Full title of trial	A study to evaluate the performance of en-face fluorescence confocal microscopy (LaserSAFE) for margin analysis during radical prostatectomy
Short title	The LaserSAFE study
Version and date of protocol	Version 1.1, [14/01/2026]
Sponsor:	University College London (UCL)
Sponsor reference number:	EDGE 199328
Funder (s):	UCLH Charity no 7298 Samantree Medical S.A.
IRAS Number:	IRAS Project ID: 364428
ISRCTN / Clinicaltrials.gov no:	TBC
UCL Data Protection Number:	No Z6364106/2025/10/66 medical research
Intervention:	LaserSAFE analysis

Chief investigator:	Sponsor Representative:
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PROTOCOL VERSION HISTORY

Version Stage	**Versions Number**	**Version Date**	**Protocol updated & finalised by;**	**Reasons for Update**
Final/IRAS submission	1.1	14/01/2026	Ricardo Almeida-Magana	Amended threshold for secondary resection and associated endpoints
Draft	1.0	17/12/2025	JRO	Monitoring
	1.0	01/12/2025	Ricardo Almeida-Magana	Updated Funder and EDGE details
	0.2	29/10/2025	Ricardo Almeida-Magana	Peer review suggestions
	0.1	13/10/2025	Ricardo Almeida-Magana	Original version

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the U.K. Policy Framework for Health and Social Care Research 2017 (3rd edition) (as amended thereafter), the EU General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018), Sponsor SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the research investigation without the prior written consent of the Sponsor.

I (investigator) agree to ensure that no research activity or recruitment will commence at participating research sites until the appropriate regulatory approvals and NHS confirmations of Capacity and Capability have been issued, and Sponsor green light confirmed.

I (investigator) also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given. Any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature: ..  **..... Date..15/1/2026**

Print Name (in full): Gregory Shaw

Position: Professor of Urology

On behalf of the Study Sponsor:

Signature: .....  **..... Date.16./.01./.2026**

Print Name (in full): .....Pushpsen Joshi.....

Position: .....Research Governance Manager.....

STUDY SUMMARY

Identifiers	
IRAS Number:	ID: 364428
REC Reference No.:	TBC
Sponsor Reference No.:	EDGE 199328
Other research reference number(s):	UCL Data Protection number: No Z6364106/2025/10/66
Full (Scientific) title:	A study to evaluate the performance of en-face fluorescence confocal microscopy (LaserSAFE) for margin analysis during radical prostatectomy.
Short title:	The LaserSAFE study
Health condition(s) or problem(s) studied:	Prostate cancer.
Study Type:	Prospective cohort clinical trial.
Aim(s):	The main aim is to investigate the ability of the LaserSAFE technique to detect positive margins during radical prostatectomy compared to final paraffin analysis
Objectives:	Primary objective • To establish the sensitivity of pathology led LaserSAFE image interpretation to guide nerve-sparing decisions during radical prostatectomy Secondary objectives • To evaluate the accuracy metrics of pathology led LaserSAFE image interpretation against FFPE • To establish the optimal cut-off criteria to suggest a secondary resection should be performed based on LaserSAFE results • To describe the prevalence of PSM in the cohort • To evaluate the rate of PCa recurrence within 12 months of surgery • To evaluate the urinary incontinence and erectile function scores of patients at 3 and 12 months after surgery using the EPIC-26 questionnaire
Type of trial:	Prospective cohort non-randomised clinical trial in patients diagnosed with localised prostate cancer.

Trial design and methods:	This trial will be a multi-site, prospective, non-randomised cohort study. Participants will undergo a robotic assisted radical prostatectomy with bilateral intrafascial nerve-sparing. The LaserSAFE technique will be used to analyse the posterolateral surfaces of the prostate. In cases where a PSM is found which fulfils the criteria for secondary resection this will be carried out by the operating surgeon before the end of the procedure. All samples will be processed using standard FFPE that will act as the reference standard. Patients will be monitored according to the standard of care at each centre. Quality of life questionnaires will be collected at before surgery, at 3 and 12 months after surgery. An adaptive design will allow monitoring of accuracy metrics thought the trial and adjust secondary resection criteria to maximise nerve-sparing.
Trial duration per participant:	12 months.
Key Study milestones:	Submission for REC and HRA approval: December 2025 Acquire REC and HRA approval: TBC Commence recruitment at primary site: TBC Open secondary sites: TBC Proposed completion: TBC
Estimated total trial duration:	60 months
Planned trial sites:	Multisite study UCLH
Total number of participants planned:	693 patients
Main inclusion/exclusion criteria:	Inclusion criteria: • Patients diagnosed with clinically significant operable cT2-T3a N0 M0 PC. • Medically fit to undergo RARP. • Scheduled for robot-assisted RARP with a recommendation against intrafascial nerve sparing on at least 1 side based on multidisciplinary meetings informed by MRI, biopsy result and clinical factors. • Ability to read English sufficiently to understand PIS and able to give informed consent. Exclusion criteria: • Patients who received neo-adjuvant ADT.

	• MRI informed very low likelihood for extra prostatic extension in the proximity of NVB (Based on EPE Likert 1 score or tumour away from the posterolateral areas of the prostate) • MRI informed high likelihood for extra prostatic extension in the proximity of NVB (based on Likert 5 score or bulging tumour on MRI T2 images) • Patients in whom preoperative imaging shows rectal involvement or seminal vesicle invasion in which nerve-sparing is deemed not feasible due to oncological safety concerns. • Patients who received previous treatment for prostate cancer: External beam radiotherapy, brachytherapy, focal therapy, chemotherapy.
Statistical methodology and analysis:	Statistical analysis The primary analysis will evaluate the sensitivity of LaserSAFE to diagnose positive surgical margins per side against the final paraffin analysis. Specificity and positive and negative predictive values will be reported. Measures of accuracy will be presented with 95% confidence intervals. A definitive protocol for statistical analysis will be finalised before recruitment is finished.
Funding & Other	
Funding:	UCLH Charity Number 7298
Other support:	SamanTree Medical SA
Key Study Contacts TBD	
Committees	TMG
Sub-contractors	None

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC and JRO of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and JRO.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

OTHER: add other key personal/entity responsibilities where relevant to the study

TRIAL PERSONNEL

See protocol cover page for Chief Investigator and Sponsor contact details.

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KEY WORDS

Prostate cancer, robotic radical prostatectomy, frozen section analysis, fluorescence confocal microscopy

LIST OF ABBREVIATIONS

Abbreviations

Abbreviations	***Definition***
BCR	*Biochemical Recurrence*
CI	*Chief investigator*
CIV	*Cite Initiation Visit*
DRE	*Digital Rectal examination*
EF	*Erectile Function*
EPE	*Extra-Prostatic Extension*
EPIC-26	*Expanded Cancer Index Composite-26*
FCM	*Fluorescence confocal microscopy*
ICF	*Informed Consent Form*
IFS	*Intra-operative Frozen Section*
IIEF-5	*International Index of Erectile Function*
LPF	*Lateral Prostatic Fascia*
mpMRI	*Multi-parametric Magnetic Resonance Imaging*
NHS	*National Health Service*
NIHR	*National Institute of Health Research*
NS	*Nerve-sparing*
NVBs	*Neurovascular bundles*
NSM	*Negative surgical margin*
OR	*Operating room*
PC	*Prostate Cancer*

PDE5i	*Phosphodiesterase Type 5 Inhibitor*
PI	*Principal Investigator*
PIS	*Participant Information Sheet*
PPI	*Patient and Public Involvement*
PROMs	*Patient Reported Outcome Measure*
PSA	*Prostate-Specific Antigen*
PSM	*Positive Surgical Margin*
RARP	*Robotic assisted radical prostatectomy*
RCT	*Randomised Control Trial*
REC	*Research Ethics Committee*
SAP	*Statistical Analysis Plan*
SAEs	*Serious Adverse Events*
SIV	*Site initiation visit*
SR	*Secondary Resection*
TMG	*Trial Management Group*
UCL	*University College London*
UCLH	*University of London College Hospitals*
UK	*United Kingdom*

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Study summary

Prostate cancer is the most common solid cancer affecting male patients worldwide. When diagnosed early, it can usually be cured with surgery (radical prostatectomy). However, this procedure can be associated with side effects such as urinary incontinence and decrease or loss of erectile function. To reduce the risk of these side effects, surgeons can preserve the nerve bundles that surround the posterolateral aspect of the prostate. However, if the tumour is extending beyond the prostate (extra-prostatic extension) close to these nerves, sparing them increases the risk of leaving cancer cells behind (positive margins). Although small positive margins appear to not be of risk to patients, larger positive margins are associated with cancer recurrence and the need for additional treatment.

