Protocol Number: MicroUSgFLA 001

Protocol Title: Micro-ultrasound-Guided Focal Laser Ablation (MicroUSgFLA) Treatment for Management of Intermediate-Risk Prostate Cancer: Evaluation of Safety and Effectiveness

Study Team:

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Objective: The main objective of this study is to evaluate the safety and effectiveness of MicroUS-guided focal prostate cancer (PCa) laser ablation.

Study Population: Males, ages 40-85 with biopsy confirmed, organ-confined intermediate-risk (Gleason score 7 (3+4, 4+3), no Grade 5 pattern) early clinical stage PCa (T1c or T2, N0, M0) and identifiable lesion on multi-parametric-MRI (mp-MRI) and MicroUS, with a PSA of < 15ng/mL, who have not yet undergone pelvic radiation or hormonal deprivation therapy and who may not wish to pursue these treatments, radical prostatectomy or Active Surveillance at this time.

Study Design: 6 month, prospective, interventional single-arm safety and effectiveness study (patients would continue to be followed as per Active Surveillance protocol following completion of the study).

Treatment Extent: Less than 30% of the gland will be treated. Treatment will include the Index Lesion visible on MRI and also visible on MicroUS plus margins of 8 to 10 mm; tumour-free margins will not extend beyond the posterior aspect of the prostate capsule. Urethral and bilateral neurovascular bundle preservation will be preferred whenever clinically justified.

Population Size: 7 men.

Primary Outcome Measure: This study will evaluate the safety and feasibility of focal MicroUSgFLA in patients with organ-confined intermediate-risk PCa.

Feasibility measures will include time taken to treat in the span of a typical operating room-like minimally-invasive procedure (Treatment schedule pg. 10), the ability to guide the insertion trocars to the target easily under Micro-ultrasound guidance and the continued compliance of study participants to complete follow-up tests and questionnaires.

To assess the treatment effect on patients' Quality of Life (QoL) the following validated self-reported urogenital functioning assessment instruments will be used before, and following treatment at 3- and 6-months.

a. Urinary symptoms – IPSS.
b. Urinary continence - ICIQ-UI-SF.
c. Sexual function - IIEF-15.

PSA levels and post-treatment PSA kinetics will also be assessed.

Safety Outcome Measure

Occurrence of any treatment associated adverse events during and after treatment, classified according to Clavien-Dindo and CTCAE Version 5.0.

Secondary Outcome Measure:

1. The proportion of patients with organ-confined intermediate-risk PCa undergoing focal MicroUSgFLA treatment free of clinically significant PCa at 6 months, which requires definitive treatment.
2. The proportion of patients with negative 6-month follow-up biopsy results in the treated part of the prostate.
3. The final extent of ablation directly under therapy measured with assistance of MicroUS (and ultrasound contrast agents).
4. The extent of ablation as measured after approximately 5 days with MRI.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men. A recent study of over 18,000 healthy men has shown a 24.5% cumulative histology prevalence of the disease in healthy men over 45 years.[1,2] It is estimated that 248,530 new cases of PCa will be diagnosed clinically in the U.S.A. in 2021, with 34,130 men dying of the disease.[3] Similar proportional statistics apply to Canada. The discordance between histology prevalence, clinical incidence, and mortality forces a reappraisal of the conventional treatment modalities radical prostatectomy, radiation therapy, brachytherapy and hormone therapy because they are associated with the possibility of severe side effects such as bladder dysfunction and impotence,[4,5] osteoporis and risk of fracture[6] to name a few.

Given the indolent nature of many PCa's another option is Active Surveillance, in which the cancer is simply tracked over time with periodic imaging and biopsy, thus avoiding the side effects of active treatment but at the potential expense of missing an opportunity for cure with the risk of subsequent catastrophic disease progression and death.[7]

Ideally the patient with early-stage PCa should have a treatment option that is curative, minimally or non-invasive, single session and is associated with none of the side effects mentioned above. Minimally invasive focal therapy, which involves the image-guided application of a therapeutic source such as high-intensity ultrasound, high power laser light or microwave radiation, intended to thermally coagulate the tumour by raising it to a temperature of greater than 55°C for several minutes while leaving the remainder of the prostate untouched is an attractive option, and indeed there is much evidence of the promise of focal therapy of the prostate in the literature[8,9,10] and with our group's

experience in UHN-REB approved protocols for both MRI- and trans-rectal ultrasound (TRUS)-guided interstitial laser prostate focal therapy.

