Study Protocol Title:

Application of Cold Plasma Energy for Reduction of Lymphoceles Following Pelvic LymphNode Dissection During Robot-Assisted Radical Prostatectomy

Study Sponsor:

Bovie Medical Corporation
5115 Ulmerton Road
Clearwater, FL 33760-4004 USA
Phone: (800)537-2790
Fax: (800)323-1640

Principal Investigator:

Dr. Vipul Patel
Global Robotics Institute
Florida Hospital Celebration Health
410 Celebration Place, Suite 300
Celebration, FL 34747
(407)303-4673

Table of Contents:

List of Abbreviations: 4
Introduction 5
Background Information and Scientific Rationale 5
Study Objectives 6
Primary Objective/Aim/Goal/Hypothesis 6
Secondary Objective/Aim/Goal/Hypothesis 6
Study Design 6
Research Design 6
Study Agent, Device, and/or Intervention Description 6
Study Site(s)/Location(s) and Number of Subjects 7
Multi-Site Research Logistics/Communication Plan 7
Research Conducted in a Foreign Country 7
Community-Based Participatory Research 7
Subject Selection 7
Vulnerable Populations (if applicable) 7
Inclusion Criteria 7
Exclusion Criteria 7
Resources Available 8
Study Procedures 8
Subject Recruitment and Screening 8
Consent Process and Documentation 8
Waiver of Written Documentation of Consent or Waiver of Consent 8
Documentation of Informed Consent Process 9
Randomization 9
Study Visits 9
Study Duration 10
Materials of Human Origin: Collection, Preparation, Handling and Shipping 10
Study Outcome Measures (Endpoints) 10
Data Management and Quality Plan 11
Data De-identification 11
Data Confidentiality, Storage, and Retention 11
Data Quality 11
Data Sharing (outside of Florida Hospital) 11

Sample Size Determination 12
Statistical Analysis Plan 12
Primary Objective Analysis 12
Potential Risks and Benefits 12
Potential Benefits 12
Potential Risks 12
Mitigation of Risks 13
Provisions to Protect the Privacy Interest of Subjects 13
Early Withdrawal of Subjects 13
Investigator Withdrawal of Subjects 13
Subject Request for Withdrawal from Study 13
Data Collection and Follow-up for Withdrawn Subjects 13
Adverse Event Reporting: 14
Adverse Events 14
Recording and Notification of Adverse Events 14
Safety Monitoring Plan 15
Data and Safety Monitoring Board (DSMB) or Equivalent 15
Ethical Considerations 15
Sharing of Results with Subjects 15
Funding Source 15
Subject Stipends or Payments 15
Publication Plan 15
References 16

List of Abbreviations:

PCa	Prostate Cancer
CH	Celebration Health
ESU	Electrosurgical Generator Unit
FDA	Food and Drug Administration
FH	Florida Hospital
IFU	Instructions for Use
PI	Principal Investigator
PLND	Pelvic Lymph Node Dissection
RARP	Robot-Assisted Radical Prostatectomy
RF	Radiofrequency
USA	United States of America

Introduction

This document is a protocol for a human research study. This study is to be conducted according to United States standards of Good Clinical Practice in accordance with applicable Federal regulations and institutional research policies and procedures.

Prostate cancer (PCa) is the third most common cause of cancer related death in the United States and is the most prevalent non-cutaneous cancer [1]. Pelvic lymph node dissection (PLND) following robot-assisted radical prostatectomy (RARP) is an established technique for determining lymph node metastases [2]. The most frequent post-operative complication of PLND is lymphocele formation. Lymphoceles occur as a result of lymph leakage from lymphatic channels that have been cut during dissection. The Principal Investigator (PI) has previously published findings of an occurrence rate of 51% for lymphocele formation with 15.4% from them being clinically symptomatic. The overall frequency of symptomatic lympocele in patient's that underwent bilateral PLND was equal 6.6% of the evaluated group in this publication [3]. We hypothesize that the incidence of lymphocele's should decrease significantly by attending to careful sealing of these channels using adequate hemostatic tools [3].