Combining clinical, prostate biopsy information and magnetic resonance imaging (MRI) is the current standard method to pre-operatively predict the extent of the tumour and plan the degree of nerve-sparing deemed safe. However, these methods are poor predictors of extra-prostatic extension, resulting in many patients not being offered nerve-sparing when this could have been a safe option, placing them at risk of poor functional outcomes.

To overcome this challenge a technique called NeuroSAFE was developed in Germany. It involves taking samples of tissue from the surface of the prostate adjacent to the peri prostatic nerves, to perform a frozen section (FS) analysis. A pathologist then examines these FS samples for the presence of cancer cells at the edge of the prostate. If NeuroSAFE is positive, the surgeon can remove the corresponding nerve-bundle during the same operation to achieve a negative margin (secondary resection). This technique allows more patients to be eligible for nerve-sparing. Our group has published the results of a phase 3 randomised controlled trial which confirmed that guiding nerve-sparing decisions with NeuroSAFE can improve patient reported erectile and urinary continence outcomes. However, performing NeuroSAFE is not possible in many centres across the UK and the world. This is because it requires an expert team of pathologist and 2 technicians and is both time and resource intensive.

An alternative technique called fluorescence confocal microscopy (FCM), can be used to examine the surface of tissues to produce digital images with cellular level detail. It is much more straightforward to perform than NeuroSAFE and requires less time and resources. Furthermore, the microscope can be placed in the operating room, eliminating the need to transport samples from the operating room to the pathology laboratory. We have developed a standardised FCM technique to evaluate the posterolateral aspect of prostatectomy specimens, which we have called LaserSAFE. We recently completed and reported a feasibility study where the accuracy outcomes of LaserSAFE appear equivalent to NeuroSAFE. However, before this technique is incorporated in clinical practice, a study evaluating its clinical impact when used to guide nerve-sparing decisions is necessary.

We aim to evaluate the accuracy of LaserSAFE to detect positive margins, and define the best cut-off point to tolerate small positive margins which may bear no clinical risk to patients while maximising the potential for nerve sparing and maintaining oncological safety. Patients with localised prostate cancer undergoing radical prostatectomy will undergo bilateral nerve-sparing, the prostate specimen will be analysed using LaserSAFE and the result will inform the need for secondary resection. A pathologists will then review the final paraffin embedded specimens for the presence of positive margins. At pre-specified intervals we will evaluate the accuracy metrics of LaserSAFE against final pathology results to monitor its safety. Additionally, the length of positive margin that triggers a secondary resection will be evaluated at pre-specified intervals. This will determine the best

threshold to guide nerve-sparing decisions using LaserSAFE. If proven to be accurate and safe, the LaserSAFE technique will help expand access to nerve-sparing to many patients across the world.

1.2. Lay Summary

Prostate cancer is the most common cancer in men. If it is found early, it can often be cured with surgery to remove the prostate (radical prostatectomy). However, this surgery can cause side effects such as urine leakage (incontinence) and problems with erections. To reduce these risks, surgeons try to preserve the delicate nerves that run alongside the prostate. Unfortunately, if the cancer has spread just beyond the prostate, sparing these nerves can increase the chance of leaving cancer behind.

Currently, doctors use scans and biopsy results to decide whether it is safe to spare the nerves, but these methods are not very accurate. This means many men miss out on nerve-sparing when it could have been safe, leading to worse quality of life.

A technique called NeuroSAFE was developed to improve these decisions. During surgery, samples from the edge of the prostate are checked under the microscope. If cancer is seen, the surgeon can remove the nearby nerves straight away. By enabling more patients to receive nerve-sparing safely, NeuroSAFE has been shown to improve both early urinary control and sexual function. However, it is complex, time-consuming, and requires a large specialist team, making it hard to use in many hospitals.

A new approach called LaserSAFE may overcome these problems. It uses a type of microscope (fluorescence confocal microscopy) that produces detailed images of tissue directly in the operating room, without the need for a full pathology team. Our early research has shown that LaserSAFE can be as accurate as NeuroSAFE.

This study will evaluate LaserSAFE further to confirm how well it detects cancer at the prostate edge and to find the best “cut-off” point for when a small amount of cancer may be safe to leave, while still protecting patients from cancer recurrence. If successful, LaserSAFE could make nerve-sparing surgery safer and more widely available, helping men keep both cancer control and quality of life after surgery.

2. BACKGROUND AND RATIONALE

Prostate cancer (PCa) is the most frequently diagnosed non-cutaneous cancer in male patients worldwide (1). While many cases are indolent and progress slowly, PCa remains a significant cause of morbidity and mortality in Europe, with over 110,000 deaths recorded in 2020 (2). In its localised stage, clinically significant PCa can be treated with curative intent using local therapies such as radical prostatectomy (RP), radical radiotherapy (RT), brachytherapy or focal ablative treatments (3). RP is the most common surgical treatment, with approximately 8,000 robot-assisted radical prostatectomies (RARP) performed in the UK each year. However, RP is associated with important side effects, most notably erectile dysfunction and urinary incontinence, which can are associated with decreased quality of life (4).

To decrease the incidence of these side effects, surgical refinements such as nerve-sparing (NS), bladder neck sparing, dorsal venous complex “hood-sparing” and Retzius-sparing techniques have been developed (5). These approaches improve preservation of tissues around the prostate and are associated with better functional outcomes (6). However, they require dissection closer to the prostatic capsule, which increases the risk of positive surgical margins (PSM) (7). The risk is particularly high when the tumour extends beyond the prostate (extra-prostatic extension, EPE) in

the posterolateral areas of the prostate (8). In such cases, attempting nerve preservation may increase the risk PSM, which could only be detected once the final histopathology formalin-fixed paraffin-embedded analysis (FFPE) results are reported.

Retrospective studies suggest that small, unifocal, low-grade PSMs on FFPE are not associated with cancer recurrence. In contrast, larger, multifocal or high-grade PSMs significantly increase recurrence risk and often necessitate salvage treatments, which carry their own side effects (9). Therefore, careful pre-operative planning is essential to identify men who can safely undergo tissue-sparing RARP without compromising oncological outcomes. Current decision-making relies on combining clinical features, prostate biopsy histology and mpMRI in nomograms or independently (10). However, predictive nomograms have poor external validity (11, 12), and mpMRI has limited accuracy in detecting EPE (13, 14). As a result, many men are denied nerve-sparing surgery when it could have been performed safely.

To address this limitation, the Martini-Klinik in Germany developed the NeuroSAFE technique, which involves intraoperative frozen section (FS) analysis of the posterolateral prostate margins (15). We recently completed a phase III randomised controlled trial demonstrating that NeuroSAFE improves post-operative erectile function and early urinary continence (17). The rate of bilateral nerve-sparing was significantly higher in the NeuroSAFE arm (82.1%) compared with controls (56.4%), facilitated by pre-specified criteria that allowed small, unifocal or low-grade PSMs to be left in place without secondary resection. Patients in the NeuroSAFE arm who would not otherwise have received nerve-sparing surgery derived the greatest benefit in terms of erectile function recovery.

Despite its efficacy, NeuroSAFE is labour- and resource-intensive. It requires at least two dedicated histopathology technicians and a uropathologist, and takes a median of 68 minutes to perform while the patient remains under general anaesthesia. Although this did not result in patient harm, it poses a substantial burden on pathology and urology services, limiting widespread adoption (18).

Fluorescence confocal microscopy (FCM) is an emerging imaging technique that uses fluorescent dyes to generate high-resolution cellular-level images of fresh tissue (19). FCM can reliably differentiate between tissue types and has demonstrated strong diagnostic performance in detecting cancer (20). Compared with FS, FCM requires less time, expertise and consumables, making it more feasible for routine use. FCM is already established in dermatological oncology (21) and has shown promise for diagnosing PCa in core biopsies (22). A systematic review, including five studies assessing 148 prostate specimens, reported aggregated sensitivity and specificity above 85% (23). In a prospective study, Baas et al. found a concordance rate of 0.8 between FCM and NeuroSAFE (24).

