The rationale for this number is provided in the sample size section of the statistical analysis (Section 10.5)

### 4.2 Duration of Study Participation

The research study will involve follow up every 3 months for the first 12 months. After this we will follow patients annually with PSA measurements and an assessment of any secondary therapies for 5 years post surgery.

### 4.3 Study Randomization

Randomization of study patients will be done in equal proportion to Arm I (membrane placement) and Arm II (no membrane placement, standard of care surgery) using a permuted block design stratified by baseline SHIM score (<17 vs. ≥=17), and use of **ANY** erectile aids (Yes vs. No) in the last 3 months.

Randomization lists for each stratum will be prepared by SCCC Biostatistics prior to the first patient enrollment and provided to the SCCC CRS-Informatics office where they will be programed and customized as per randomization requirement using the CIERRA system. Members of the study team, including those responsible for patient enrollment, will not have access to the randomization lists.

After each patient's study eligibility is confirmed and the informed consent is signed, CRS coordinators will enter the required patient information into the CIERRA system in order to register the patient. The CRS coordinators will receive the designated patient ID, study arm, randomization number, and randomization date. CRS coordinators will print the randomization confirmation form from the CIERRA system and place it in the patient's research chart and then notify the requesting member of the study team of the treatment assignment for the new randomized patient.

### 4.4 Follow Up and Analyses

Patients will be followed up every three months (± 1 month) for a total of one year. This follow up schedule meets the current standard of care after radical prostatectomy. At each follow up a serum PSA will be assessed for recurrence on prostate cancer. To investigate primary and secondary endpoints a self-reported validated questionnaire will be provided assessing measures of potency. Finally, the use of pads for urinary leakage will be

assessed at each time point. After the first year, there will be annual follow up with PSA measurements and an assessment of any secondary therapies for 5 years. Further details regarding the primary and secondary endpoints can be found in Section 3. The analyses will be performed as an intention to treat analysis. More details regarding the analyses of primary and secondary endpoints can be found in Section 10.

## 5. STUDY ENTRY AND ENROLLMENT AND WITHDRAWAL

### 5.1 Nerve sparing robotic assisted radical prostatectomy

In the USA, enthusiasm for the robotic- assisted technique currently overshadows conventional laparoscopic radical prostatectomy. Two series in the US have demonstrated the successful transfer from the open to laparoscopic technique by aid of the robotic device [12,13]. Similar functional and oncological outcome have been noted between open and robotic prostatectomy, [14,15]. However, the robotic approach has the advantage of faster recovery and less blood loss. As a result the majority of the University of Miami cases are done robotically.

The operative procedure for nerve sparing RARP has the following steps:

- Incision is done on the peritoneum overlying the vas deferens and seminal vesicle.
- Seminal vesicle and the vas deferens are dissected out bilaterally.
- The plain below the prostate and above the rectum is developed towards the apex of the prostate.
- Anterior dissection (dropping) of the bladder is performed and the endo-pelvic fascia is opened bilaterally.
- Junction of the prostate and bladder is identified.
- Incision is taken at the bladder neck both anteriorly and posteriorly.
- The neuro-vascular bundle is identified and dissected from the prostatic pedicle.
- Prostatic pedicle will be ligated and cut with the use of hemo clips.
- Then the apical dissection will be conducted by dividing the dorsal venous complex and urethra
- A *vesico-urethral anastomosis* will be conducted and will be checked for no leakage.
- If indicated a bilateral pelvic lymph node dissection may be performed.

## 5.2 Use of membranes during the procedure

The placement of amnionic membranes to enhance the recovery of potency and urinary control is available at many centers, despite the lack of proper validation of this technique. The procedure has been performed at UM, as well as other community based and academic practices around the nation. Amniotic membranes will be placed over the neurovascular bundle after extirpative RARP, and before the urethrovesical anastomosis. The membrane will cut into two longitudinal pieces and it will be placed over each neurovascular bundle separately. The membrane will be accessed from the Um tissue bank who will provide it to the OR (Operatory room) to ensure availability during cases. The membrane will be identified by a stock number on the packaging but not in the membrane itself.

