A single blinded, IDEAL stage 3, multi-centre, randomised controlled trial to assess NeuroSAFE Robotic assisted radical prostatectomy (RARP) vs standard Robotic assisted radical prostatectomy (RARP) in men with prostate cancer

Acronym: NeuroSAFE PROOF

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DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant 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 clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the trial will be given; and that any deviations from the trial as planned in this protocol will be explained and reported accordingly.

Chief Investigator: Greg Shaw

Signature: 

Date: 14 Feb. 23

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TRIAL SUMMARY

Title	A single blinded, IDEAL stage 3, multi-centre, randomised controlled trial to assess NeuroSAFE Robotic assisted radical prostatectomy (RARP) vs standard Robotic assisted radical prostatectomy (RARP) in men with prostate cancer
Version and Date	7.0 dated 14 February 2023
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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1.0	20 Oct 2017	Chris Brew-Graves	N/A
2.0	06 Feb 2018	Jack Grierson	Single centre trial amended to multi-centre
3.0	03 Sept 2018	Jack Grierson	Feasibility phase amended to pilot phase
4.0	29 Aug 2019	Jack Grierson	Pilot phase amended to fully powered RCT
5.0	21 April 2021	Jack Grierson	Research team changes, COVID mitigation strategies, trial methodology changes & change of CTU
6.0	03 August 2022	Nick Roberts	Research team changes, update of BCR definition, IIEF source clarification, addition of details on analysis of patients with measurable persistent PSA after surgery, addition of EPIC-26 questionnaire
6.1	07 September 2022	Nick Roberts	Update of BCR definition made in Version 6.0, redaction of

			control arm baseline proportion % described in statistics section
7.0	14 February 2023	Nick Roberts	Addition of patient long term follow up beyond 5 years (Visit 8). Funding duration extension.

Contents

1 ABBREVIATIONS AND GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ADT	Androgen Deprivation Therapy
APR	Annual Progress Report
BCR	Biochemical Recurrence
C	Celsius
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
CMI	Centre for Medical Imaging
CRF	Case Report Form
eCRF	Electronic Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Application
CTU	Clinical Trials Unit
CVs	Curricula Vitae
DCE	Dynamic Contrast Enhanced
DRE	Digital Rectal examination
DSUR	Development Safety Update Report
DWI	Diffusion Weighted Imaging
EC	Ethics Committee
EF	Erectile Function
EQ-5D	EuroQol Group Patient Questionnaire
ERSPC	European Randomised Study of Screening for Prostate Cancer
ET	Early Termination
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
HIFU	High Intensity Focused Ultrasound
HRQoL	Health-Related Quality of Life
H&E	Haematoxylin & Eosin
IB	Investigator's Brochure
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICIQ	International Consultation on Incontinence Questionnaire
IFS	Intra-operative Frozen Section
IIEF	International Index of Erectile Function
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LUTS	Lower Urinary Tract Symptoms
LPF	Lateral Pelvic Fascia
MCCL	Maximum Cancer Core Length

MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µm	Micrometer
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Milliliter
mm	Millimeter
MDT	Multi-Disciplinary Team
mpMRI	Multi-parametric Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
N or n	Number
NCITA	National Cancer Imaging Translational Accelerator
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Healthcare Research
NNT	Number Needed To Treat
NS	Nerve-sparing (technical part of RARP or RP)
NOAEL	No Observed Adverse Effects Level
OAB	Overactive Bladder
OCT	Optimal cutting temperature compound
PDE5i	Phosphodiesterase Type 5 Inhibitor
PET	Positron Emission Tomography
pH	Hydrogen Ion Concentration
pT	Pathological Tumour stage prostate cancer according to TNM
PIS	Participant Information Sheet
PRN	Pro re nata (taken as needed)
PROM	Patient Reported Outcome Measure
PSA	Prostate-Specific Antigen
PSM	Positive Surgical Margin
PSS	Prescribed Specialised Services
PV	Prostate Volume
QoL	Quality of Life
RARP	Robotic assisted radical prostatectomy
RP	Radical Prostatectomy
RCT	Randomised Control Trial
REB	Research Ethics Board
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