Background Information and Scientific Rationale

Bovie Medical Corporation's J-Plasma® helium based plasma technology is a hemostatic tool with FDA clearance for the cutting, coagulation, and ablation of soft tissue. The J-Plasma® system consists of an electrosurgical generator unit (ESU), a handpiece, and a supply of helium gas. Radiofrequency (RF) energy is delivered to the handpiece by the ESU and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows for conduction of the RF energy from the electrode to the patient in the form of a precise helium plasma beam. The energy delivered to the patient via the helium plasma beam is very precise and cooler in temperature in comparison to other surgical energy modalities such as standard RF monopolar energy. Previous studies comparing J-Plasma® to other energy sources demonstrated less or comparable lateral and depth of thermal spread for J-Plasma® in porcine peritoneum, bladder, and small intestine [4]. The precise delivery of energy and minimal thermal injury to collateral tissue makes J-Plasma® a useful surgical tool in procedures such as radical prostatectomy where minimizing damage to collateral tissue is crucial to preserving sexual function and continence. As an example, J-Plasma® has been shown to be clinically effective in the treatment of endometriosis on fallopian tubes, ovaries, and other delicate structures where current RF energy sources cannot be used due to risk of damage [5,6].

This study protocol will evaluate the efficacy of the J-Plasma® helium based plasma technology in the reduction of lymphoceles following PLND during RARP. The J-Plasma® handpiece will be used during the PLND by dissecting the lymph nodes and sealing the lymphatic channels to prevent lymph leakage.

Study Objectives

The primary objective of this study is to evaluate the efficacy of the J-Plasma® helium based plasma technology in the reduction of lymphoceles following PLND during RARP.

Primary Objective/Aim/Goal/Hypothesis

J-Plasma® helium based plasma technology will reduce the occurrence of lymphoceles when used to perform PLND during RARP.

Secondary Objective/Aim/Goal/Hypothesis

N/A

Study Design

Research Design

The study will be a single institution, single arm prospective trial where by 100 patients will be enrolled.

Participants evaluated and scheduled for a PLND during Robotic Assisted Radical Prostatectomy by Dr. Vipul Patel who have met the study inclusion criteria and who have also given informed consent will be enrolled. Enrolled participants will have their PLND performed using J-Plasma® for dissection and sealing of lymphatic channels. An abdominal-pelvic ultrasound will be completed at a follow-up period ranging from 4-12 weeks post operatively to determine if a lymphocele is present as this is the standard of care within Dr. Vipul Patel's clinical practice for all patients who undergo a PLND during RARP. The occurrence rate of lymphoceles in this trial group of 100 patients will be compared to retrospective data of 100 patients acquired from the IRB approved Urologic Robotic Surgery Outcomes Registry # 237998 using the same inclusion/exclusion criteria as defined for enrollment in this protocol and from other published data to determine if the occurrence rate has been reduced.

Study Agent, Device, and/or Intervention Description

The study will be conducted using components of the Bovie Medical J-Plasma® system that have received FDA clearance and are currently commercially available. The J-Plasma® handpieces were cleared under FDA 510k numbers K112233 and K151325 for the delivery of helium gas plasma for cutting, coagulation, and ablation of soft tissue. The Bovie Ultimate high frequency electrosurgical generator was cleared under FDA 510k number K142975 for delivery of RF energy and/or helium gas plasma to cut, coagulate, and ablate soft tissue. Therefore, the cutting, coagulation, and ablation of soft tissue during PLND would be considered on label for the study devices.

STUDY SITE(S)/LOCATION(S) AND NUMBER OF SUBJECTS

Florida Hospital Celebration Global Robotics Institute:
Estimated number of subjects at Florida Hospital sites: 100

Total number of all sites: 1
Estimated number of subjects at all sites combined: 100

MULTI-SITE RESEARCH LOGISTICS/COMMUNICATION PLAN

N/A

RESEARCH CONDUCTED IN A FOREIGN COUNTRY

N/A

COMMUNITY-BASED PARTICIPATORY RESEARCH

N/A

Subject Selection

VULNERABLE POPULATIONS (IF APPLICABLE)

N/A

Employees: If an FH employee meets inclusion criteria their non-participation will not affect their employment status.

INCLUSION CRITERIA

Must answer yes to all:

1. Age 18 – 80
2. Primary diagnosis of Prostate Cancer (ICD-10:C61)
3. Prostate Specific Antigen (PSA) level ≥ 10ng/mL and/or Gleason Score ≥ 7
4. Planned Elective Robotic Assisted Radical Prostatectomy with planned pelvic lymph node dissection.
5. Willing and able to return to clinic for standard of care abdominal ultrasound within 12 weeks post operatively.
6. Able to provide informed consent

EXCLUSION CRITERIA

Must answer no to all:

1. Patient is unwilling or unable to sign or understand informed consent
2. Patient resides outside of the United States
3. Performance of Lymph node dissection was aborted.
4. Presence of implanted mechanical cardiac device.