## 5.3 Follow up

Measurement of PSA is a cornerstone in follow-up after treatment. Patients will be followed-up as per the usual standard of care with a PSA every 3 months. PSA measurement and history and physical are recommended at 3, 6, 9 and 12 months (± 1 month) postoperatively, and as per the clinician's discretion afterwards. During each follow up functional assessment for urinary and sexual quality of life with be performed as per the study calendar. After the first year, follow up will occur annually with a PSA measurement and an assessment of any secondary therapies for 5 years post surgery. If a patient is unable to continue a minimum annual follow after the first year post surgery at UM, then a call to inquire about the receipts of any salvage therapies and measurement of serum PSA will suffice.

## 5.4 Erectile rehabilitation

Many men undergo a procedure called penile rehabilitation, where they will use oral phospodiesterase inhibitors (PDE5i) after surgery to help improve the recovery of potency. In some cases, oral medications will not be enough and further intervention is required in the way of vacuum pumps, intracorporal injections, or even penile prosthesis. These medications may impact the association between membrane use and potency and therefore every consideration should be made to balance the use of these medications between the trial arms. To ask men to abstain from these medications would be unethical. However, to attempt to standardize the use of these medications between the arms may be difficult due to the cost of these medications and the variable coverage that different insurance companies provide for their usage, notwithstanding the variable views men may have towards using these medications.

We will offer men a standard of care penile rehabilitation program post RARP using oral PDE5i therapy, with the option of advancing to other

interventions (such as intracorporal injections, vacuum pumps, or penile prosthesis) after 3-6 months post RARP if the oral medications are not sufficient. We will stratify the randomization of men based on their current usage of oral PDE5i medications between the arms. We will also ascertain each man's ability to use these medications post-surgery (based on willingness to use and ability to cover the cost of the medication) to further balance the usage of these medications as best possible between the arms. Finally, we will ascertain the frequency and quantity of use of these meds by each man at all follow up intervals so we can control for their use during the analysis.

## 5.5 Study Entry

Study entry, as used in this protocol, will be defined as a subject signing informed consent. Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist. As per University of Miami policy, each study participant who signs an informed consent form should be entered into the Velos system within 48 hours of consent being obtained

## 5.6 Enrollment Procedure

As per UM/SCCC Clinical Research Services policy, a CRS director or designee must also review eligibility. The investigator or study coordinator will provide the following to a CRS representative
Completed and signed protocol-specific eligibility checklist;
All pages of the original signed informed consent forms (ICFs), including HIPAA Form B;
Relevant source documents such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

## 5.7 Cancellation Guidelines

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

- A subject does not meet the eligibility criteria, (the subject will be considered a screen failure).
- A subject withdraws consent,
- A subject dies during protocol participation or
- A study investigator decides the subject should be withdrawn from the study (e.g. subject non-compliance)

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

## 6. PATIENT SELECTION/ELIGIBILITY CRITERIA

### 6.1 Inclusion (Eligibility) Criteria

- Men age 40-80 with localized prostate cancer who are undergoing bilateral nerve sparing RARP at the University of Miami

### 6.2 Exclusion (Eligibility) Criteria

- Men with poor urinary control at baseline requiring the use of pads for leakage
- Previous treatment for prostate cancer
- Previous history of pelvic radiation
- Men who are using non-oral erectile aids such as vacuum pump, intra-cavernous injections, MUSE, penile prosthesis.

### 6.3 Gender and Ethnicity

Prostate cancer is a disease of adult men, with exceptionally few diagnosed at 35 years of age. Therefore, women and children are not candidates for this protocol. Based on standard NIH definitions, we estimate that approximately 40% of patients will be White, 24% African American, 35% Hispanic and 1% other at the University of Miami.

## 7. CLINICAL, RADIOLOGICAL, LABORATORY AND SURGICAL EVALUATIONS

### 7.1 Screening Evaluations

- History and physical exam within 3 months prior to protocol enrollment.
- Baseline SHIM and EPIC 26 Scores within 3 months of RARP

### 7.2 Evaluations During Intervention

- SHIM and EPIC 26 Scores at 0, 3, 6, 12 months (± 1 month).
- Urinary incontinence measured by the number of pads used per day at 3, 6, 9 and 12 months (± 1 month).
- Serum PSA every three months (± 1 month) for first year post surgery, and then annually for 5 years.

### 7.3 Early discontinuation of study participation

Subjects that discontinue participation in part of or all the interventions in this study due to progression or other (patient or physician decision) reasons will be followed for clinical data and analyzed by intention to treat. Those who experience a biochemical or clinical recurrence and undergo radiation will be analyzed by intention to treat and their analysis adjusted for the receipt of secondary treatments. There will be no stopping rules for safety, as previous observational studies have suggested no increased risk of any adverse events with placement of membranes during the surgery. All adverse events will still reported, as discussed in Section 8.