In protocol 08-0926-c, 4 patients were treated with TRUS-guided laser focal ablation through a transperineal approach followed 1-2 weeks later with radical prostatectomy. The prostate was carefully step sectioned and whole-mount pathology was compared with imaging, confirming that the laser created a confluent burn, limited to the prostate, with no viable tumour cells in the ablated volume. Only one patient suffered a mild adverse event (self-limited constipation).[11] In protocol 06-0670-c, 12 patients were treated with transperineal interstitial laser therapy under TRUS guidance and no patient experienced peri-operative or post-operative complications, with all maintaining potency and continence levels.[12] In both these studies, the tumour target was identified on multi-parametric MRI (mpMRI, consisting of T2-weighted, diffusion-weighted and dynamic contrast agent-enhanced imaging), and images at the ultrasound-guided FLA procedure were fused to the MR images using in-house image fusion software to locate the target accurately since standard TRUS on its own is not a reliable tool to identify a tumour against the backdrop of normal prostate parenchyma.

Employing a completely MRI-based imaging and transperineal treatment guidance platform, under protocol 08-0926 54 patients were treated successfully with MR-guided focal laser ablation (MRgFLA), with the vast majority experiencing no significant impact on urinary continence, erectile function or obstructive symptoms, and approximately 70% having a favourable oncologic outcome (manuscript in preparation). The same treatment under protocol 15-9002 with longer follow-up is underway in 50 more patients with intermediate-risk PCa and continues to show much promise.

Micro-ultrasound

While MRI has shown utility in identifying suspicious cancerous lesions within the prostate where traditionally, barring very obvious hypoechoic lesions conventional TRUS has not, a new ultrasound platform known as micro-ultrasound (MicroUS) is showing promise for detecting clinically significant PCa lesions. Studies have shown it to be comparable to MRI in detection of clinically significant PCa.[13] To the patient it is no different from a standard TRUS imaging system; an ultrasound console situated beside the bed operated by the physician or ultrasound technologist and a trans-rectally-inserted ultrasound probe. What is different is that this ultrasound operates at a much higher frequency of sound than standard TRUS (though the acoustic power output is no different). Standard TRUS probes operate at a centre frequency of 6 to 9 MegaHertz (MHz) with frequency bandwidths of approximately 45%, but the MicroUS probe operates at a centre frequency of 21 MHz, with a 75% frequency bandwidth 13 MHz – 29 MHz providing a 300% improvement in spatial resolution of the image, down to 70 microns. At this increased frequency, subtle features of the tumour that are not identifiable with standard TRUS become discernable and distinguishable from non-cancerous prostate tissue.

Evidence from a large randomized clinical trial (clinical trials.gov ID NCT02079025) suggests that the MicroUS system is more sensitive than conventional TRUS to detect PCa. During the course of the RCT, the PRI-MUS (Prostate Risk Identification Using Micro-Ultrasound)[14] scoring system was developed and validated to assess the risk of PCa for targeted biopsy with the MicroUS platform, similar to the PIRADS scoring system for suspicious areas on mpMRI.[15] Some sonographic features described in PRI-MUS were also noted to correlate with histo-pathology subtypes such as cribriform pattern, which have prognostic implications for patients.

In a recent feasibility study comparing conventional TRUS, MicroUS and MRI in 9 Active Surveillance patients, MicroUS outperformed mpMRI by detecting 89% of clinically significant PCa lesions compared to 56% by mpMRI. There were four clinically significant PCa lesions (Gleason score ≥ 3+4) that were prospectively detected by MicroUS but not on mpMRI.[16] One of the postulated reasons for superior sensitivity of MicroUS may be that small infiltrative tumours intermixed with normal tissue may not show restricted diffusion on diffusion-weighted imaging and therefore may not be detected on mpMRI.[17]

MicroUS-guided biopsy in the Princess Margaret Cancer Centre continues under UHN REB-approved Protocol Micro-US/MRI 001, performed by an Interventional Radiologist (SG) with 17 years experience performing TRUS prostate biopsies and 3 years and approximately 200 patients experience performing MicroUS-guided imaging and biopsies, with confidence at identifying the sonographic features typical of suspicious lesions at high frequency.