These studies required slicing the prostate margins before sampling, which required the presence of pathologist to perform and complicated subsequent pathological assessment. To overcome this, we developed LaserSAFE, a standardised technique for assessing intact specimens using FCM (25). In a pilot study, LaserSAFE demonstrated encouraging sensitivity across both expert and novice readers blinded to final histopathology results (26). More recently, we completed a feasibility study comparing LaserSAFE and NeuroSAFE, showing 91% sensitivity for detecting margins greater than 0.5 mm. However, we could not expand the feasibility study to other sites due to challenges associated with adopting NeuroSAFE in other National Health Service (NHS) centres.

The available evidence supports LaserSAFE as a promising alternative to NeuroSAFE, sharing the same underlying goal of enabling safe nerve-sparing in patients who might otherwise not receive it. The NeuroSAFE PROOF study has already demonstrated, with level 1 evidence, that this approach

can lead to improved patient outcomes (17). However, as previously reported and confirmed in our feasibility study, implementing NeuroSAFE in the NHS is not currently feasible due to the resource and time demands required.

Several important knowledge gaps must be addressed before LaserSAFE can be safely introduced into clinical practice. Unlike standard FFPE analysis, LaserSAFE evaluates tissue en face rather than in cross-section (19). This change in orientation presents a challenge for pathologists, who must adapt to interpreting margins from a new perspective. Therefore, the most critical parameter to assess is the sensitivity of the technique, as false-negative results, or failing to detect a PSM, could expose patients to adverse oncological outcomes.

An important caveat is, that evidence suggests that the length of a PSM correlates with the risk of recurrence, with margins smaller than 2 mm not associated with increased recurrence risk (27). Consequently, the NeuroSAFE protocol recommends secondary resection only when the PSM exceeds 2 mm, representing a clinically significant margin. However, margins assessed en face appear larger than those evaluated in cross-section, due to differences in orientation and tissue shrinkage during frozen or paraffin processing. Resecting small, non-significant margins could therefore compromise functional outcomes without providing oncological benefit.

At present, there is no established threshold for what constitutes a clinically significant positive margin in en-face analysis that would justify secondary resection. This study protocol adaptive design will answer this critical gap in knowledge. Addressing these questions will be crucial to ensure the safe adoption of LaserSAFE. If validated, this technique could enable many more centres to provide real-time margin analysis, broadening access to nerve-sparing surgery and potentially improving patients' quality of life. We have conducted several patient and public events during the conduct of the NeuroSAFE PROOF study where participants have expressed support for the exploration of new technologies that could expand access to real time analysis of surgical margins.

We therefore propose the first prospective study to assess the clinical performance of LaserSAFE in guiding nerve-sparing decisions for men undergoing RARP for localised PCa. The study aims to define its accuracy metrics and establish the optimal margin length threshold to maximise nerve preservation without compromising oncological safety.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives are set in the context of patients diagnosed with localised prostate cancer scheduled for robot-assisted RP with a relative contraindication on surgical to perform intrafascial nerve sparing on at least 1 side of the prostate, who have not had previous PCa treatment.

3.1. Primary Objective

- To establish the sensitivity of pathology led LaserSAFE image interpretation to guide nerve-sparing decisions during radical prostatectomy

3.2. Secondary Objective(s)

- To evaluate the accuracy metrics of pathology led LaserSAFE image interpretation against FFPE
- To establish the optimal cut-off criteria to suggest a secondary resection should be performed based on LaserSAFE results
- To describe the prevalence of PSM in the cohort
- To evaluate the rate of PCa recurrence within 12 months of surgery
- To evaluate the urinary incontinence and erectile function scores of patients at 3 and 12 months after surgery using the EPIC-26 questionnaire

3.3. Outcome Measures/Endpoints

- Primary endpoint
    - Sensitivity of LaserSAFE to detect positive margins in the posterolateral area of the prostate of more than 3 mm
        - Sensitivity will be monitored across the trial when the first 150, 300 and 500 participants have been recruited.
        - If sensitivity decreases below 85%, trial methodology will be reviewed and if considered appropriate the trial will be stopped.
- Secondary endpoints
    - Define the cut-off point for triggering secondary resection based on the prevalence of residual prostate cancer in secondary resections.
    - Overall sensitivity, specificity, PPV and NPV of LaserSAFE compared to FFPE analysis for any length of PSM
    - Overall specificity, PPV and NPV of LaserSAFE compared to FFPE analysis for any PSM > 3 mm.
    - Rate of residual prostate cancer in secondary resections of the neurovascular bundle
    - Prevalence of PSM detected by paraffin analysis in the overall cohort.
    - Prevalence of PCa biochemical recurrence or salvage treatment within 12 months after surgery
    - Mean score for EPIC-26 urinary incontinence domain at baseline, 3 and 12 months after surgery
    - Mean score for EPIC-26 erectile function domain at baseline, 3 and 12 months after surgery

4. TRIAL DESIGN

This trial will be a multi-site, prospective, non-randomised cohort study. Participants will undergo a robotic assisted radical prostatectomy with bilateral intrafascial nerve-sparing. The LaserSAFE technique will be used to analyse the corresponding posterolateral surfaces of the prostate. In case a PSM is found which fulfils the criteria for secondary resection this will be carried out by the operating surgeon before the end of the procedure. All samples will be processed using standard FFPE that will act as the reference standard. Patients will be monitored according to the standard of care at each centre. Quality of life questionnaires will be collected at before surgery, at 3 and 12 months after surgery. An adaptive design will allow monitoring of accuracy metrics thought the trial and adjust secondary resection criteria to maximise nerve-sparing.

5. SAMPLING METHODS

The study will be conducted at UCLH and at least 1 other NHS centre. Participating centres will require first to have completed a site initiation visit and have experience using the Histolog Scanner as described in the training section. Potential participants will be screened from the patients referred for radical prostatectomy to the participating sites. Patient selection criteria are as follows:

5.1. Inclusion Criteria

- Patients diagnosed with clinically significant operable cT2-T3a N0 M0 PC.
- Medically fit to undergo RARP.
- Scheduled for robot-assisted RARP with a recommendation against intrafascial nerve sparing on at least 1 side based on multidisciplinary meetings informed by MRI, biopsy result and clinical factors.
- Ability to read English sufficiently to understand PIS and able to give informed consent.

5.2. Exclusion Criteria

- Patients who received neo-adjuvant ADT.
- MRI informed very low likelihood for extra prostatic extension in the proximity of NVB (Based on EPE Likert 1 score or tumour away from the posterolateral areas of the prostate)
- MRI informed high likelihood for extra prostatic extension in the proximity of NVB (based on Likert 5 score or bulging tumour on MRI T2 images)
- Patients in whom preoperative imaging shows rectal involvement or seminal vesicle invasion in which nerve-sparing is deemed not feasible due to oncological safety concerns.
- Patients who received previous treatment for prostate cancer: External beam radiotherapy, brachytherapy, focal therapy, chemotherapy.

5.3. Recruitment

Eligible patients will be identified at each centre during a preoperative multidisciplinary meeting where candidates for RARP based on a diagnosis of localised PCa are referred. Special emphasis will be made to recruit patients with good erectile function who have a recommendation against intrasfascial nerve sparing on at least 1 side. To ensure diversity and equity in patient representation, we will actively encourage the recruitment of individuals from Black, Asian, and minority ethnic groups. We have previously worked with charities and focus groups aimed at increasing participation of Black African and Afro-Caribbean patient populations in research and will continue to do so during the recruitment phase of this study. Furthermore, we will closely monitor the proportion of patients recruited from these communities and if necessary adjust recruitment strategies by reaching out to community support groups.

Participant recruitment at a site will only commence when the trial has:

- Been confirmed by the Sponsor (or it's delegated representative), and
- Been issued with Confirmation of Capacity and Capability from each participating site.

Once a potential participant has been identified, they will be approached via telephone before the planned surgery date and eligibility for the study will be confirmed. If interested, they will receive a patient information sheet (PIS) sent via NHS email or post.