SITU	Surgical & Interventional Trials Unit
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCCL	Total Cancer Core Length
TRUS	Transrectal Ultrasound
UCL	University College London
UCLH	University of London College Hospitals
UK	United Kingdom
US	United States
WHO	World Health Organization
Wk	Week
w/v	Weight Volume Ratio
3D	Three-Dimensional

2 TRIAL OVERVIEW

Trial Title	A single blinded, IDEAL stage 3, multi-centre, randomised controlled trial to assess NeuroSAFE Robotic assisted radical prostatectomy (RARP) vs standard RARPs in men with prostate cancer
Short Title	NeuroSAFE at prostatectomy to optimise oncological and functional outcome. (NeuroSAFE PROOF)
Aim	This is an RCT to assess the differences in functional and oncological outcomes between RARP using the NeuroSAFE intraoperative frozen section technique to navigate safe nerve sparing and standard UK practice RARPs
Inclusion criteria	1. Men opting to undergo RARP for organ confined prostate cancer (including radiological t3a). 2. Potent men (IIEF score of 22-25 without any erectile function medical assistance)(from baseline PROM or clinical notes) 3. Men who are continent of urine (no self-reported urinary incontinence) 4. Has given written informed consent 5. Ability to read English sufficiently to answer questionnaires and understand PIS
Exclusion criteria	1. Unable to undergo RARP 2. Known overactive bladder 3. Any previous treatment for prostate cancer 4. Previous/current hormone treatment for prostate cancer 5. Nerve sparing deemed futile due to locally advanced disease by surgeon and radiologist
Withdrawal criteria	1. Unable to perform nerve sparing RARP as planned due to anatomical/technical difficulty during surgery 2. Withdrawn consent
Trial procedures	Control arm - standard RARP: Nerve-sparing strategy during RARP guided by routinely available pre-operative and intra-operative patient/disease information; mpMRI, biopsy tumour histology, DRE. Intervention arm – NeuroSAFE RARP: Nerve-sparing strategy during RARP guided by routinely available pre-operative and intra-operative patient/disease information; mpMRI, biopsy tumour

	histology, DRE *and* the NeuroSAFE technique during RARP.

Outcomes and Analysis	Primary outcome:
	
	• Comparison of the proportion of men who recover erectile function at 12-months according to allocated treatment arm (i.e. NeuroSAFE RARP [intervention] vs. standard RARP [control]). Erectile function is measured using the IIEF-5 questionnaire, where recovered function is defined as a score of 21 or more.
	
	  ○ Pre-defined sub-group analysis: comparison of the proportion of men who recover erectile function at 12-months according to treatment arm, restricted to men who did not receive a pre-operative radiologist recommendation for bilateral nerve sparing.
	
	For further sub-group analyses and sensitivity analyses, please see body of protocol, Outcomes Section.
	
	Secondary outcomes:
	
	There are 6 secondary outcomes:
	
	1) Urinary Continence
	
	• Comparison of the proportion of men who are continent at 3 months, measured using the ICIQ questionnaire, where continence is defined as a score of 5 or less between intervention and control arms.
	  ○ Additional subgroup analysis: restricted to men who did not receive a pre-operative radiologist recommendation for bilateral nerve sparing.
	
	For further sub-group analyses and sensitivity analyses please see body of protocol, Outcomes Section.
	
	2) Biochemical Recurrence (BCR)

	Comparison of the proportion of men with BCR between NeuroSAFE and control arms within 12 months of surgery. BCR will be considered to have occurred when the post operative PSA measures >0.2ng/mL, or where the PSA level is less than 0.2 ng/mL but the trajectory suggests inevitable rise above 0.2 ng/mL according to the clinician looking after the patient. If PSA fails to nadir after surgery, this will not be considered BCR as this is probably related to micro metastatic disease not detected by preoperative imaging. For further descriptive analyses, sub-group analyses, and sensitivity analyses please see body of protocol, Outcomes Section. 3) Additional oncological treatments • 'Adjuvant treatment' refers to men who undergo additional cancer treatment without having BCR. A descriptive analysis of the proportion of men undergoing adjuvant oncological treatments (ADT and/or radiotherapy and/or chemotherapy) at or before 12 months of surgery will be conducted. • 'Salvage treatment' refers to men who undergo additional cancer treatment following BCR. A descriptive analysis of the proportion of men undergoing adjuvant oncological treatments (ADT and/or radiotherapy and/or chemotherapy) at or before 12 months of surgery will be conducted. 4) Quality of Life • A comparison of the proportion of men achieving the best quality of life according to the EQ-5D-5L between intervention and control arms. • Analysis of EQ-5D-5L scores to produce QALYs at 12 months by arm • Analysis of RAND36 scores to produce QALYs at 12 months by arm • Analysis of EPIC-26 scores at 36, 48 and 60 months after surgery and a maximum frequency of annually thereafter 5) Positive Surgical Margins (PSM)

