UNIVERSITÀ
DEGLI STUDI
FIRENZE

DIPARTIMENTO DI
MEDICINA SPERIMENTALE
E CLINICA

*Nerve-**SPAR**ing Robotic Prostatectomy: The Impact of Patient Baseline Profiles on **E**rectile **F**unction. (The SPARE-EF Registry)*

Florence, 01/05/2026

STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

Radical prostatectomy remains a cornerstone in the management of localized prostate cancer. With the advent and widespread adoption of robot-assisted radical prostatectomy (RARP), surgical precision has significantly improved. A critical component of RARP is the nerve-sparing (NS) technique—which can be performed unilaterally or bilaterally—aimed at preserving the delicate cavernous nerves responsible for erectile function.

Despite advanced robotic visualization and microscopic dissection capabilities, post-operative erectile dysfunction (ED) remains a prevalent and distressing quality-of-life issue for patients. The success of functional recovery is not dictated by surgical technique alone; it is highly dependent on a complex interplay of pre-operative patient characteristics. Baseline erectile function, chronological age, metabolic comorbidities (such as diabetes, hypertension, and hyperlipidemia), smoking history, and psychiatric factors like baseline anxiety or depression heavily influence the neurovascular recovery cascade.

Currently, clinicians lack a robust, individualized framework to accurately counsel patients on their specific probability of erectile function recovery when weighing their pre-operative risk profile against the planned degree of nerve sparing (unilateral vs. bilateral). Therefore, there is a critical need to systematically analyze how these baseline patient variables interact with the surgical technique to dictate long-term functional outcomes. This study seeks to bridge this gap, providing data-driven insights to optimize pre-operative patient counseling and manage post-prostatectomy expectations. In order to overcome the bias related to the experience and skill of the surgeon, all the NS RARP will be performed by one-single highly-trained robotic surgeon.

2. STUDY AIMS

Primary Objective

- To evaluate the quantitative value and clinical impact of unilateral and bilateral nerve-sparing techniques on the recovery of erectile function at 12 months post-RARP.
- Creating a nomogram to predict erectile function at 12 months post- NS RARP

Secondary Objectives

*Nerve-**SPAR**ing Robotic Prostatectomy: The Impact of Patient Baseline Profiles on **E**rectile **F**unction. (The SPARE-EF Registry)*

Florence, 01/05/2026

- To identify and risk-stratify independent pre-operative predictors (e.g., age, baseline IIEF-5 scores, comorbidity indices) that significantly influence the trajectory of erectile recovery.
- To compare the oncological safety (via positive surgical margin rates) of unilateral versus and nerve-sparing approaches in localized prostate cancer.
- To assess the time-to-recovery dynamics of sexual function within the first year following surgery.

3. STUDY DESIGN

General Architecture

This is a unicentri, prospective, observational cohort study. Because the decision to perform unilateral, bilateral, or non-nerve-sparing surgery is dictated strictly by oncological safety, tumor characteristics (e.g., biopsy Gleason score, clinical stage, multiparametric MRI findings), and baseline patient anatomy, randomization is neither ethical nor feasible. Patients will be managed according to standard clinical pathways, and investigators will prospectively observe and record outcomes without interfering with the surgical strategy or post-operative rehabilitation protocols.

Surgeries will be performed by a single highly-experienced robotic surgeon with more than 5000 robotic procedures.

Patient Selection Criteria

Inclusion Criteria

1. Age ≥ 18 and ≤ 75 years at the time of screening.
2. Histologically confirmed, clinically localized prostate cancer (cT1-cT2, Nx/0, Mx/0).
3. Candidates for robot-assisted radical prostatectomy (RARP) with a planned nerve-sparing approach (unilateral or bilateral) as determined by the attending urologist.
4. Patient is willing and able to complete validated quality-of-life questionnaires at baseline and during follow-up.
5. Signed informed consent prior to enrollment.