5.4. Informed Consent

Potential participants will be seen in person or called by a designated member of the research team to obtain informed consent within a week of patients receiving a PIS. Adequate explanation of the aims, methods, anticipated risks and potential benefits of participating in the study will be given. The investigator will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason and without prejudicing his/her further treatment. No trial procedures, including the collection of identifiable participant data will be conducted prior to the participant giving consent by signing the consent form. Consent will not denote enrolment into trial.

If they verbally consent to be enrolled in the study, participants will sign a paper consent form if seen face to face or a secure electronic consent form if approached via phone call. The electronic consent platform will be developed within the RedCAP service hosted behind the UCL Data Safe Haven, which conforms to NHS Data Security & Protection Toolkit, General Data Protection Regulation, and ISO 27001 Information Security. We have previously used a similar E-Consent method during the NeuroSAFE PROOF study and LaserSAFE feasibility study.

A copy of the consent form will be given to the patient, a copy uploaded to the electronic health records of the patient and the original will be stored in the ISF. All members of the team consenting patients will be suitably qualified, experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

It will be recorded in the patient medical notes (or electronic health record system) when the participant information sheet (PIS) has been given to the participant.

The PIS and consent form will be reviewed and updated if necessary, throughout the trial according to analysis of thresholds to define secondary resection of periprostatic tissue and participants will be re-consented as appropriate.

6. TRIAL PROCEDURES

6.1. Pre-Intervention Assessments

6.1.1. RARP Planning Meeting

Eligibility for the trial will be determined during a preoperative planning meeting with a radiologist and a surgeon, who will use mpMRI images, clinical and biopsy information to give a recommendation on the grade of nerve sparing deemed safe by side, this can be based on a Likert scale for EPE or site-specific scale:

- Not eligible for the trial
    - EPE Likert 1 / Intrafascial nerve sparing recommended on both sides
    - EPE Likert 5 / Bulky disease on MRI, on both sides, nerve-sparing deemed futile

- Eligible for the trial:
    - Unilateral or bilateral EPE Likert 2, 3 or 4 / Interfascial or limited nerve sparing recommended

These criteria are based on the results of the NeuroSAFE study, where to detect EPE, mpMRI had a good predictive value in the extremes but in equivocal cases had poor sensitivity (14). The results of the LaserSAFE Feasibility study confirmed these findings (30), where EPE Likert 1 had 0% positivity vs EPE Likert 5 that had 100% positivity, as seen below:

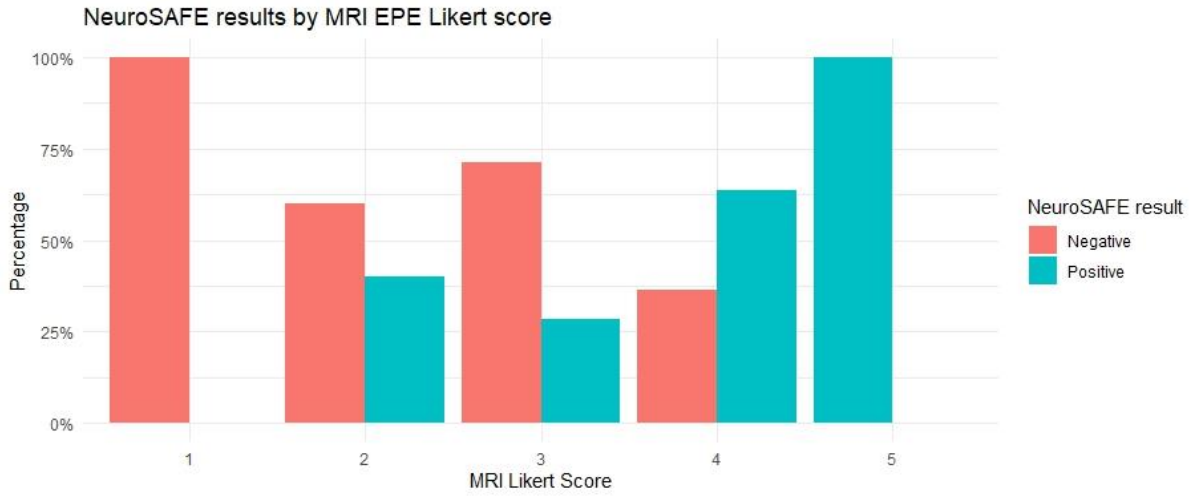


Image-based mpMRI surgical planning is aimed to assist surgeons, but the surgeon's discretion will take precedence in case nerve sparing is deemed unsafe due to intraoperative findings.

6.2. Registration Procedures

Participant registration will be undertaken centrally by the coordinating trial team/remotely at sites using RedCAP. Each patient will be assigned a unique ID, and this ID will be used for identifying the patient. All LaserSAFE images will be pseudo-anonymised using this ID. Completed consent forms will be stored in the ISF in a locked cabinet for secure storage. Patient identifiable data and the above clinical data will be held securely in a database Data Safe Haven RedCAP service.

6.3. Baseline and Intervention Procedures

6.3.1. Baseline Data

The following clinical data will be collected for each patient by the CRF:

- Age
- Preoperative function using EPIC-26 questionnaire
- Prostate biopsy histology report
- Clinical stage
- Prostate Specific Antigen (PSA) before surgery
- Imaging results (mpMRI)
- LaserSAFE results
- Final paraffin embedded analysis results
- PSA results up to 12 months of follow-up
- Additional postoperative therapies

Table 2. Patient recruitment, sample collection and follow-up procedure

Procedure	Screening/Baseline	Recruitment	Treatment	Pathology review	3 months	12 months
Eligibility assessment	x					
Approaching patients		x				
Informed Consent		x				
Quality of life questionnaire (EPIC-26)		x			x	X
RARP and LaserSAFE			x			
Medical record review			x	x	x	x

6.3.1.1. Radical Prostatectomy

Patients will undergo RARP using the DaVinci® surgical system as per the standard of care in the NHS. The operating surgeon must have performed a minimum of 100 cases. The procedure will be performed in accordance with the LaserSAFE technique. It differs from standard RARP in that the initial insertion of the robotic camera port is through a modified incision using the Alexis Laparoscopic System® (Applied Medical, Rancho Santa Margarita, CA). Surgical dissection will be carried out in the standard technique according to surgeon preference. NS will be performed following an intrafascial plane on both sides, if an intrafascial plane cannot be achieved due to

technical difficulty interfascial or extrafascial dissection will be registered. Immediately after the prostate is free from all attachments the specimen is removed from the patient using the Alexis port. Whilst the analysis is taking place the robot will be re-docked and pneumoperitoneum established. The robotic instruments will be reinserted. The surgeon will proceed to fashion the urethra-vesical anastomosis and perform a pelvic lymphadenectomy (where indicated) whilst the LaserSAFE procedures are being performed.

6.3.1.2. Lasersafe Technique

The LaserSAFE procedure is performed using an FCM called the Histolog® scanner developed by Samantree® which can be placed within the operating room. Histolog Scanner, Histolog Viewer, and accessories will be used according to the Instructions for Use. No modification to the CE-Mark/UKCA-Mark/FDA 510k clearance approved intended use will be made. The Histolog® scanner produces digital images with high, micrometre-range resolution and enables the visualization of tissue microstructures down to the cellular level. The microscope can image an area of 48x36 mm in approximately 60 seconds. Its operating principle is based on non-ionizing, low-power optical radiation (Laser) with a wavelength of 488±5 nm, and it uses a point illumination conjugated with a pinhole in front of the detector to eliminate out-of-focus signals.

The protocol of image acquisition is as follows: the prostate is cleaned using damp gauze and completely submerged in a solution that contains a photoreactive agent Histolog Dip® for 10 seconds. The specimen is rinsed with 0.9% NaCl solution, placed on the Histolog® scanner and lightly compressed using a mouldable weight. An initial live view scan confirms adequate positioning and stability of the specimen to avoid movement artefacts. If the preliminary scan is deemed satisfactory, a high-resolution digital image is acquired and stored in the microscope hard drive. The prostate is rotated to image the contralateral side. Once both posterolateral surfaces are imaged the prostate is placed in a container and fixed with formalin. Image acquisition takes less than 5 minutes. A pathologist will interpret the images on site or remotely depending on site specific requirements and complete a reporting case report form. The findings will be communicated directly to the surgeon.