Motivation for this study

Performing interstitial laser thermal therapy in a simpler setting than MRI but with equally reliable abilities to visualize and target the tumour is being investigated in this pilot study of 7 patients. The ability to reliably destroy the tumour target under MicroUS guidance while sparing damage to surrounding critical structures, as with MRgFLA, in this small cohort will be extremely suggestive of the promise of MicroUS-guided FLA (MicroUSgFLA) in treating foci of localized PCa in the greater population. It would spare the expense of procedures performed under MRI guidance, would allow for treatment of men in remote communities that might not have local access to MRI imaging and treatment delivery systems, and operator expertise, and would allow those who are contraindicated for MRI due to such conditions as severe claustrophobia or metallic implants to still receive treatment, under an ultrasound-based platform instead.

STUDY OBJECTIVES

The main objectives of this study are to evaluate the safety, and effectiveness of MicroUSgFLA of the tumour based on mp-MRI and biopsy of the treated area at 6 months. Treatment will include the PCa lesion, which must be visible on MRI and MicroUS plus negative margins of 8 to 10 mm; margins will not extend beyond the posterior aspect of the prostate capsule.

INVESTIGATOR

The investigators have the overall responsibility for the conduct and compliance of this clinical trial according to this protocol and Good Clinical Practices.

ADMINISTRATIVE REQUIREMENTS AND QUALITY ASSURANCE

Research Ethics Board (REB)

This protocol and its associated Informed Consent form must be reviewed and approved by the appropriate Research Ethics Board (REB) associated with the study site. All protocol amendments must be approved by the REB prior to their implementation. A copy of the letter signed by the Chair of the REB to the Principal Investigator indicating REB approval of the protocol must be received by the PI and maintained in the study file prior to study initiation.

Informed Consent

The risks and benefits of participating in the study will be explained to each potential patient prior to entering into the study. The Principal Investigator's designee must obtain a signed Informed Consent Form for each patient. Receipt of the signed Informed Consent Form will be documented in the Case Report Form and a copy retained by the Investigator. A copy of the signed Informed Consent Form is given to each patient.

Reports to REB/Ethics Committee (EC)

The Investigator will make an accurate and adequate final report to the REB within one (1) month after completion or termination of the study.

STUDY DESIGN

General design

This is a single centre, single-arm, open-label study to evaluate the safety and feasibility of MicroUS-guided focal PCa laser ablation in patients with organ-confined intermediate-risk PCa who have not yet received treatment for their cancer. Patients fulfilling the inclusion criteria, having none of the clinical exclusion criteria and who may not wish to pursue whole gland therapy or Active Surveillance at this time will be enrolled into the study after they (or their legal representative) have signed the Informed Consent Form. No control group will be utilized and all patients will receive MicroUS-guided FLA for their focal PCa. As part of the screening process, patients will provide a medical history, blood and urine samples, and undergo a physical examination including a digital rectal examination (DRE). At the first visit, patients will also be given a copy of the Informed

Consent and a copy of QoL and performance questionnaires to assess urinary and erectile function (IPSS and ICIQ-UI-SF questionnaires for urinary function, IIEF-15 questionnaire for erectile function). Men with a single focus of disease ≤15mm suspected on standard of care MRI will undergo prostate biopsy using either a standard frequency ultrasound machine with or without the MRI-TRUS fusion device Artemis 2.0, at the physician's discretion, or under MicroUS guidance. A systematic biopsy consisting of 12 cores to 12 sectors plus an additional 2-4 cores targeted to any MRI/MicroUS suspicious finding will be performed. For inclusion, all patients will have MRI and prostate biopsy within 12 months of treatment. On preoperative examination (Visit 1) - blood and urine samples will be taken. If the screening biopsy was not performed with the MicroUS device then a MicroUS imaging session will be performed at Visit 1 to be sure that the tumour target is visible on MicroUS (it will be known a priori that the tumour target is visible on MicroUS if the screening biopsy was performed with this device). At Visit 2 – the focal treatment will be performed under appropriate anesthesia (regional or general anesthesia, or conscious sedation, as determined by the anesthesiologist) - in the TGH research Interventional Radiology suite (or similar facility). The treatment is expected to last approximately 2-3 hours, and patients are not expected to experience any pain during the procedure. Laser ablation will be monitored by real-time ultrasound tracking of the ablation zone and ensuring that treatment does not extend to critical structures, and by one or more temperature probes placed into the prostate in the vicinity of the target treatment area. At the physician's discretion, an additional one or more temperature probes will be placed at the rectoprostatic angle to monitor the temperature close to the rectum as a precautionary measure.