### 7.4 Quality of life and/or Outcomes

Psychosocial assessments will be provided to the subjects by a trained and fully bilingual clinical coordinator/research nurse with experience in conducting psychosocial assessments in prostate cancer populations. Subjects can fill in the assessments on their own, if they need help answering or understanding the question a nurse\coordinator will be available. We will make every effort to pair our psychosocial assessment visits with scheduled clinic appointments to reduce participant burden. The psychosocial battery will last between 30-40 minutes. All assessments will be conducted in private rooms in our clinics. All psychosocial data will be de-identified and only coded by participant number. Should a participant display any significant signs of distress (e.g., high levels of anxiety, depressed mood or spontaneous comments suggesting a need for psychosocial care), we will refer participants to appropriate psychosocial resources within our medical center.

## 8. ADVERSE EVENT REPORTING

In this therapeutic trial, all patients will undergo the standard of care for men undergoing radical prostatectomy. The only difference is the implantation of amniotic membrane in men who are allocated to the implantation arm. The only adverse event that could be anticipated from Membrane Implantation is infection, but there is no data to suggest an increased risk of this. Adverse effects from RARP include bleeding, infection, urinary incontinence and impotence but these are all well known to be associated with surgery. Secondly, surgery is not the intervention being assessed in this trial and therefore we will stick to reporting on adverse events that are more likely to be related to the graft itself. Regardless, all serious adverse events will be captured. In the unlikely event that a study patient experiences an adverse reaction to a study related procedure, this will be reported the University of Miami Institutional Review Board as per their policies and using the grading scales of the NIH CTCAE version 4.0

## 9. DATA AND SAFETY MONITORING PLAN

The study investigators will report to the Sylvester Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC) to ensure data quality and subject safety. The investigators will conduct continuous reviews of the data and subject safety, keeping track of the number of subjects, significant toxicities in accordance with the protocol and observed responses, which will be discussed at DSMC committee meetings. All grade 3-5 adverse events, regardless of association with the membrane implantation, will be entered into Velos and reviewed at DMSC meetings. In addition, all adverse reactions considered "serious" will be entered into Velos and reviewed by the DSMC on an ongoing basis. If a death occurs within 30 days of radical prostatectomy and membrane implantation and is determined to be related to the study, the investigators will notify the DSMC chair within 1 business day. If an increase in the frequency of grade 3 or 4 adverse events is noted in the study, a report will be submitted to the DSMC at the time the increased rate is identified. If at any time the principal investigator stops enrollment or stops the study due to safety issues, the DSMC chair and manager will be notified within 1 business day and a formal letter will be sent to the DSMC to be received within 10 business days.

## 10. STATISTICAL CONSIDERATIONS

This is a blinded two-arm randomized phase 2 trial. Patients will be randomized in a ratio 1:1 to study arms, the experimental Arm I (membrane placement) and control Arm II (no membrane placement, standard of care surgery), using a permuted block design stratified by baseline SHIM score (<17 vs. >=17), and use of ANY erectile aids (Yes vs. No) in the last 3 months.

All analyses will be performed as an intention to treat and as per Protocol. Although there is no data to suggest an increased risk of any potential adverse effects with placement of a sling, we will monitor adverse events as per section 10.7.2. An interim analysis of the primary efficacy endpoint, change in SHIM score, will be performed as part of the analysis plan as described in section10.7.3..

### 10.1 Primary Study Endpoints

The difference in average change in SHIM score, between baseline and 12 months post RARP between the membrane and control arms will be assessed as the primary endpoint.

### 10.2 Secondary Endpoints

- Among men with a SHIM greater than or equal to 17 at baseline, we will compare the proportion of men in each group with mild ED or better, defined by a SHIM greater than or equal to 17, at 3, 6, 9 and 12 months post RARP.

- Among men with a SHIM greater than or equal to 17 at baseline, we will compare the proportion of men in each group who are able to achieve an erection sufficient for intercourse more than 50% of the time at 3, 6, 9 and 12 months post RARP.
- Among men with a SHIM greater than or equal to 17 at baseline, we wil evaluate the proportion of men in each group who require the use of more invasive erectile aids (intra-cavernosal injection, vacuum pump, or penile prosthesis) at 3, 6, 9, and 12 months post RARP.
- Rates of urinary control as measured by no pads per day at 3, 6, 9, and 12 months.