Exclusion Criteria

1. Pre-existing severe erectile dysfunction (baseline IIEF-5 score less than or equal to 7) unrelated to prostate cancer.
2. History of prior pelvic radiation, cryotherapy, or extensive pelvic surgery that disrupts neurovascular anatomy.

3. Neo-adjuvant androgen deprivation therapy (ADT) or chemotherapy.
4. Severe psychiatric or cognitive illness preventing reliable self-reporting.

Data Collection & Follow-up Timeline

Patients will be evaluated at four distinct time points: Baseline (Pre-operative), 3 months, 6 months, and 12 months post-operatively.

Evaluation Window	**Data/Variables to be Collected**
Baseline (Pre-operative)	Demographics (Age, BMI), Comorbidities (Charlson Comorbidity Index), PSA, Biopsy Gleason, mpMRI stage, Baseline IIEF-5 score
Intra-operative	Degree of nerve sparing achieved (Extrafascial, Interfascial, Intrafascial), operative time, estimated blood loss, surgical margins.
3 & 6 Months Post-op	IIEF-5 score, use of phosphodiesterase-5 inhibitors (PDE5-i) or intracavernosal injections, oncological status (PSA).
12 Months (End of Study)	Final IIEF-5 score, return to baseline sexual function, total oncological control status, and margin analysis.

4. STUDY ENDPOINTS

Primary Endpoint

- **Erectile Function Recovery Rate at 12 Months:** Defined as achieving an International Index of Erectile Function (IIEF-5) score $\geq$17 (or a return to within $\leq$ 5 points of baseline score) at the 12-month post-operative mark, with or without the use of PDE5 inhibitors.

Secondary Endpoints

1. **Potency Maintenance Over Time:** Changes in the mean total IIEF-5 domain scores from baseline to 3 and 6 months post-RARP.

*Nerve-**SPAR**ing Robotic Prostatectomy: The Impact of Patient Baseline Profiles on **E**rectile **F**unction. (The SPARE-EF Registry)*

Florence, 01/05/2026

2. **Oncological Safety Margins:** The incidence of positive surgical margins (PSM) on final pathology, stratified by unilateral versus bilateral nerve-sparing cohorts.
3. **Predictive Interaction Models:** The statistical correlation weight between pre-operative comorbidity scores and the degree of nerve-sparing on 12-month potency rates.
4.

5. STATISTICAL ANALYSIS PLAN

1. STUDY POPULATION & DATA MANAGEMENT

- **Analysis Sets:** The primary analysis will be based on a Full Analysis Set following the per-protocol principle, including all enrolled patients who undergo nerve-sparing RARP by the designated single surgeon and have at least one post-baseline functional assessment.
- **Missing Data Handling:** Missing baseline data will not be imputed. For the primary endpoint (12-month IIEF-5), missing values due to loss to follow-up will be handled using Multiple Imputation (MI) by chained equations, assuming data are Missing At Random (MAR). Sensitivity analyses will be performed using Complete Case Analysis (CCA) to evaluate the robustness of the imputation model.

2. DESCRIPTIVE STATISTICS

- **Demographic and Baseline Characteristics:** Continuous variables (e.g., Age, BMI, Baseline IIEF-5, PSA) will be expressed as means $\pm$ standard deviations (SD) for normally distributed data, or medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables (e.g., Comorbidities, Biopsy Gleason, mpMRI stage, Degree of nerve sparing) will be presented as absolute frequencies and percentages.
- **Stratification:** Baseline characteristics and clinical demographics will be stratified by the degree of nerve-sparing achieved: **Unilateral vs. Bilateral**. Stratification will also be exploratory across the fascial dissection planes (**Extrafascial vs. Interfascial vs. Intrafascial**). Groups will be compared using the Student's t-test or Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables.

3. PRIMARY ENDPOINT ANALYSIS

- **Endpoint Definition:** Erectile Function (EF) Recovery at 12 months, defined a binary outcome: Success (IIEF-5 $\geq$ 17 or within $\leq$ 5 points of baseline) vs. Failure.