At the physician's discretion, a contrast agent-enhanced MicroUS scan will be performed during and/or immediately after the procedure as an additional way to track the ablation volume, by demonstrating a lack of enhancement of the ultrasound signal within the ablation volume due to the coagulated and locally sealed blood vessels against the backdrop of enhancing, unaffected prostate tissue. The contrast agent will be administered by intravenous injection using the existing iv-access catheter that was placed by the anesthesiologist, and the MicroUS device will be set to the contrast agent imaging mode.

The size and location of the ablation volume will be measured and compared to the planned target volume and the proximity of the lesion to the urethra and rectum. If the ablation volume does not encompass the target volume and is still a safe distance from either critical structure, FLA may be continued or repeated.

After the treatment the patient will be transferred to an appropriate recovery area for monitoring. Patients will be able to return home the day of the procedure.

On days 5 (+/- 3 days), 90 (+/- 7 days) and 180 (+/- 14 days) following the procedure, patients will be assessed for clinical signs of urinary, rectal, and erectile complications and will complete validated self-assessment tools for these functions at days 90 and 180. All patients will undergo mpMRI of the prostate at day 5 (+/- 3 days) following treatment

to confirm that ablation covered the tumour target. Free/Total PSA will be monitored at the preoperative examination (Visit 1) and after treatment at days 90 and 180 (Visits 4 and 5), in order to try to understand the initial effect of MicroUSgFLA on PSA. Six months after the procedure (Visit 5),a study biopsy using MicroUS or the fusion device Artemis 2.0 will be performed with 3-8 needle cores aimed to the ablated lesion and the margins surrounding it to verify the oncological effectiveness of the treatment.

Study duration

The duration of the study for each patient is 6 months.

Number of patients

Seven (7) patients will be enrolled in this study. All patients who are eligible will be evaluated for inclusion.

Stopping rules

The study will be discontinued if an unwanted effect (adverse event) related to the procedure is considered severe by the Investigator and/or the Research Ethics Board and endangers the health of enrolled patients.

PROCEDURES OF THERAPY

Tumour localization

Eligible patients will have a transrectal, ultrasound-guided biopsy-confirmed PCa, with NCCN intermediate-risk characteristics (primary Gleason score ≤ 4, maximum Gleason score 7, and PSA below 15 ng/mL). Specific tumour location will be confirmed by mpMRI with all images reviewed by a single radiologist (SG) experienced in prostate MRI interpretation. Following the MRI, patients will undergo MicroUS imaging to locate the same lesion for biopsy or, if the biopsy is performed with a standard frequency ultrasound device then MicroUS imaging will be performed only to be sure the tumour target can be visualized on MicroUS, prior to proceeding to therapy.

Light delivery

The insertion location of the laser applicator(s) will be performed tranperineally and determined according to maximum overlap between the expected treatment zone and the location of the tumour as determined by the MRI and MicroUS analysis. The light dose will be determined based on previous experience from MRI-guided Laser Interstitial Thermal Therapy.

Light source and light delivery laser applicator

The laser unit and laser applicators to be used in this study are part of the CLS TRANBERG® Thermal Therapy System which is FDA approved, is indicated for use in surgical applications requiring the ablation, vaporization, excision, incision and coagulation of soft tissue, and which has already been UHN-REB approved for use in our MRgFLA clinical trials.

Details of its operation and technical specifications are listed in Protocol 15-9002. Briefly, a variable power diode laser feeds laser light at the wavelength 1064 nm into tissue through an interstitially placed sterile optical fibre (laser applicator). At this wavelength, the light is preferentially absorbed by tissue, creating an elevated temperature and thus thermal coagulation. Coagulation of the tumour ensures no bleeding or collateral damage and the diffusing tip design reduces the possibility of charring of the tissue.

Laser applicator and temperature probe insertion

The placement of the light-delivery laser applicators will be performed transperineally into the prostate for the treatment of PCa. Following appropriate anesthesia, the patient will be placed in a semi- or full-lithotomy position, to be decided at the physician's discretion, the insertion area will be disinfected and draped, and the single use devices will be inserted into the patient’s perineum under MicroUS guidance until they reach the target.