	• Descriptive tabulation of PSM rates between NeuroSAFE RARP and standard RARP arms. PSMs will be grouped as: 0. Negative margin 1. Intraprostatic margins 2. Non-intraprostatic margins ≤ 1mm (included) 3. Large non-intra prostatic margins and >1mm 4. Very large non-intraprostatic margins and >3mm and/or multifocal ○ Additional subgroup analysis: restricted to men who did not receive a pre-operative radiologist recommendation for bilateral nerve sparing. 6) Health Economic Analysis • Use of the Health Economics Questionnaires to inform a health cost analysis of NeuroSAFE RARP vs. standard RARP. ○ Economic analysis to assess healthcare resources use by arm and cost analysis to assess: ○ Cost of intervention and control ○ Cost of NHS resource use (medications, physiotherapy, ○ Cost of private health care resources (medication, physiotherapy) ○ Other private/societal costs (productivity losses, caregivers costs, out of pocket cost for transport, equipment) For further sub-group analyses and sensitivity analyses please see body of protocol, Outcomes Section.
Funding Duration	This trial is funded until 30th November 2023
Ethics	All subjects must give signed informed consent. Subjects' data will be handled according to regulatory requirements and be protected according to the EU Directive 2016/679 on data protection as well as local data protection requirements. UK Research Governance guidelines will be adhered to. The protocol must be approved by an independent Ethics Committee before use.

3 LAY SUMMARY

3.1 Why is this research needed?

Prostate cancer is very common and results in the death of many men in the developed world. Prostate cancer that has not spread outside the prostate can usually be cured by surgical removal of the prostate gland (radical prostatectomy). Radical Prostatectomy can be associated with urinary incontinence due to damage to the involuntary sphincter and erectile dysfunction due to damage of the nerves that run within the outer coverings of the prostate. Surgical sparing of these nerves to preserve quality of life may risk leaving cancer cells behind often meaning that the patients need extra treatment with radiotherapy. This trial is designed to evaluate a new method designed to decrease the risk of compromising cancer control associated with sparing of the nerves as well as evaluate effects on the need for radiotherapy after surgery if cancer is left behind. We will also evaluate effects on the quality of life in patients who have undergone RARP. The trial is needed now because the nature of prostate cancers treated surgically is changing rapidly. The techniques developed in low-risk cancer to spare the nerves which run alongside the prostate, may not necessarily be safe when used on the more aggressive cancers we operate on nowadays and if they are adopted without adequate investigation, the risk is that patients will be exposed to increased risk of cancer recurrence and needing extra treatment with radiotherapy with consequent side effects and extra cost to the NHS.

On the outside of the prostate, within its outermost coverings, run the nerves thought to be responsible for producing erections. Preservation of these nerves has also been linked to more rapid reestablishment of urinary continence following surgical removal of the prostate. Robotic technology has been developed which allows the prostate to be removed through very small incisions. The surgeon's view is magnified in 3D, which facilitates the peeling off of the outer layers, containing the nerves (so called nerve sparing). With nerve sparing the nerves controlling erections are left intact whilst the prostate itself, along with the cancer within it, is removed. This increases the patient's chances of getting erections of sufficient quality for penetrative sex. Data from several case series, including our own, suggest that the higher the degree of nerve sparing performed, the more likely a patient is to be potent and continent of urine. In our series, bilateral nerve sparing results in 85% of men being able to get usable erections*, whereas only 45% of men will have usable erections * when only one side is spared.