Nerve sparing decisions will be guided by the result of the LaserSAFE technique.

The presence of cancer cells at the surface margin of the specimen will constitute a positive margin. Detailed results including the length of positive margin in 2 dimensions and multifocality, will be collected and included in the results.

In the presence of a posterolateral PSM, the performance of secondary resection (SR) of the ipsilateral neurovascular bundle (NVB) will be made if any of the following are present:

(1) Multiple areas of PSM where the sum of each maximum dimension is >3 mm
(2) any single PSM area >3 mm in maximum dimension

The resection of the NVB has been shown to result in oncological outcomes equal to negative surgical margin had been achieved in the first place.

SR of the ipsilateral NVB is performed in the following way: all tissue from the cut edge of Denonvilliers' fascia medially, the pararectal fat laterally, the pedicle cranially, and just beyond the urethrovesical anastomosis (including the puboprostatic ligament and Walsh's pillar) caudally is removed en bloc. Secondarily resected tissue is sent for routine paraffin-embedded histological analysis and is not analysed as part of the intraoperative FCM.

6.3.1.3. LaserSAFE Image Analysis

Images stored in the confocal microscope will have a unique identifier for each patient and will be annotated to describe the side and orientation. These images will be interpreted by a pathologist with expertise in Uro-pathology and who have been trained in the interpretation of confocal images using an image databank with representative examples. A specially designed case report form (Figure 2) will be used to describe the findings.

6.3.1.4. Histolog Remote viewer

The Histolog Viewer is an image management software intended to access, display, annotate, manage, store and share collections of digital Histolog Scanner images and their associated metadata. I will allow pathologist to access the images obtained in the operating room in real time and provide a diagnosis on the margin status of a prostatectomy specimen. Results of the analysis will be communicated via telephone directly to the surgeon.

6.4. Subsequent Assessments and Procedures

6.4.1. Follow Up

Clinical follow-up will be performed according to each participating centre's standard procedures after RARP.

For study follow-up patients will receive a paper or electronic copy of the EPIC-26 questionnaire before RARP, at 3 and 12 months after surgery. The Expanded Prostate Cancer Index Composite (EPIC) is an instrument designed to evaluate quality of life after PCa treatment. The instrument was developed by the University of Michigan (28) and has been validated to be used as an electronic instrument (29). It assesses health-related quality of life across five domains relevant after diagnosis and treatment of PCa. It has 26 items grouped into 5 domains:

1. Urinary Incontinence (4 items)
2. Urinary Irritative/Obstructive (4 items)
3. Bowel (6 items)
4. Sexual (6 items)
5. Hormonal/Vitality (6 items)

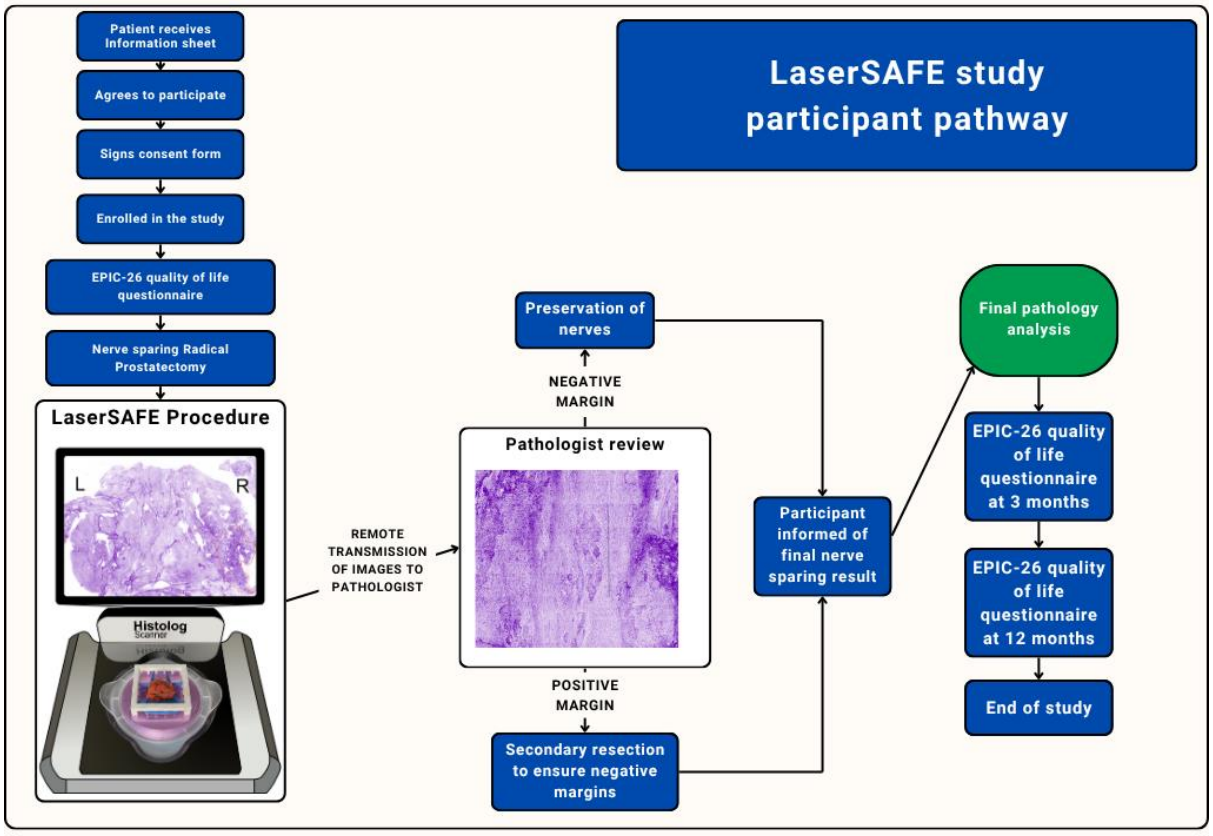
Each item has a Likert-type response scale (e.g. "no problem" to "big problem"), scored 1–5. Items in each domain are averaged, then transformed linearly to a 0–100 scale. Interpretation relies on domain-specific means, with MIDs (4–12 points depending on domain) to guide whether changes are clinically meaningful.

FFPE reports of the radical prostatectomy specimen will be reviewed and reported in a case report form, the presence or absence of PSM will be documented.

PSA assessments will be performed according to the standard of care at each centre. Biochemical recurrence and the need for secondary treatments will be recorded at 12 months. Adverse events within 90 days of the surgery will be recorded according to the description below.

A schedule of all trial assessments and procedures is set out in Appendix 1.

6.4.2. Participant pathway diagram



6.5. Samples

6.5.1. Sample Storage

In the study, prostate specimens will be collected from patients in accordance with the patient consent form and patient information. The radical prostatectomy specimens and secondary resections will be appropriately sent to the pathology department of the participating institution for standard of care pathology assessment.

The participating pathology departments will process, store and dispose of surgical specimens, in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

No samples will be stored for any additional analysis related to the procedures outlined in this study.

6.5.2. Sample Transfer

The surgical specimens will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent. After ethics approval for the study has expired, the prostatectomy specimens will be disposed of in accordance with the Human Tissue Act 2004 and any amendments thereto or transferred to a licensed tissue bank.

6.6. Discontinuation/Withdrawal of Participants

Participants may be withdrawn from the trial for the following reasons:

- Unable to undergo RARP as planned due to medical reasons
- Unable to perform nerve sparing RARP as planned due to anatomical/technical difficulty during surgery.
- Patient expresses desire to withdraw the consent to continue participating in the study.
- Patients' death

The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes/electronic health record system. If a participant withdraws consent no additional data will be collected and if requested the participants information will be deleted from the study records.

6.7. Definition of End of Trial

The trial will close 12 months after the last surgery of the last participant when the final follow up data will be collected.

7. FINANCE AND SUPPLY OF EQUIPMENT

The research costs for the study will be supported by a collaborative research grant from SamanTree Medical SA. SamanTree will reimburse the participating centres in the Post-Market Registry to Collect Real-World Clinical Data on the Use of the Histolog® Scanner.