Specifically, an insertion catheter is first placed into the prostate by means of a stiff trocar contained within. Once the catheter has arrived at the target site the trocar is removed and the laser applicator is inserted. The catheter is then retracted a few centimetres, enough to expose the light diffusing part of the laser applicator. The entire process is monitored by MicroUS to ensure the laser applicator arrives at, and remains at the tumour target. The design allows light to emanate 360^{o} around its circumference into the surrounding tissue, creating a coagulation volume in the shape of a sphere or an ellipse. The maximum laser power to be used in this protocol is 15W, and the power can be adjusted based on MicroUS and temperature monitoring. The temperature probes are inserted in a similar manner to the laser applicators; the connectors of these probes attach to the laser base unit which converts the returned signal into temperature and displays this in real time. In practice, the patient will undergo a total of 2 to 8 trans-perineal punctures.

During the previous interstitial photo-thermal focal therapy studies, conducted safely with no side effects, the placement of laser applicators went without difficulty and none of the procedures had to be stopped due to excessive heat in neighbouring structures (urethra or rectum), which can be evaluated by tissue temperature probes placed at the recto-prostatic angle.

Procedures to protect the bladder and rectum

The primary approach to ensure that the bladder, rectum, and urethra do not receive a significant interstitial laser thermal dose will be to limit the light fluence reaching these

structures through the accurate and verified placement of the laser applicators under MicroUS guidance. It has been established in pre-clinical studies that the zone of laser thermal damage in the prostate is sharply delineated.[18] The planned size of the damage zone will be based on the previous UHN-REB approved studies conducted by our group. These studies indicate that the typical ablation zone diameter is approximately 12±1.7 mm. The planned treatment volume will encompass the tumour volume plus a margin of 8 to 10 mm where feasible and safe to do so. Treatment will not extend beyond the posterior aspect of the prostate capsule.

Where these planning rules conflict, the safety margins defined above will take precedence. The treatment boundary may extend to the capsule in other regions of the prostate.

Additionally, CLS TRANBERG® tissue temperature probe(s) may be inserted into the recto-prostatic angle to further ensure the rectum remains at a safe temperature.

Treatment schedule

The schedule and time estimation (in minutes) of the total procedure is provided below:

Time	Action Taken
0 to 30	Induction of anesthesia, ongoing vital signs monitoring.
30 to 60	Positioning of the patient, disinfecting, draping, insertion of Foley catheter.
60 to 80	MicroUS probe insertion and tumour visualization/localization and treatment planning.
80 to 100	Insertion and localization of introducers and potential tissue temperature probes.
100 to 120	Replacement of insertion trocars with laser applicators and repositioning of applicator for complete coverage.
120 to 150	Illumination, parameter monitoring.
150 to 160	Removal of laser applicators, ongoing vital signs monitoring.

Following the procedure and appropriate post-procedure recovery and assessment, the patient will be discharged. Catheter removal at the post-procedure day 3 follow up will be determined by clinical characteristics and a trial of void will be conducted. All patients will be monitored for adverse events on an ongoing basis.

LABORATORY INVESTIGATIONS

Standard haematological Tests

Hemoglobin (mmol/l)

Red cell count (T/l)
M.C.V. (fl)
Haematocrit (%)
M.C.H. (fmol)
White cell count (G/l
Differential white cell count (%)
Platelet count (G/l)
Prothrombin Time (sec)
aPTT (sec)

Standard blood chemistry tests

Creatinine (micromol/l)
Specific blood chemistry test
Prostate-Specific Antigen (PSA)
Standard urinalysis
C&S Urine

PATIENT POPULATION

This study is designed to include 7 patients who have histologically proven organ-confined intermediate-risk adenocarcinoma of the prostate.

INCLUSION CRITERIA

Patients meeting all of the following inclusion criteria will be eligible for the study:

- Men 40-80 years of age.
- Histologically-proven intermediate-risk PCa (Gleason score 7, primary grade ≤ 4).
- PCa clinical stage T1c or T2.
- MRI/MicroUS site suspicious for cancer or cancer mapped to one prostate lobe.
- Maximum dimension of MRI/MicroUS visible tumour ≤15mm.
- Suspicious site on Prostate MRI/MicroUS must coincide with sector positive for cancer on biopsy.
- Prostate specific antigen (PSA) level < 15 ng/mL.
- IPSS, ICIQ-UI-SF, IIEF-15 questionnaires completed prior to the procedure.
- Life expectancy of greater than 10 years, based on co-morbidity not related to PCa.

EXCLUSION CRITERIA

Patients with any of the following criteria will be excluded from study participation:

- Maximum dimension of MRI/MicroUS visible tumour > 15 mm.