Resources Available

The research team assigned to the study for screening, consenting and data collection purposes will the Research Coordinator who is a RN and three data abstractors that work on post-operative RARP patient follow up. Two members are medical assistants with experience of screening and consenting in research as well as clinical experience in urology.

- Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. Dr. Patel's clinical practice sees approximately 900 patients a year in consultation for RARP as treatment for prostate cancer. Approximately 11% will be needed for enrollment.
- There is no additional surgical time needed for this study. The approximate surgical time is 90 minutes.

Study Procedures

Subject Recruitment and Screening

Participants for enrollment will be recruited from the clinical practice of Dr. Vipul Patel. A researcher will screen the patient's medical record specifically looking at diagnostic lab and path reports to verify inclusion/exclusion criteria for potential enrollment. If the patient indicates he would like more information, a qualified researcher will approach the patient, in a private room, to provide an overview of the study.

Consent Process and Documentation

If the patient meets the criteria for enrollment and is interested in participating in the study, a researcher will be notified and the informed consent process will commence. Patients will be informed that their participation in the study is voluntary and the decision to participate in no way will affect their care for prostate cancer. If the patient continues to express interest in the study, a copy of the IRB approved informed consent form will be given to the patient to read. The patient will be able to ask questions and have a sufficient amount of time prior to signing the informed consent document. After signing the informed consent form, a complete and signed copy will be given provided to the patient.

In the unlikely event that a non-English speaking patient meets criteria for enrollment, then IRB Short Form procedures will be initiated.

Waiver of Written Documentation of Consent or Waiver of Consent We are requesting a HIPAA waiver for the de-identifiied comparison group that will be looked at

to compare findings of lymphocele formation. This group whose data already exists will be extracted from our urological outcomes database identified in IRBnet as #237998 which has a waiver of consent in place for data used in research.
N/A

Subjects who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

- During screening the health and physical is examined for inclusion and exclusion criteria including information about their past medical and social history. Information from the patient record as well as verbal questioning will be used to identify possible impairment.

Adults Unable to Consent

N/A- informed consent by the patient is a requirement for inclusion.

DOCUMENTATION OF INFORMED CONSENT PROCESS

Documentation of the informed consent process is required to establish that the subject was accurately and adequately informed and that no study-related procedures were initiated prior to obtaining informed consent. A research team member will note in the source documentation the consent process, date consent was obtained and that consent was obtained prior to initiating any research procedures.

RANDOMIZATION

N/A

STUDY VISITS

Visit 1: Inclusion and exclusion criteria will be reviewed. If the patient meets criteria, he will be invited to participate in the research study. The patient will be given the informed consent and it will be reviewed with the patient and all questions will be answered.

Visit 2: Day of Surgery. The only non-standard of care item will be with the use of The Bovie J plasma at lymph node dissection and will not be billed to patient.

Visit 3: Patient returns to Dr. Patel's clinical practice for routine standard of care exam and abdominal ultrasound done at Florida Hospital Celebration.

The following table identifies the procedures in relation to the study timeline.

STUDY VISIT SCHEDULE	*Visit 1 Screening/Consent*	*Visit 2 Surgery day*	*Visit 3 Abdominal US 8wks post op* ***+/- 4 weeks***	
Inclusion and Exclusion Criteria	*X*			
Informed Consent	*X*			
RARP with PLND		*X*		
Abdominal US			*X*	

STUDY DURATION

The study is projected to begin February 2016 once ORA and IRB approval are awarded.

The estimated duration to enroll all study subjects is one year from study approval date.

Participants will remain in the study for 4 months following their robotic assisted radical prostatectomy with pelvic lymph node dissection.

The estimated date for investigators to complete the study and analysis of data July 2017.

MATERIALS OF HUMAN ORIGIN: COLLECTION, PREPARATION, HANDLING AND SHIPPING

N/A

Study Outcome Measures (Endpoints)

The primary outcome to be measured will be the incidence of lymphocele formation as diagnosed upon post- operative abdominal ultrasound. The incidence of lymphocele formation in patients undergoing pelvic lymphnode dissection using the JPlasma® will be compared to de-identified retrospective data of lymphocele formation without the use of JPlasma® extracted from Dr. Patel's urologic outcomes registry identified by IRBnet #237998.