The Histolog Scanner and consumables has been purchased with the support of the UCLH Charity.

8. DATA MANAGEMENT

8.1. Confidentiality

The study is compliant with the requirements of the General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018). All Investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCL is the data controller, Data protection registration No Z6364106/2025/10/66; the UCL Data Protection Officer is data-protection@ucl.ac.uk . The data processors will be designated in the trial delegation log.

The study will be collecting the following identifiable personal data: Patients name, date of birth, height, weight, hospital number, email address extracted from the medical records. Any patient identifiable data will only be stored for consent purposes. After patient enrolment the anonymised patient ID assigned by RedCAP will be used on all trial records. This trial number will be known by all LaserSAFE study site staff. All clinical information including scans, biopsy results and blood results will be kept in trial records and analysed at the end of the trial. The records will be kept in a secure manner in the research offices with access available to named individuals from the trial group only. All imaging data will be held confidentially and processed by the named investigators for the purpose of image registration analysis. The paper records will be retained for a minimum of 20 years after the end of the trial, according to the local hospital's guidelines.

8.2. Data Collection Tools and Source Document Identification

Data will be collected from sites from source medical notes directly into the electronic CRFs developed in RedCAP. No copies of source data will be kept by the research team. The following clinical data will be collected for each patient by the CRF: Histology reports; clinical stage; Prostate Specific Antigen (PSA) (pre- and post-surgery); imaging (mpMRI, PSMA-PET/CT and bone scan); results and record of additional postoperative therapies.

The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

8.3. Completing Case Report Forms

All CRFs will be completed and signed by staff listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF. Reports from the LaserSAFE and NeuroSAFE procedures will be done in paper CRFs, these will be uploaded to an electronic database. All paper CRFs will be kept in a secure cabinet in the ISF and kept by the study site.

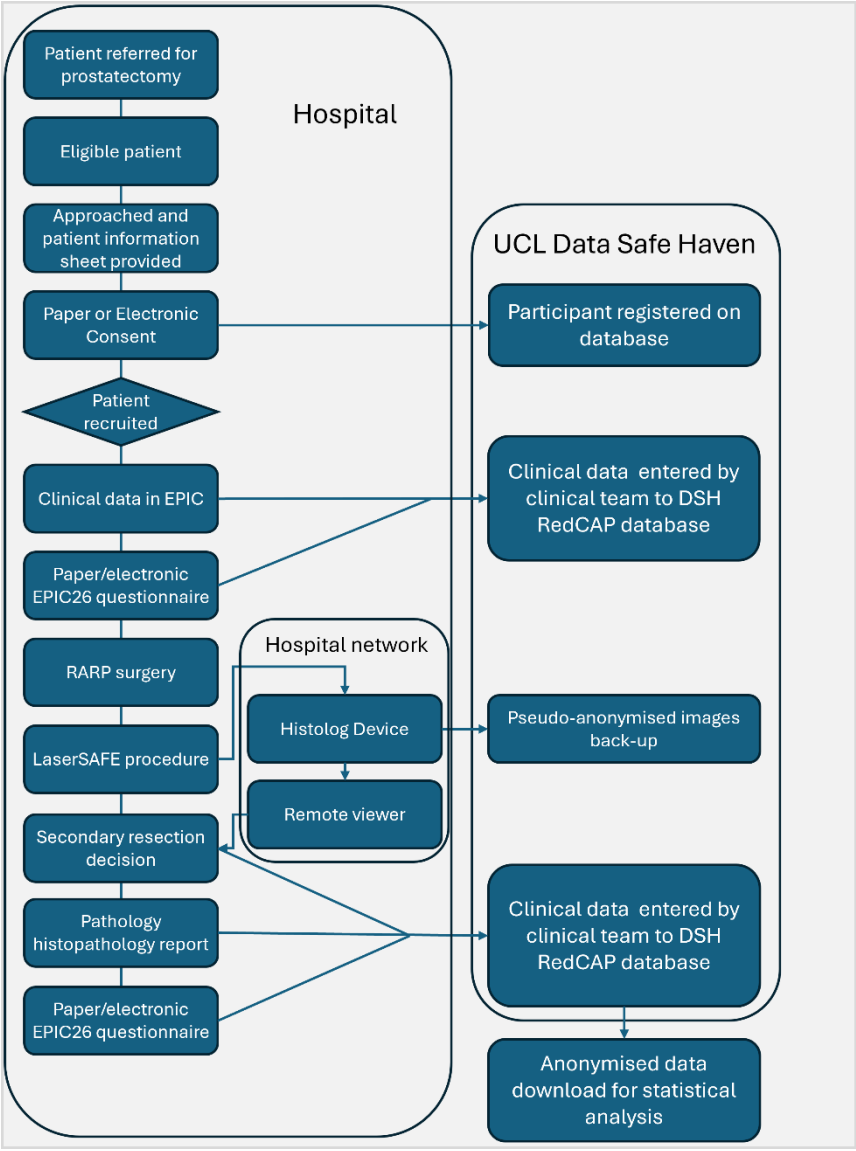
8.4. Data Handling

Research staff under the supervision of the principal investigator will process, store and dispose of the paper CRFs and data in paper form in accordance with all applicable legal and regulatory

requirements, including the Data Protection Act 2018 and any amendments thereto. All patient data will be stored centrally at site in a locked filing cabinet controlled by the principal investigator in each site.

Data entered electronically (e-CRFs) will be stored on secure servers hosted within UCL Data Safe Haven RedCAP service. UCL will remain the data controller. A back-up of pseudo-anonymised Histolog Images will be performed at least every 3 months by the study teams in secure hard drives which will be password protected.

8.5. Data Flow Diagram



8.6. Personal Data breaches

Personal data breaches will be immediately reported to the UCL Information Security Group (ISG) and the UCL Data Protection Officer data-protection@ucl.ac.uk , and to the Sponsor via the UCL JRO research incident reporting form (as per form and guidance: https://www.ucl.ac.uk/legal-services/guidance/reporting-loss-personal-data). The following information will be provided: full details as to the nature of the breach, an indication as to the volume of material involved, and the

sensitivity of the breach (and any timeframes that apply). Sites will additionally follow their Trust incident reporting mechanisms, and will document this within their TMF/ISFs.

9. STATISTICAL CONSIDERATIONS

9.1. Primary Outcome

The primary objective is to evaluate the accuracy of using the LaserSAFE technique to evaluate margin status during radical prostatectomy compared to the FFPE. The primary endpoint will be the sensitivity of LaserSAFE to detect positive margins in the posterolateral area of the prostate of more than 3 mm.

- Sensitivity will be monitored across the trial when the first 50, 150, 300 and 500 participants have been recruited.
- If sensitivity decreases below 85%, trial methodology will be reviewed and if considered appropriate by the trial will be stopped.
- This would minimise the risk of introducing an inferior alternative that would put patients at risk worse oncological outcomes

9.2. Secondary Outcomes

- Evaluate the accuracy metrics of LaserSAFE image interpretation against FFPE.
    - The following items will be calculated and reported:
        - Sensitivity, specificity, PPV and NPV of LaserSAFE compared to FFPE analysis for any length of PSM
        - Specificity, PPV and NPV of LaserSAFE compared to FFPE analysis for PSM > 3 mm.
- Determination of Margin Length Cut-off for Secondary Resection

The study will evaluate the optimal cut-off for positive margin length that should trigger a secondary resection, with the aim of maximising nerve-sparing without compromising oncological safety.

- Decision Rules:

    - Interim analyses will be performed after recruitment of 150, 300, and 500 participants.
    - At each interim analysis, the prevalence of residual tumour in secondary resections will be calculated across margin length thresholds in 1 mm increments.
    - If the prevalence of residual tumour at a given threshold is <15%, the cut-off for secondary resection in the next cohort will be increased in 1 mm increments, up to a maximum cut-off of 6 mm.
    - If the prevalence of residual tumour is ≥15% at any threshold, that cut-off will be retained and applied to all subsequent cohorts for the remainder of the study.
    - No further upward adjustment will be made once the 6 mm maximum cut-off is reached.

This adaptive design ensures that the margin length threshold used to guide secondary resection is based on prospective evidence, optimising oncological safety while maximising opportunities for nerve-sparing.