- Patients medically unfit for focal therapy of the prostate.
- Patients who are unwilling or unable to give informed consent.
- Patients who have received androgen suppression therapy.
- Patients who have received or are receiving chemotherapy for prostate carcinoma.
- Patients previously treated with surgery to the prostate (traditional, endoscopic or minimally invasive) including HIFU, TUNA, RITA, microwave, cryotherapy or any curative treatment.
- Patients who have undergone radiation therapy for PCa or to the pelvis.
- Any condition or history of illness or surgery that, in the opinion of the Investigator, might confound the results of the study or pose additional risks to the patient (e.g. significant cardiovascular conditions or allergies).
- Patients with a history of non-compliance with medical therapy and/or medical recommendations.
- Patients who are unwilling or unable to complete the patient self-assessment questionnaires.
- Chronic or acute prostatitis, neurogenic bladder, urinary tract infection, sphincter abnormalities, or any other symptom that prevents normal micturition.
- Patients who have participated in a clinical study and/or received treatment with an investigational treatment and/or product within the past 90 days.
- Patients with contraindication to MRI (i.e. pacemaker, hip prosthesis, severe claustrophobia, brain aneurysm clip, allergy to MRI contrast agent)

EVALUATION OF SAFETY AND TOLERABILITY

Criteria

The evaluation of safety will be based on reported adverse events, changes in vital signs and laboratory tests throughout the course of the study.

Distinctions will be made between adverse events that are not related to the study treatment, related to the study treatment, or related to the technical laser thermal therapy procedure. The protocol will be re-evaluated for any serious adverse event that is considered related to the study treatment and/or the laser thermal treatment procedure.

The following specific examinations are scheduled to monitor particular organs or functions that require attention following treatment by interstitial laser thermal therapy:

- Urinary function (specific Inclusion Visit and post-treatment evaluations including patient questionnaires (IPSS), ultrasound and MR Imaging, and urinalysis).

- Urinary Continence, ICIQ-UI-SF.

- Erectile function will be monitored with a specific IIEF-15 questionnaire.

Adverse events

Each patient must be carefully monitored for adverse events. This includes abnormal laboratory values that are outside the parameters of the protocol or are considered clinically significant by the Investigator. An assessment for adverse events must be made regarding the seriousness, intensity and relationship to the FLA.

Adverse events (AEs) are illnesses, signs or symptoms that have appeared or worsened during the course of the study. All AEs volunteered by the patient or elicited by the Investigator must be recorded. All AEs must be recorded whether or not they are considered by the Investigator to be treatment and/or procedure-related. Whenever the Investigator is confident of the diagnosis, he/she should group together related signs, symptoms and abnormal laboratory test results as a single illness.

Patients experiencing AEs that result in discontinuation from the study or that are ongoing at the end of the study should have appropriate follow-up until such time as the event resolves, the patient's condition stabilizes, or until it is determined that the event is not due to the test device procedure.

A serious adverse event (SAE) means any complication whose clinical significance is greater than anticipated, or which occurs with a frequency greater than is usually seen and reported for this type of treatment.

Criteria for SAE may also include the following:

- Is life threatening.
- Prolongs hospitalization.
- Results in permanent impairment of a bodily function or permanent damage to the body structure.
- Necessitates immediate medical or surgical treatment to preclude permanent damage or impairment.

Unanticipated adverse events means any SAE that was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problems associated with a device that relates to the rights, safety, or welfare of patients.

In the event of an incident that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, report the incident and the circumstances surrounding it to the Director and the manufacturer or importer of the device, within 72 hours after its discovery.

Any other serious and unanticipated adverse device effects noted during the study should immediately be evaluated and reported no later than ten (10) working days to the reviewing REB.

The contact person for this study is:

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The following should be determined and recorded on the case report forms:

(1) frequency
(2) severity
(3) type
(4) relation to thermal therapy
(5) action taken
(6) outcome

The **severity** of the adverse event will be characterized as mild, moderate or severe as follows:

Mild - effects are usually transient, requiring no special treatment and not interfering with the subject's daily activities.

Moderate - effects usually introduce a low level of inconvenience or concern to the subject and may interfere with daily activities but are generally alleviated by simple therapeutic measures.

Severe - effects interrupt a subject's daily activities and usually require systemic drug therapy or other treatment.