The following data variables and materials will be collected for analysis in this study:

- Age at day of surgery
- Pre-operative Gleason Score
- Pre-operative PSA lab value
- Clinical variables: pathology report from RARP, radiology report from abdominal ultrasound, physician notes, nurses notes.

Data Management and Quality Plan

DATA DE-IDENTIFICATION

- Unique identifiers will be generated by the researcher at the time of enrollment. The number will consist of the last two digits of the year enrolled as well as the number to designate the order in which enrollment occurred.
  Ex: first patient enrolled during 2016 would be designated as patient 16-01
- Data is linked by the research coordinator creating a master log containing patient Name, DOB, DOS MRN and study ID number.
- This link will be used for auditing purposes.
- The linked study master file will be kept on the FH H: drive in a password protected file.
- Members of the GRI Study team as listed on the Delegation Log will have access to this linked file.
- Data will be stored for a minimum of 7 years after the closure of the study.
- The link will be kept for a minimum of 7 years after study closure.

DATA CONFIDENTIALITY, STORAGE, AND RETENTION

All electronic data will be stored in the FH H: drive. Only FH employees will have access to this drive. All files with identifiable data will be encrypted with password protection. Only those indicated on the Delegation Log will have access to the data. The study documentation and paperwork will be stored at Florida Hospital Global Robotics Institute in a locked storage closet during the course of the study. After study closure data will be retained for 7 years at Iron Mountain Records Facility. After that period of time, all individual patient study information will be shredded.

DATA QUALITY

Quality control procedures for this research study include source data verification by randomly selecting 10% of subject records with comparison between the paper case report form (CRF) and the medical record and/or electronic database record of those same data. If errors are common, data will be completely checked prior to data analysis.

DATA SHARING (OUTSIDE OF FLORIDA HOSPITAL)

If any data is to be shared outside of Florida Hospital a formal request will be made to the ORA and FH legal.

Sample Size Determination

The primary outcome measure is the incidence of lymphocele after robot assisted pelvic lymph node dissection. A previously published paper by Dr. Patel on this topic using a cohort of 76 patients was referred to for sample size determination [3].

Statistical Analysis Plan

Primary Objective Analysis

The primary variable of interest is the incidence of lymphocele formation measured at approximately 8 weeks post-operatively. The incidence of lymphocele formation will be compared between the 100 enrolled "treatment" group and a propensity matched "non-treatment" group that will be established using equal inclusion/exclusion criteria, this retrospective lymphocele data will be retrieved from the Urologic Robotic Surgery Outcomes Registry identified by IRBnet #237998. Additional comparisons of demographic (age, race/ethnicity) and oncological information will be accessed to ensure no differences between the two groups.

Potential Risks and Benefits

Potential Benefits

Lymphocele's can lead to symptoms and secondary complications such as abdominal pain, leg pain, lower limb edema, constipation, urinary frequency, deep vein thrombosis and infection or sepsis.

The potential benefits of enrollment of this study will be a hypothesized reduction in the incidence of lymphocele formation thus resulting in a decrease of the symptoms associated with such formation.

Potential Risks

Risks associated with robotic radical prostatectomy as discussed and stated by the physician and included in the surgery consent signed by the patient regardless of enrollment in this study include: severe loss of blood, damage to surrounding organs, tissues, vessels, infection / any of which may necessitate a return to surgery, cardiac arrest which may result from the performance of any surgery/ procedure(s), and in some cases, may lead to partial or permanent disability or death. Additional risks may include, but are not limited to: urinary incontinence, erectile dysfunction, rectal/bowel/ureter injury, bladder neck contracture, pulmonary embolism, urine leak, pneumonia, problems related to positioning and endotracheal tube, blood transfusion, embolus from pneumo-peritoneum, unrecognized injuries and lymphocele formation.

JPlasma® has minimal lateral and depth of thermal spread in a variety of tissue types however; possible risks associated with JPlasma® are: unintended surgical site burns due to direct contact with the cutting tip electrode. Inadvertent activation or movement of the cutting tip instrument outside the field of vision may result in injury to the patient or

surgical team. Electrosurgical devices may cause interference with pacemakers or other implants.

Mitigation of Risks

Side effects will be monitored during follow-up study visits.