Nerve sparing has largely been developed and the effects have been evaluated in the USA where prostate cancer is detected at an earlier stage because PSA screening is performed commonly. In the UK, where PSA screening is not commonly carried out, tumours resected at surgery are larger and more aggressive, often having spread

* At 2 years following surgery using Viagra or an equivalent PDE5i.

through the capsule of the prostate. In addition, the move away from surgery for small low-grade tumours in the UK means that the prostate cancers treated by surgery are larger and more aggressive overall. This means that the tumours are closer to the outer limit of the prostate because the more aggressive tumours tend to work their way out through the outer capsule of the prostate. A nerve sparing approach is associated with an increased risk that tumour will be left on the surface of the resected specimen. This is referred to as a positive surgical margin (PSM). One of the principles of (radical) cancer surgery is that cancerous tissue should be removed with a covering of non-cancerous tissue to give the best chance of cure (a so called negative or clear surgical margin). Positive surgical margins are associated with an increased chance of recurrence following surgery and require further treatment, usually with radiotherapy, which is expensive and engenders its own side effects.

We plan to evaluate the use of a modified version of a frozen section technique called NeuroSAFE (1) in promoting nerve sparing without diminishing the oncological effects of surgery by generating PSMs.

During this frozen section technique, once the prostate is removed, the areas of prostate adjacent to the spared nerves are sliced from the surgical specimen and rapidly frozen and stained so that they can be examined carefully by a pathologist. If the pathologist identifies a positive surgical margin, the spared nervous tissue on that side will be surgically resected before the patient is woken up at the end of the operation. When this is done the cancer behaves as if it had been resected with a negative surgical margin at the outset.

Frozen section analysis does not add much time to the surgical procedure, as once the prostate is removed, the rest of the operation (joining the bladder to the urethra and removing pelvic lymph nodes) can proceed whilst the frozen section analysis is performed. Patients enrolled to the trial will be randomised between A) standard UK nerve sparing practice, wherein the degree to which the nerves can be spared is determined by the operating surgeon based on clinical examination, biopsy results and multi-parametric MRI and B) bilateral nerve sparing with frozen section analysis.

We recently surveyed UK robotic prostatectomists and confirm that currently UK surgeons predominately rely on MRI, biopsy and Digital Rectal Exam (DRE) findings to determine whether they can spare nerves, but that there is little consistency in the means by which a surgeon decides whether or not they can spare nerves in a particular case. Our survey tells us that UK surgeons do not use frozen section to direct nerve sparing with only 5% of UK prostatectomists ever having used it at all.

What are the potential outcomes of this research?
This trial will provide a thorough evaluation of a new technique designed to minimise the occurrence of PSM and exposure to extra treatment or cancer recurrence. It will generate vital data regarding the cost/benefit of using this procedure. The relationship between the degree and frequency of nerve sparing on quality of life

will be evaluated in terms of sexual potency and urinary continence in UK patients undergoing RARP. The assessment of these functions will include patient reported outcomes.

In summary this trial will test whether this new surgical technique can be used to make surgery safer and more effective whilst allowing improved quality of life for patients having surgery for prostate cancer. If the technique is proven effective, we will use the experience gained to promote its use throughout the NHS through training courses and publication and dissemination of the resultant data. Staff from centres participating in this trial will be fully trained in the NeuroSAFE technique.

A patient and public involvement afternoon was held for participants of the NeuroSAFE PROOF feasibility trial, family members, men with prostate cancer, and staff members at UCLH. The event was supported by the charity Orchid Cancer appeal. The high levels of attendance were demonstrative of the support within our patient group for the work of this trial. We listened to the comments made by participants and members of the public and have made some changes to the design of our trial as a result of this feedback.

4 BACKGROUND

4.1 Prostate Cancer

Prostate cancer is now the most common cancer in men in the UK. More than 41,700 men were diagnosed in the UK in 2011 with areas of London identified as having some of the highest incidence rates nationally. While survival has increased substantially over the last 40 years, prostate cancer is the second highest cause of male cancer death in the UK (2). The incidence of prostate cancer in Northeast London (142.8 per 100,000) is higher than the national average (105.8 per 100,000). Consequently, prostate cancer is the most commonly diagnosed cancer across Northeast London with the number of men living with and after prostate cancer in the UK predicted to rise. (3) Despite being very effective at curing localised prostate cancer, RARP is associated with distressing physical and psychological symptoms, including urinary incontinence and erectile dysfunction, which can affect individuals for many years. (4) Following radical prostatectomy 5% of men have long term urinary incontinence and need to wear pads or consider further surgical treatment to stop the leakage. 95% of men who undergo non-nerve sparing radical prostatectomy suffer erectile dysfunction, which is resistant to treatment with drugs like Viagra, even after a period of 2 years following surgery.