Every effort should be made to determine the cause of each AE since a judgment must be made as to whether or not it is related to the interstitial laser thermal therapy procedure. The relation needs to be graded and recorded on the case report form as follows:

Not Related - the AE is due to the underlying disease state or is due to concomitant medication or therapy not related to the interstitial laser thermal therapy.

Possibly Related - the AE had a minimal temporal relationship to the interstitial laser thermal therapy and/or an alternative etiology is more likely.

Probably Related - the AE had a strong temporal relationship to the interstitial laser thermal therapy and alternative etiology is less likely compared to the potential relationship to the interstitial laser thermal therapy.

Definitely Related - the AE had a strong temporal relationship to the interstitial laser thermal therapy, and another etiology is unlikely.

Unknown - temporal relationship to the interstitial laser thermal therapy cannot be determined and alternative etiology is equal compared to the potential relationship to the interstitial laser thermal therapy.

DISCONTINUATION FROM STUDY

Patients may be withdrawn for any of the following reasons: patient choice, patient non-compliance, patient loss to follow-up, serious adverse effect, severe illness, need for re-treatment or Investigator decision.

DATA COLLECTION

Case report form completion

A Case Report Form (CRF) will be provided for each subject. CRFs will be completed in a timely manner by study personnel. All fields and blanks must be completed. If an entry on the CRF needs to be changed during the study, the correction will be made as follows:

- Draw a single line through the incorrect entry leaving it identifiable, and enter the correct information.
- Date and initial the change.
- White-out or erasure on the CRF is not permitted under any circumstances.

The following abbreviations will be used when values or answers cannot be provided:

NA = Not Applicable
ND = Not Done
UNK = Unknown

Reporting and recording of data

All study data will be recorded on the Case Report Forms (CRF). All CRFs must be made available to the Study Monitor as soon as they have been completed so that the validity and completeness of the forms can be determined. If possible, all CRF data should originate from a verifiable medical record. All data should be recorded in black ink on the CRF for ease of duplication, interpretation and analysis. Any corrections should be made by scoring through the original value with a single line and writing the new value next to the initial entry with the Investigator initialling and dating the new entry.

Only the Investigator or designated staff may amend or otherwise alter any data entered onto the CRF. Also, any changes must be made on all copies of the document so that there is no difference between copies. If the reason for the correction is not apparent, then when appropriate, a brief explanation of the reason for the correction should be made. Correction fluids should never be used on any document.

DATA HANDLING, RECORD KEEPING AND RETENTION

A copy of all study data and documentation must be retained in the files of the responsible Investigator for 10 years. The information will be kept in a locked and secure area by the Principal Investigator. Only the study team and representatives of the University Health Network, including the Research Ethics Board will have access to the study-related records.

All information collected during the study, including personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. The patient will not be named in any reports, publications, or presentations that may arise from this study.

The subject's recruitment information along with medical record number **will not** be stored along with the patient's CRF binder. It will be kept in the study coordinator's office during the study. All files of screen failure subjects and the CRFs of the patients who complete the study will be transferred and stored within PMCC for 10 years.

If the Principal Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility.

PROTOCOL DEVIATIONS

In medical emergencies, the Investigator will use medical judgment and remove the participant from immediate hazard, then notify the REB regarding the type of emergency and course of action taken. Any other changes or deviations from the protocol will be made as an amendment to the protocol and must be approved by the REB before being implemented.

REPORTING & PUBLICATION OF RESULTS

Results will be published in a peer-reviewed journal(s).

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1. APPENDIX A: SCHEDULE OF EVENTS

Procedure	Screening Visit 1		Visit 2 FLA Procedure	Visit 3 Post-Focal Day 5 (+/- 3 Days)	Visit 4 Month 3 (+/- 7 Days)	Visit 5 Month 6 (+/- 14 Days)
	Screening/Inclusion	Pre-op Consult.				
Informed Consent	X					
Physical Exam	X			X	X	X
Medical History	X					
Inclusion/Exclusion	X					
DRE	X					X
MRI				X		X
MicroUS for Biopsy or Confirmation of Tumour Target Visibility	X					
Biopsy						X
Catheter removal				X		
PSA Level	X				X	X
Free/Total PSA	X				X	X
Urinalysis	X				X	X
Blood Chemistry and Hematology	X					
Adverse Events	X		X	X	X	X
Vital Signs	X		X	X	X	X
Patient Questionnaires	X				X	X
Concomitant Medications	X		X	X	X	X
Meeting with Study Anesthetist		X				