- Descriptive outcomes:
    - Rate of residual prostate cancer in secondary resections of the neurovascular bundle

- Prevalence of PSM detected by paraffin analysis in the overall cohort.
- Prevalence of PCa biochemical recurrence or salvage treatment within 12 months after surgery
- Mean score for EPIC-26 urinary incontinence domain at baseline, 3 and 12 months after surgery
- Mean score for EPIC-26 erectile function domain at baseline, 3 and 12 months after surgery

9.3. Sample Size Calculation

The sample size was calculated to estimate the sensitivity of the LaserSAFE technique with a 95% confidence interval and a precision of ±5%. Assuming an expected sensitivity of 91% and a positive margin prevalence of 20%, at least 126 disease-positive participants are required. This corresponds to a total of 630 participants. Allowing for up to 10% missing or non-evaluable data, the adjusted target sample size is 693 participants.

The assumptions for sample size calculations were based on the results of our previous studies where LaserSAFE demonstrated in blinded analysis of a small cohort of patients a sensitivity of 91% to detect positive margins.

9.4. Planned Recruitment Rate

This study will take place in high volume centres across the UK where more than 300 RARPs are performed each year. Given that in the BAUS UK national dataset (29) more than 70% of patients undergoing RARP do not receive bilateral nerve-sparing a large pool of potential recruits is expected at each site. Therefore, we expect to recruit at least 12 patients every month to be able to finish the recruitment phase of the study within 60 months. This recruitment rate is similar to the one observed during the NeuroSAFE PROOF trial.

9.5. Randomisation Methods

Randomisation will not be done in this trial.

9.6. Statistical Analysis

9.6.1. Summary of Baseline Data and Flow of Participants

Baseline variables that will be collected include age at diagnosis, weight, height, self-reported ethnicity, PSA at diagnosis, MRI PIRADS/Likert score, T stage, prostate volume, nerve sparing recommendation, biopsy grade group and histological subtype. Variables registered at the time of the intervention are outlined in the CRF.

9.6.2. Primary outcome analysis

The primary analysis will evaluate the sensitivity of LaserSAFE interpretation for detecting positive surgical margins greater than 3 mm in the posterolateral prostate, using FFPE histopathology as the reference standard.

Interim analyses of sensitivity will be conducted after recruitment of the first 50, 150, 300, and 500 participants. If the observed sensitivity falls below % at any interim analysis, the trial will be stopped for futility. The final analysis will be undertaken once the target sample size of 693 participants has been reached. Sensitivity will be reported with a two-sided 95% confidence interval, calculated using the Wilson score method. Indeterminate or missing LaserSAFE results will be considered non-diagnostic and classified as false negatives in the primary analysis.

9.6.3. Secondary Outcome Analysis

1. Diagnostic accuracy metrics. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LaserSAFE image interpretation will be calculated with corresponding two-sided 95% confidence intervals. These will be reported in two ways:
    a. For detection of any positive surgical margin (PSM), regardless of length, compared with FFPE analysis.
    b. For detection of PSMs greater than 3 mm, compared with FFPE analysis.
    Two-sided 95% confidence intervals will be calculated using the Wilson score method.
2. Descriptive outcomes. The following will be summarised using descriptive statistics (means, proportions, and 95% confidence intervals as appropriate):
    a. Rate of residual prostate cancer in secondary resections of the neurovascular bundle.
    b. Prevalence of PSMs detected by paraffin analysis in the overall cohort.
    c. Prevalence of biochemical recurrence or salvage treatment for prostate cancer within 12 months post-surgery.
    d. Mean scores for the EPIC-26 urinary incontinence and erectile function domains at baseline, 3 months, and 12 months post-surgery.

10. ASSESSMENT AND MANAGEMENT OF RISK

Intervention	Potential risk	Risk Management
LaserSAFE procedure	Time delay to finalise surgery False negative result which results in positive margin	Performed by trained personnel to minimize time delay. Follow standard operational procedure. Previous experience with the LaserSAFE technique has shown high accuracy and safety of the procedure. From NeuroSAFE PROOF study 200 NeuroSAFE procedures with 0 adverse reactions using a similar intervention.

11. RECORDING AND REPORTING OF ADVERSE EVENTS

11.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect. • Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences
* A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

11.2. Assessments of Adverse Events

Each adverse event (AEs) will be assessed for severity, causality, seriousness and expectedness from consent to 90 days post op as it unlikely any SAEs past this point will be related to surgery. Adverse event assessment will be carried out using the patient electronic clinical records. This will reduce site reporting workload. Trial follow up should continue according to schedule once the SAE is resolved, if applicable.

11.2.1. Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort

Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

11.2.2.Causality

Although in previous studies no evidence of adverse events related to real time analysis of surgical margins using NeuroSAFE has been found. We will still monitor and assess relationship of adverse events. The differentiated causality assessments will be captured in the trial specific CRF SAE form.

The following categories will be used to define the causality of the adverse event:

Category	**Definition**
Related	A causal relationship between the intervention and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Not related	There is no reasonable possibility of a causal relationship between the intervention and an adverse event.
Not Assessable	Unable to assess on information available.

11.2.3.Expectedness

All SAEs assigned by the Investigator or delegate as suspected to be related to the intervention will be assessed for expectedness against the list defined in this protocol.

Category	Definition
Expected	An adverse event which is consistent with the information about the intervention **clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the intervention **or clearly defined in this protocol.**

The following are expected adverse events following a radical prostatectomy with their corresponding likelihoods. These should be recorded in the patient's medical records but do not need an Adverse Event CRF to be submitted. These will be recognised as expected for trial treatment.

- **Intra-operative**
    - Bleeding – (requiring transfusion) - 1%
    - Visceral injury requiring laparotomy – 1%
    - Vascular injury requiring laparotomy – 1%
    - Cardiac event (Myocardial infarction 0.1%, Atrial Fibrillation 1.6%, syncope 1.2%).
- **Early post-operative**
    - Wound related problems; infection (2%), incisional hernia (2%)
    - Thromboembolic event (deep vein thrombosis or pulmonary embolus 0.8%) Lymphoedema – 1% (higher incidence when eLND performed)
    - Anaesthetic problems requiring admission to intensive care unit (2%)
    - Gastrointestinal; ileus/damage to bowel requiring temporary colostomy (0.5%)
    - Seroma – 1%
    - Urethral Stricture – 2%
    - Vesicourethral anastomosis leak – 5%
- **Expected longer term outcomes or side effects of surgery**
    - Urinary incontinence (temporary) –100%
    - Erectile dysfunction – (up to 100%)
    - Long term urine leak – 10%
    - Adjuvant therapies (including radiotherapy and ADT) – 30%

11.2.4. Recording of Adverse Events

All adverse events will be recorded in the medical records in the first instance. Expected adverse events related to RARP listed above will not require reporting. All related adverse events will be recorded in the CRF until 90 days after surgery.

All related adverse events will also be recorded on the non-CTIMP Adverse Event (AE) log, and stored in the site files.

11.3. Procedures for Recording and Reporting Serious Adverse Events (SAEs)

All serious adverse events related to the intervention will be recorded in the medical records and the CRF, and the sponsor's SAE log. The AE and SAE logs will be stored in the TMF Investigator Site File and may be subject to Sponsor monitoring and auditing.

Participants will be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up will continue after completion of protocol treatment and/or trial follow-up if necessary.

All SAEs (except those specified in the protocol as not requiring reporting to the Sponsor) will be reported to the Sponsor within 24 hours of becoming aware. The CI/PI or designated individual will complete the Sponsor's online Research Incident Reporting Form (https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo) within 24 hours of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

11.4. Incidental Findings in Research

Should any incidental findings be identified during the pre-operative assessment, operative procedure, or postoperative care phases of the study, these will be managed in accordance with each participating centre's standard clinical pathway. Participants will be informed of any such findings and referred for appropriate clinical management as per local protocols. However, given

that the LaserSAFE intervention specifically analyses the posterolateral prostatic margins during radical prostatectomy, and all participants are undergoing standard-of-care surgical treatment with established pre-operative imaging and postoperative follow-up, no incidental findings directly related to the study intervention are anticipated. All research staff must follow participating sites' incidental findings policies, and training will be provided as part of initiation to the research study

11.5. Protocol Deviations and Violations

Protocol Violations

A reportable protocol violation is defined as a breach which is likely to affect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or (b) the scientific value of the trial.