Treating cancer and dealing with the side effects of treatment is expensive. The modern NHS is challenged with needing to develop and evaluate the effectiveness of new treatments whilst minimising treatment toxicity.(5)

4.2 Radical prostatectomy and nerve sparing

The first radical retropubic prostatectomy was performed by Millen in 1947. In the 1980s Walsh and co-workers identified the parasympathetic nerves derived from the pelvic plexus as they pass across the tips of the seminal vesicles and then along the posterolateral aspect of the prostate, between the true capsule and the lateral prostatic fascia, to the corpora cavernosae. Stimulation of these nerves brings about penile erection. (6) The function of these nerves has also been linked to urinary continence. (7)

4.3 Robot-assisted radical prostatectomy (RARP)

The 1990s saw the advent of minimally invasive radical prostatectomy using manually controlled laparoscopic equipment. (8) Advancing robotic technology means that nowadays, surgical removal of the prostate using a robotic system is possible with the first RARP performed in 2000. (9) Since then, RARP has become the gold standard in prostate cancer surgery to such an extent that in 2008 80% of radical prostatectomies performed in the USA were done robotically. The National Prostate Cancer Audit report 2020 shows that 89% of UK radical prostatectomy is now performed by RARP(10). RARP is associated with a lower operative blood loss,

blood transfusion rate than laparoscopic surgery and a shorter hospital stay than open surgery. RARP results in oncological outcomes which are at least non-inferior to open or laparoscopic surgery.(11) (12)

A recent investigation, on behalf of the NIHR Health Technology Assessment, of the cost effectiveness of robotic radical prostatectomy (without frozen section analysis) concluded that avoidance of the need for adjuvant treatment by prevention of positive surgical margins contributed significantly to the cost effectiveness of robotic prostate surgery. (13) An economic means by which to decrease the rate of PSMs further has the potential to make RARP more cost effective still.

4.4 Quality of life versus oncological outcome

The majority of localised prostate cancer can be cured by surgery, with 10 year prostate cancer specific survival reported at 92% (14). Radical prostatectomy has been shown to be more effective than watchful waiting (15) and radical radiotherapy for treating significant prostate cancer (16). RARP is a significant physiological challenge for the patient. Since alternative treatment with radiotherapy is available, men with medical comorbidities usually opt to have radiotherapy. Younger, fitter men tend to have surgery. (16) These men are more commonly potent and sexually active as well as continent of urine compared with their older, less well counterparts. Thus, these are the men who have most to lose in terms of quality of life as well as a longer life expectancy over which to have to deal with any functional deficit.
In order to try to limit the detrimental effects on Quality of Life (QoL), the neurovascular bundles can be carefully peeled off the sides of the prostate at surgery (17). In doing so, the prostate capsule is necessarily exposed, and less tissue intervenes between the prostate capsule and the edge of the resected specimen. Thus, the rate of PSM is increased. This is more likely with high volume or aggressive tumour, which is more likely to have breached the prostate capsule (pT3a) where any overlying connective tissue coverings (if present) will become the margin of the resected specimen. If pT3a disease is suspected the nerves cannot be spared without risking a positive surgical margin, often necessitating adjuvant radiotherapy. Pre-operative MRI is not very good at distinguishing organ confined prostate cancer from that which has breached the prostatic capsule. (18) Radiotherapy compounds urinary incontinence and erectile dysfunction, as well as resulting in gastrointestinal toxicity and an, albeit low, risk of inducing secondary neoplasms.

Current UK nerve sparing practice involves the operating surgeon deciding which nerves he feels he can spare based on the clinical examination, mp-MRI and biopsy findings. However, our ability to detect capsular breach by DRE, mp-MRI or from biopsy results is very limited. For example mp-MRI has been shown in a recent systematic review of 4001 patients to have a sensitivity of only 57% for detecting capsular extension. (18) Unsurprisingly, little consensus exists as to when a patient should have nerve sparing on a particular side or not for a given set of DRE/biopsy and MRI findings, as demonstrated with our recent survey of UK robotic surgeons who perform radical prostatectomy. A Delphi process to identify consensus around

nerve sparing amongst UK radical prostatectomists has been initiated by the research team.