### 10.3 Safety Parameters

- Rates of Adverse Events categorized by type, short name, grade, and relationship to treatment using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 criteria
- Rate of recurrence will be assessed and reported at 60 months

### 10.4 Endpoint definitions

- Potency as measured by well-validated questionnaires: SHIM and EPIC 26. A SHIM greater than or equal to 17 defines mild ED or better
- Urinary continence or control is defined as no pads per day
- Recurrence post-radical prostatectomy defined as a PSA > 0.2 ng/ml on 2 or more consecutive reads or the receipt of any salvage therapy.

### 10.5 Sample size, accrual and study duration

Exploratory data analyses on 140 men who underwent radical prostatectomy at the University of Miami (between 2008 and 2012) suggests that men typically drop from a mean SHIM score of 19 at baseline down to approximately a score of 9 one-year post radical prostatectomy. Assuming that the control (no membrane) group will experience declines in SHIM scores similar to this historical cohort, with a mean reduction of 10 SHIM points and a standard deviation on the change scores between the observed 8.5 SD and the pessimistic one sided 80% upper confidence limit of 9.8, and allowing one interim analysis at 50% accrual, our study with 70 patients per group can detect, with 80% power, an effect size of 0.335, as shown in Table 10.1 in this section.. (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.) For instance, our proposed study with 70 per group has 80% power to detect a difference of 2.68, between sexual function mean reductions of 10 and 7.32 in treatment groups without and with the membrane respectively, assuming a common standard deviation of 8. As

expected with larger standard deviations only larger absolute differences can be detected with 80% power (See rows 2 and 3 in Table 10.1).

**Table 10.1: Estimated effect size that can be detect with our proposed study with 140 total patients (70 per arm)**

| Power | N1 | N2 | N | Mean1 | Mean2 | S1 | S2 | Alpha | Effect size | Alpha |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 70 | 70 | 140 | 10 | 6.20 | 8 | 8 | 3.80 | 0.475 | 0.05 |
| 0.80 | 70 | 70 | 140 | 10 | 5.73 | 9 | 9 | 4.27 | 0.474 | 0.05 |
| 0.80 | 70 | 70 | 140 | 10 | 5.26 | 10 | 10 | 4.74 | 0.474 | 0.05 |

Effect size = (Mean 1 – Mean 2) /S (standardized mean difference).

Note: These results assume that 2 sequential z-test are made using the O'Brien-Fleming spending function to determine the test boundaries. The study will stop early at 50% accrual, for either futility or superiority, if the interim analysis result is significance at p< 0.03. The nominal significance level at the second test is 0.049. (PASS 14).

## 10.6 Statistical Analysis

The difference in the SHIM score decline in each group from baseline to 12 months post RARP with 95% CIs will be reported as the primary endpoint for the study. Linear regression models will be fitted to determine the likely decline in SHIM scores based on receipt of a membrane during RARP. These models will control for baseline SHIM scores, age, and a binary indicator of the use of any oral erectile aids, in addition to other important demographic and clinic factors.
Among men with a SHIM greater than or equal to 17, the proportion of men in each group with a SHIM of 17 or greater, able to achieve an erection sufficient for intercourse more than 50% of the time, or not requiring any invasive erectile aids at each follow up interval will be reported and compared using counts and percentages with 95% CLs. Logistic regression models will be fitted to determine the likelihood of having achieving each result controlling for age and a binary indicator of the use of any oral erectile aids, in addition to other important demographic and clinic factors. Both unadjusted and adjusted odds ratios with 95% CIs and their corresponding p-values will be reported

In addition, we will report by treatment group adverse event rates by grade and attribution, and the number and percentage of men not needing pads.

## 10.7 Interim Monitoring

### 10.7.1 Role of the Research Team and the DSMC

The Research Team will continuously monitor study accruals and adverse events from both treatment arms. Patients will be monitored closely ***during treatment and subsequently over 30 days*** for any **adverse event** potentially related to treatment. All toxicities, regardless their grade, will be recorded in the patient case report form using NCI/CTEP Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In addition, a one interim analysis **of the primary efficacy endpoint** is planned in first 50% of study patients.