*Nerve-**SPAR**ing Robotic Prostatectomy: The Impact of Patient Baseline Profiles on **E**rectile **F**unction. (The SPARE-EF Registry)*

Florence, 01/05/2026

- **Primary Effect Estimation:** The proportion of patients achieving EF recovery at 12 months will be calculated along with 95% confidence intervals (CI) for both the unilateral and bilateral nerve-sparing cohorts.
- **Hypothesis Testing:** The primary comparison between the two main surgical groups (Unilateral vs. Bilateral) will be conducted using a multivariable logistic regression model to estimate the Adjusted Odds Ratio (aOR) and its corresponding 95% CI, controlling for chronological age and baseline IIEF-5 scores.

To determine independent pre-operative predictors influencing the trajectory of erectile recovery:

- **Univariable Screening:** Logistical regression will be utilized to screen baseline variables (Age, BMI, Charlson Comorbidity Index, Smoking history, Baseline IIEF-5). Variables displaying a significance of $p < 0.10$ will be selected for multivariable entry.
- **Multivariable Logistic Regression:** A backward stepwise elimination selection method will be applied to build the final predictive model for 12-month potency. Multicollinearity among predictors will be evaluated using the Variance Inflation Factor (VIF), with a VIF > 3 indicating significant collinearity.

4. SECONDARY ENDPOINT ANALYSIS

To assess the time-to-recovery dynamics across the 3, 6, and 12-month time points:

- **Continuous Trajectory:** Linear Mixed-Effects Models (LMM) for repeated measures will be implemented to analyze changes in the continuous mean total IIEF-5 domain scores over time. The model will include fixed effects for time, surgical technique (unilateral vs. bilateral), and their interaction term (time x technique), utilizing a random intercept per patient to account for within-subject correlation.
- **Time-to-Event Analysis:** Kaplan-Meier survival curves will be constructed to visualize the "time-to-potency recovery" within the 12-month period, utilizing the log-rank test to compare curves between surgical cohorts. Patients without recovery at 12 months or those dropping out early will be censored at their last known assessment date.

Oncological Safety Analysis

- The incidence of Positive Surgical Margins (PSM) will be compared between the unilateral and bilateral nerve-sparing cohorts using the Chi-square test or Fisher's exact test.

*Nerve-**SPAR**ing Robotic Prostatectomy: The Impact of Patient Baseline Profiles on **E**rectile **F**unction. (The SPARE-EF Registry)*

Florence, 01/05/2026

- Multivariable logistic regression will be used to ensure that the preservation of nerves (especially bilateral) is not an independent risk factor for PSM after adjusting for pathological T-stage, preoperative PSA, and specimen Gleason score.

5. NOMOGRAM DEVELOPMENT AND VALIDATION

A predictive visual nomogram will be constructed based on the final multivariable logistic regression model determining 12-month post-NS RARP erectile function.

- **Model Performance & Discriminative Ability:** The discriminative power of the nomogram will be quantified using the Area Under the Receiver Operating Characteristic (ROC) curve, yielding the Concordance index (C-index). A C-index of 0.5 indicates random chance, while 1.0 indicates perfect discrimination.
- **Calibration:** Calibration will be evaluated graphically via a calibration curve plotting the nomogram-predicted probabilities against the observed recovery rates at 12 months. The Hosmer-Lemeshow goodness-of-fit test will also be implemented ($p > 0.05$ indicating adequate calibration).
- **Validation:** Due to the unicentric nature of the design, internal validation will be performed using bootstrapping (1,000 resamples) to calculate the over-optimism-corrected C-index and ensure the stability of the predictive tool.

6. SIGNIFICANCE THRESHOLDS

For all statistical tests, a two-sided p-value < 0.05 will be considered statistically significant. All statistical analyses, modeling, and nomogram plotting will be executed using R software (version 4.3 or later) or SPSS.