At UCLH where we perform approximately 800 RARPs per annum. Of these, approximately 40-50% are performed for high-risk disease according to the EAU pre-operative risk classification score. Accordingly, relatively few (approximately 40% in 2018) are afforded the potential functional recovery benefits of a bilateral nerve-sparing RARP due to an excess perceived risk of leaving PSM and exposing patients to the need for subsequent adjuvant cancer therapies (ADT and radiotherapy) (data not published, available on request).

Surgeons from the USA have developed the technique for nerve sparing. In an unscreened UK population, resected prostate cancer volume is greater than in a screened population like that of the USA. (20) Widespread adoption of nerve sparing has taken place in the USA despite a lack of level-one evidence. (21) Adoption of nerve sparing in the UK should be undertaken with care unless our patients are to be exposed to unjustifiable risk.

Should a positive surgical margin occur, the patient is at significantly higher risk of treatment failure (biochemical recurrence) and a consequential need for salvage treatment compared to those in whom the surgical margins were clear. (22) (23)

4.5 Frozen section technique (NeuroSAFE).

The NeuroSAFE technique was developed at the Martini Klinik in Germany. NeuroSAFE has been shown to increase the rate of nerve sparing and reduce the rate of PSM at RARP in observational studies. Currently, almost all patients treated with nerve sparing radical prostatectomy at the Martini Klinik undergo a NeuroSAFE procedure. However, the procedure is relatively costly as it is labour intensive and requires a consultant pathologist to examine the sections. (1)

The technique itself does not result in a significant increase in operative time. This is because the specimen is extracted immediately when it is detached from the adjacent tissues and sent for frozen section analysis. Whilst this analysis is underway, the lymphadenectomy and fashioning of the urethro-vesical anastomosis can be performed. With this technique >99 % of pathologically organ-confined cancers and >90% of capsular-penetration (pT3a) or seminal vesicle (pT3b) invading tumours can be offered a nerve-sparing procedure, while reducing the rate of positive margins at the dorsolateral aspect to <1% and by more than 50% overall. If a posterolateral positive surgical margin is detected, resection of the NVB has been shown to result in oncological outcomes similar to if a negative surgical margin had been achieved in the first place. (24)

A further modification of the NeuroSAFE system has been developed and piloted at the Lister Hospital in Stevenage by the collaborators on this project. The Lister

Hospital is currently the only UK centre offering frozen section analysis of the neurovascular bundles routinely, outside of this trial.

A systematic review has been performed by our group on intra-operative frozen section (IFS) evaluation of the prostate margin during RP. Medline, EMBASE and the Cochrane Library were systematically searched without time nor language limitations (CRD4201912594). Ten non-randomized comparative studies (including 16, 897 patients) were retrieved. According to risk of bias assessment, seven studies suffer from serious risk of bias, whereas three studies suffer from moderate risk of bias. Performance of IFS greatly differed technically between studies. Eight studies report a reduction in rates of PSM (-1.4% to -14.5%) with the use of IFS and two studies report higher PSM rates (+0.4% to +10%) in IFS group. Four studies that perform IFS systematically at the posterolateral margin of the prostate all report either improved NVB preservation or improved erectile function (EF) recovery. Our groups' conclusions included that, no RCTs were identified, and most included studies are at high risk of bias. Furthermore, only very few of the studies included results on either long term oncological or functional outcomes. Within the limitations of this review, the evidence suggests that IFS during RP can modestly reduce PSM rates. IFS performed systematically at the posterolateral margin of the prostate (the NeuroSAFE technique) can facilitate more NVB preservation, which may contribute to improved patient functional outcome recovery, though this has not been proven in prospective studies yet. In short, randomized, prospective, standardized research with long term oncological and functional outcomes are lacking to date. We feel this further strengthens the case for the conduct of the NeuroSAFE PROOF trial.

5 HYPOTHESES & OBJECTIVES

5.1 Hypotheses

- Men undergoing NeuroSAFE RARP will experience superior EF recovery compared to men undergoing standard RARP.