Provisions to Protect the Privacy Interest of Subjects

Subjects will be assigned unique identifiers for study-related records. All precautions will be taken to make sure that only authorized individuals will access subject research records. Each member of the Florida Hospital Celebration GRI research team will have access to the securely stored medical charts within Dr. Patel's practice, also the team has a unique id and password allowing them access to electronic medical records. All research team members are trained to follow Florida Hospital's policy on the protection of patient's health and private information. The collection of sensitive information about subjects will be limited to minimum necessary to achieve the aims of the research, so that no unneeded sensitive information will be collected.

Early Withdrawal of Subjects

Investigator Withdrawal of Subjects

Patients that did not receive a pelvic lymph node dissection at the discretion of the surgeon during their robotic radical prostatectomy will be withdrawn from the study.

Patients that do not return for the abdominal ultrasound post operatively as ordered by the physician will be withdrawn from the study.

If a patient is withdrawn from the study they will be notified via telephone call by GRI Research Staff. After 3 failed attempts by phone a certified letter will be mailed to the patient as the final attempt of notification.

All withdrawn participants will be documented in the regulatory binder.

Subject Request for Withdrawal from Study

Subjects may voluntarily withdraw consent at any time during the study without penalty. In all cases of withdrawal, the date and the reason for withdrawal are to be documented per site standard operating procedure.

Data Collection and Follow-up for Withdrawn Subjects

Patients who request withdrawal prior to the post-operative abdominal ultrasound will not be included in the final analysis as there would be unsuccessful collection of the data necessary to conclude the study's end point. Patients who request to withdraw after the abdominal ultrasound will have their data maintained in the research database up to the

point of withdrawal. This data will be included in subsequent analysis because keeping these patients in the analysis is essential for study validity.

Adverse Event Reporting:

Adverse Events

An **adverse event** (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events will be documented as anticipated or unanticipated; minor or serious; and, related or unrelated to study intervention.

Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following outcomes:

- Death during the period of protocol defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in a persistent or significant disability/incapacity

All adverse events that do not meet any of the criteria for **"serious"** should be regarded as **minor adverse events**.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording and Notification of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse

events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document.
All adverse events will be reported according to Florida Hospital IRB guidelines.

Safety Monitoring Plan

Research and safety data will be reviewed by the PI. This review will take place at regular meetings for every 25 enrolled subjects or every 4 months from the first date of enrollment which ever should occur first. These meetings will be with the research coordinator. All CRF data will be source data verified using a risk-based approach to assure the accuracy of the reported data.

Data and Safety Monitoring Board (DSMB) or Equivalent

N/A

Ethical Considerations

N/A

Sharing of Results with Subjects

The ordering physician and or his staff will inform the patient of all results of their surgery. It is standard practice to review the peri-operative and post-operative findings with the patient during their post-operative clinic examination.

Funding Source

This study will be supported by funding from Bovie Medical Corporation.

Subject Stipends or Payments

N/A

Publication Plan

Publication of the results will be based upon appropriate analysis and review of the complete data, and the rules of The International Committee of Medical Journal Editors (ICMJE) for determining authorship will be followed and will guide scientific presentation and publication of the results of this study. Florida Hospital shall be entitled to use the trial results for its own internal teaching, research, education, clinical and publication purposes without the payment of royalties or other fees.

References

1. Walsh PC, Partin AW, Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. *J. Urol.* 1994; 152:1831-6.
2. Zorn KC, Katz MH, Berstein A, et al. Pelvic lymphadectomy during robot-assisted radical prostatectomy: assessing nodal yield, perioperative outcomes, and complications. *Urology*. 2009; 74:296-302.
3. Orvieto MA, Coelho RF, Chauhan S, et al. Incidence of lymphoceles after robot-assisted pelvic lymph node dissection. *BJUI*. 2011;108:1185-1190.
4. Pedroso J, Gutierrez M, Volker W. J-Plasma, monopolar pencil, argon beam and CO_2 laser electrosurgery: comparative evaluation of thermal spread in a porcine tissue model (White Paper). Bovie Medical Corporation. June 2014.
5. McCoy CE. Novel Surgical Approach Targeting Chronic Pelvic Pain with Plasma® (White Paper). Bovie Medical Corporation.
6. McCoy CE. Treating Endometriosis and Chronic Pelvic Pain with J-Plasma® (White Paper). Bovie Medical Corporation.