The Sponsor must be notified immediately of any protocol violations during the trial conduct phase by completion of the online JRO Research Incident Reporting Form: https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo. All protocol violations must be recorded on the Protocol Violation Log and filed in the site file. Sites will additionally follow their Trust incident reporting mechanisms.

Examples of protocol violations include:

1. Not following the secondary resection criteria based on LaserSAFE results
2. Failure to communicate LaserSAFE information to the surgeon

Protocol Deviations

Protocol deviations are minor unintended departures from the expected conduct of the study protocol or Standard Operating Procedures (SOPs) which do not impact participant safety or compromise the integrity of the study data. Protocol deviations will not be reported to the Sponsor but must be recorded in the Protocol Deviation Log and filed in the site file.

Examples of protocol deviations include:

- Patient does not complete a questionnaire or completes it outside the specified time window
- Minor administrative errors that do not affect data integrity or participant safety

11.6. Reporting incidents involving a medical device

Any adverse incident involving the Histolog confocal microscope will be reported to the study coordinator and manufacturer within 24 hours of occurrence. This includes equipment faults, malfunctions, or any safety or quality issues identified during use of the device. The manufacturer, SamanTree Medical SA, will provide technical service support to the site as required. Incidents involving the Histolog confocal microscope do not require reporting to the Medicines and Healthcare products Regulatory Agency (MHRA). However, local Trust reporting procedures for medical device events must also be followed, and it is the responsibility of the Principal Investigator and study site

team to ensure they are aware of and comply with any specific local requirements for reporting device incidents.

11.7. NHS Serious Incidents and Near Misses

A serious incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Serious Incidents and near misses will be reported to the Sponsor and Trust Quality & Safety department as soon as the study team becomes aware of them.

11.8. Complaints from research participants

In the first instance, research participant complaints (patients or health volunteers) will be reported to the CI/PI to investigate, as documented in the patient information sheet(s), and to the Sponsor via research-incidents@ucl.ac.uk, following the *UCL Complaints from Research Subjects about UCL Sponsored Studies and Trials* policy. For participants who are NHS patients, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures were undertaken. Complaints from NHS patients are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

12. OVERSIGHT COMMITTEES

12.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet monthly and will send updates to PIs.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

13. REGULATORY REVIEW AND PATIENT AND PUBLIC INVOLVEMENT

13.1. Regulatory Review

The Sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

The study was deemed to require regulatory approval from the following bodies (REC Favourable Opinion and HRA Approval). **Before any site can enrol patients into the study,** the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

It is the Chief Investigator's responsibility to produce the annual progress reports when required; an annual progress report (APR) will be submitted to the Sponsor and REC within 30 days of the anniversary date on which the favourable opinion was issued, and annually until the study is declared ended.

Within 90 days after the end of the trial, the CI will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

13.2. Peer Review

The study has been peer reviewed in accordance with the requirements outlined by UCL. The Sponsor considers the procedure for obtaining funding to be of sufficient rigour and independence to be considered an adequate peer review.

13.3. Patient and public involvement (PPI)

This has been a key priority for our team throughout our previous research, particularly during the NeuroSAFE PROOF study. In fact, we have conducted four PPI events, the latest of which took place in April 2024. This virtual meeting was attended by over 53 patients, funder representatives, and study site team members, who were presented with this study proposal. We are proud to report that over 90% of participants said they would recommend participation in this study to a relative or friend. Evidence of the event can be found on the NeuroSAFE PROOF website (www.neurosafeproof.com).

Thanks to valuable feedback from patients, we have made modifications to the initial proposal. For instance, we learned that even patients with weak erections prior to treatment would like to be considered eligible for studies focused on maintaining potency. With this feedback in mind, we have adjusted our eligibility criteria to include all patients who have a recommendation against nerve sparing.

14. MONITORING AND AUDITING

A trial specific oversight and monitoring plan will be established. The trial will be monitored in accordance with the agreed plan. The Chief Investigator will be responsible for the day-to-day monitoring and management of the study. The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

The UCLH/UCL Joint Research Office, on behalf of UCL as Sponsor, will conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, and in accordance with the Sponsor's monitoring and audit policies and procedures.

Monitoring Plan

Low risk- score 1-25
This is a low-risk study, therefore central monitoring is required.

Each site must email the sponsor at **6 months** from study start date and **every 12 months** following:

- Delegation log
- Adverse event log
- Deviation log

The CI or delegate must email the sponsor at **6 months** from study start date and **every 12 months** following:

- Minutes of Trial management Group (TMG) meetings plus other appropriate study committees

All monitoring documentation must be sent to the JRO via email to uclh.jro.qa@nhs.net.

Studies must complete a JRO progress report alongside the monitoring requirements above, this must be sent to uclh.randd@nhs.net.

15. TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. All trial personnel involved in performing the LaserSAFE analysis will be properly trained before getting involved in the study. Appropriate training records will be maintained in the study files. Documentation of training in Good Clinical Practice for all trial personel will be kept in the site file.

Training for FCM images interpretation

All personnel in the study participating centres responsible for interpretation of FCM images produced by the LaserSAFE technique will have completed a training on the usage of the Histolog Scanner and its accessory products (i.e., Histolog Dip, Dish, Viewer) prior to the beginning of their participation in the LaserSAFE study. For centres with no previous experience using the Histolog Scanner, a minimum of 25 cases where no clinical decisions are taken based on the LaserSAFE results will be performed. These cases will be reviewed in pair with the final pathology results, so pathologists are trained in the specific interpretation of FCM en face images. Once this has been done the SIV will begin.

In addition to this medical device training, Investigators and study site personnel will be trained on study protocol specifics during the site initiation visit.

16. INSURANCE AND INDEMNITY

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London upon request.

Additionally, UCL does not accept liability for sites such as GP surgeries in primary care; investigators/collaborators based in these types of sites must ensure that their activity on the study is covered under their own professional indemnity.

To be inserted for UCL sponsored studies where equipment is being provided to sites for the purpose of the study:

If equipment is to be provided to site(s) for the purpose of the study, [please describe what arrangements will be made for insurance and/or indemnity to meet potential legal liability arising in relation to the equipment (e.g. loss, damage, maintenance responsibilities for the equipment itself, harm to participants or site staff arising from the use of equipment)].

17. RECORD KEEPING AND ARCHIVING

The Chief Investigator confirms that he/she will archive the Trial Master File at University College London Hospital Trust, for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents in line with all relevant legal and statutory requirements. Study documents will be archived for a minimum of 5 years from the study end, and no longer than 20 years from the study end.

The Trial Master File will be archived at UCL, in accordance with the UCL Retentions Schedule. It will be archived for a minimum of 5 years from the study end, and no longer than 20 years from study end.

18. INTELLECTUAL PROPERTY

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol, the study data and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used independently of the study by each participating site, shall belong to UCL. All intellectual property rights deriving or arising from the material or any derivations of the material provided to UCL by the participating site shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it agrees hereby to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL or its funder. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

19. PUBLICATION AND DISSEMINATION

Results of scientific interest from the trial and any parallel translational work will be submitted for consideration for presentation to professional and scientific meetings, and publications in peer reviewed professional and scientific literature. They may also be included in theses and dissertations.

Any submissions are to have authorisation from the chief investigator and co-investigators. Authorship will be determined on a per paper basis. The chief investigator will have final say if agreement cannot be reached.

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings. Resulting publications and/or abstracts will be emailed to the JRO.

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21. APPENDIX

21.1. Appendix 1: Schedule of Assessments

Visit No:	Screening/Baseline	Visit 1 Treatment	Visit 2 Postoperative review 3 months	Visit 4 Final review 12 months
Informed Consent	X			
Medical History	X		x	
Eligibility confirmation	X			
MRI guided pre-op surgical planning	x			
RARP		X		
LaserSAFE procedure		x		
Pathology results review			X	
EPIC-26 questionnaire			X	X
Adverse Events review	X	X	X	

21.2. Appendix 2: Associated Documents

Document Name	Document Version	Document Date