- Men undergoing NeuroSAFE RARP will experience improved recovery of urinary continence at 3 months following surgery compared to men undergoing standard RARP.

- Men undergoing NeuroSAFE RARP will experience the same rates of cure from surgery compared to those undergoing standard RARP.

6 Objectives

6.1 Primary

To assess the difference in erectile function recovery between men undergoing standard RARP (control arm) and NeuroSAFE RARP (intervention arm) at 12 months following treatment using the IIEF-5 questionnaire.

6.2 Secondary

1. To evaluate the differences in urinary continence recovery in the early period following treatment (3 and 6 months) between men undergoing standard RARP (control arm) and NeuroSAFE RARP (intervention arm).
2. To evaluate the differences in oncological outcomes (including BCR and administration of adjuvant/salvage treatments) between men undergoing standard RARP vs. NeuroSAFE RARP at 12 months. Additional analysis is intended at 5 years post-surgery.
3. To evaluate differences in overall quality of life outcomes between men undergoing standard RARP vs NeuroSAFE RARP at 12, 24, 36, 48 and 60 months after surgery[2] and a maximum frequency of annually thereafter.
4. To evaluate differences in recovery of erections after 12-months and up to 2 years between men undergoing standard RARP vs NeuroSAFE RARP
5. Economic analysis to assess health resource use between standard RARP vs NeuroSAFE RARP at 12 months and up to 2 years post treatment.

[2] *Evaluation after 12 months dependent on future funding*

7 TRIAL DESIGN

7.1 Type of Trial

A single blinded, IDEAL stage 3, multi-centre, randomised controlled trial to assess NeuroSAFE Robotic assisted radical prostatectomy (RARP) vs standard RARP in men with prostate cancer. Men will be randomised 1:1 to NeuroSAFE RARP (intervention arm) vs Standard RARP (control arm). This trial aligns with an IDEAL framework Stage 3 Assessment for the evaluation of complex surgical interventions.

7.2 Outcome endpoints

7.2.1 Primary

Comparison of the proportion of men who recover erectile function at 12 months allocated to the NeuroSAFE intervention versus the control arm. Erectile function is measured using the IIEF-5 patient reported outcome questionnaire, where recovered function is defined as a score of 21 or more.

<u>Patient Answers to the IIEF-15</u>

- Patients should be made aware before filling in their follow-up visit questionnaire responses, that oral medications such as PDE5 inhibitors (e.g. sildenafil, tadalafil and others of the same class) will be permitted when taking into account the strength of erection achievable during intercourse or sexual stimulation.
- For the purposes of answering the IIEF-15 questions, erections achieved with the assistance of ancillary erectile aids such as the vacuum pump, intra-cavernosal injections, penile creams and prostheses should not be considered in the answers. The reason for this division is that the ancillary erectile aids (pumps, injections) are not related to cavernosal nerve preservation (NS RARP) and therefore the inclusion of these devices in the answers would introduce confounding.
- Erectile function will also be assessed, including use of erectile function aids by the additional erectile function questionnaire CRF.

Verbal questionnaire responses (telephone)

- Since the Covid-19 Pandemic and government restrictions on movement including hospital appointments, the NeuroSAFE PROOF team have been conducting trial follow-up visits via telephone. All trial questionnaires have been sent to participants in the post. In order maintain data completeness on key outcome measures (such as erectile function at 12-months [IIEF-15] and urinary continence at 3 months [ICIQ]), the trial clinical team have been administering these PROM questionnaires over the telephone.

- As of protocol version 5.0, to ensure data completeness and to avoid submitting repeated protocol deviations for each instance, this method of data capture is now an accepted method of data collection. Any paper copies returned by post will supersede verbal responses.
- In order to distinguish between source data origins, a new electronic CRF database will have the facility to record whether PROM items were obtained by paper questionnaires submitted by post, electronic versions submitted following email reminders, or verbally with a clinician over the telephone.