The Sylvester Comprehensive Cancer Center's Data and Safety Monitoring Committee (DSMC) will monitor this protocol according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual, adverse event data, and interim analysis of response to treatment. The guidelines appearing in Sections 10.7.2, and 10.7.3 are offered for DSMC consideration in assessing accrual, adverse events, and response to treatment. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

### 10.7.2 Safety: Early stopping due to adverse events

The interim monitoring guidelines for stopping due to adverse events appearing in this section will be applied separately to each arm

- If a treatment-related (possible, probable, or definite) death (grade 5 toxicity) occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC.
- **Unacceptable adverse event** is defined as any grade 3, 4, or 5 treatment-related possible, probable, or definite) adverse event, excluding grade 3 xxxx revolved or down grade to grade 2 with 14 days.
- Unacceptable adverse event is expected to occur in no more than 10% of patients. If there is evidence that the true rate of unacceptable adverse event exceeds 15%, then accrual to the particular study arm should be suspended. Specifically, we suggest as a guideline for early termination of accrual to a particular arm a posterior probability of 90% or higher that the true rate exceeds 15%. The table below shows specific instances where this guideline is met, suggesting early termination, and due to evidence of excessive unacceptable adverse event.

| Number of patients with unacceptable adverse event[#] | Patients evaluated for adverse event | Observed adverse event rate >= |
|---|---|---|
| 3 | 4 to 7 | 43% |
| 4 | 8 to 12 | 33% |
| 5 | 13 to 17 | 29% |
| 6 | 18 to 22 | 27% |
| 7 | 23 to 27 | 26% |
| 8 | 28 to 32 | 25% |
| 9 | 33 to 38 | 24% |
| 10 | 39 to 43 | 23% |
| 11 | 44 to 48 | 23% |
| 12 | 49 to 54 | 22% |
| 13 | 55 to 60 | 22% |
| 14 | 61 to 65 | 22% |
| 15 | 66 to 69 | 22% |

[#]: treatment-related (possible, probable, or definite) grade 3 or higher adverse event, excluding grade 3 xxxx revolved or down grade to grade 2 with 14 days.

To illustrate the stopping guidelines, suppose that 7 evaluable patients in the have been assessed for adverse event and 3 of them have experienced unacceptable grade 4 treatment-related adverse event. (See row 1 of the above table.) Under this circumstance, the observed rate of unacceptable adverse event is 43%, resulting in a posterior probability of 92.1% (not shown) that the true underlying rate exceeds 15%, thereby suggesting early termination.

Posterior probabilities for the above table are calculated under a weak prior beta distribution with parameters $\beta 1 = 0.2$ and $\beta 2 = 1.8$, which corresponds to an expected rate of 10% based on very limited information, roughly equal to having studied 2 patients. This prior distribution implies also a priori chance of only 21.6% that true rate is 15% or greater

### 10.7.3 Interim analysis of the primary efficacy endpoint: change in SHIM scores

While we expect that the membrane will help maintain sexual function, we plan on doing a single interim look at the change in **SHIM scores** and will stop the trial for either futility or superiority of experimental arm 1 based on analysis of 70 men in the treatment and control arms (~35 per arm) have been assessed for sexual function a year following radical prostatectomy. Using an O'Brien Fleming alpha spending rule with a total alpha error rate of 0.05 at the end of the study, an interim look will use a nominal alpha level of 0.003 and the final nominal alpha level will be 0.049.

# 11. INVESTIGATORS RESPONSIBLITIES

## 11.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects.
The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

## 11.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

## 11.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

## 11.4 Source Documentation and Investigator Files

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

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

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

## 11.5 Recording and Processing of Data

Data for this study will be entered into electronic CRFs in RedCap. A CRF is required for every patient who received any study intervention. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.**

## 11.6 Non-Protocol Research

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

## 11.7 Ethics

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

## 11.8 Essential Documents for the conduct of a clinical trial

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

The following documents will be on file:

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

## 12. REFERENCES

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## 13. Appendix I

### 13.1 Table 1: Scheduling of events

| | Baseline | 3 months (± 1 Month) | 6 months (± 1 Month) | 9 months (± 1 Month) | 12 months (± 1 Month) | Annually (± 1 Month) for 5 years post-surgery |
|---|---|---|---|---|---|---|
| | | | | | | |
| History | X | X | X | X | X | |
| Physical | X | x | x | x | x | |
| SHIM | X | X | X | X | X | |
| EPIC 26 | X | X | X | X | X | |
| PSA | | X | X | X | X | X |