Further planned analyses:

- Additional subgroup analysis: restricted to men who did not receive a pre-operative radiologist recommendation for bilateral nerve sparing.
- Additional subgroup analysis: patients who did not receive adjuvant treatment (adjuvant therapy defined as any additional treatment without a PSA>0.2 ng/ml).
- Sensitivity analyses: additional analysis at 12 months
    - (a) IIEF-5 using a threshold >=15
    - (b) IIEF-5 using a threshold of >=2 for question 3
- Descriptive analysis of IIEF-5 at 3-, 6-, 12- and 24-months post-surgery[3]

7.2.2 Secondary Endpoints

7.2.2.1. Urinary Continence

Comparison of the proportion of men who are continent at 3 months, measured using the ICIQ PROM, where continence is defined as a score of 5 or less, between the NeuroSAFE RARP arm and the standard RARP arm.

- Sensitivity analyses: Analysis of incontinence at 6 months ICIQ score of 5 or less
- Additional subgroup analysis: restricted to men who did not receive a pre-operation radiologist recommendation for bilateral nerve sparing.
- Additional subgroup analysis: patients who did not receive adjuvant treatment (adjuvant therapy defined as any additional treatment without a PSA>0.2 ng/ml)
- Descriptive analysis of ICIQ scores at 3-, 6-, 12- and 24-months post-surgery[4]

[3] *Analysis after 12 months dependent on future funding*
[4] *Analysis after 12 months dependent on future funding*

7.2.2.2. BCR

Comparison of the proportion of men with BCR between NeuroSAFE and control arms within 12 months of surgery. BCR will be considered to have occurred when the post operative PSA measures >0.2 ng/mL, or where the PSA level is less than 0.2 ng/mL but the trajectory suggests inevitable rise above 0.2 ng/mL according to the clinician looking after the patient. If PSA fails to nadir after surgery, this will not be considered BCR as this is probably related to micro metastatic disease not detected by preoperative imaging. Patients with demonstration of metastases on imaging will not be considered as BCR for the same reason.

- Follow up time of 12 months is defined as cumulative time up to the 12-month visit. Patients visits after more than 13.5 months post-surgery will not be included (12 months + 6 weeks max visit window).
- Additional descriptive analysis will report recurrences across all patients at the following times: Within 3 months (+/- visit window) and within 6 months (+/- visit window).
- Descriptive analysis of BCR for each arm according to
    - (a) Gleason grade
    - (b) TNM stage
    - (c) pre-operative PSA level
    - (d) routinely used risk classifiers (D'Amico, CAPRA, EAU) (e) time of recurrence.

If patients have a low but detectable PSA level the frequency of testing would be increased from the usual schedule (3,6,9,12 months) depending on the trajectory and level of concern of the clinician looking after the patient.

7.2.2.3. Additional oncological treatments

For men who receive additional cancer treatment, despite not having reached a PSA threshold of PSA>0.2 ng/ml post-surgery will be considered as having undergone 'adjuvant treatment.' Descriptive analysis of proportions of men undergoing adjuvant oncological treatments at or before 12 months of surgery, including tabulating the types of treatment that these men underwent. Reasons for adjuvant treatment (i.e. before BCR) will be documented where possible.

Men who receive additional cancer treatment, following a PSA at or above the threshold of PSA>0.2 ng/ml post-surgery will be considered as having undergone 'salvage treatment.' Descriptive analysis of proportions of men undergoing salvage oncological treatments at or before 12 months of surgery, including tabulating the types of salvage treatment that these men underwent.

7.2.2.4. Quality of life

Comparison of the proportion of men's quality of life on NeuroSAFE intervention compared to control arm.

- Analysis of EQ-5D-5L scores to produce QALYs at 12 months by arm
- Analysis of RAND36 scores to produce QALYs at 12 months by arm
- Analysis of EPIC-26 scores to produce QALYs at 36-, 48-, and 60 months and a maximum frequency of annually thereafter by arm

Graphical presentation and descriptive analysis of RAND36 and EQ-5D-5L at 3-, 6-, 12- and 24-months post-surgery.

7.2.2.5. Positive Surgical Margins (PSM)

Descriptive tabulation of PSM rates between NeuroSAFE RARP and standard RARP arms. PSM will be grouped as:

0. Negative margin
1. Intraprostatic margins
2. Non-intraprostatic margins ≤ 1mm (included)
3. Large non-intra prostatic margins and >1mm
4. Very large non-intraprostatic margins and >3mm and/or multifocal

Additional subgroup analysis: restricted to men who did not receive a pre-operative radiologist recommendation for bilateral nerve-sparing.

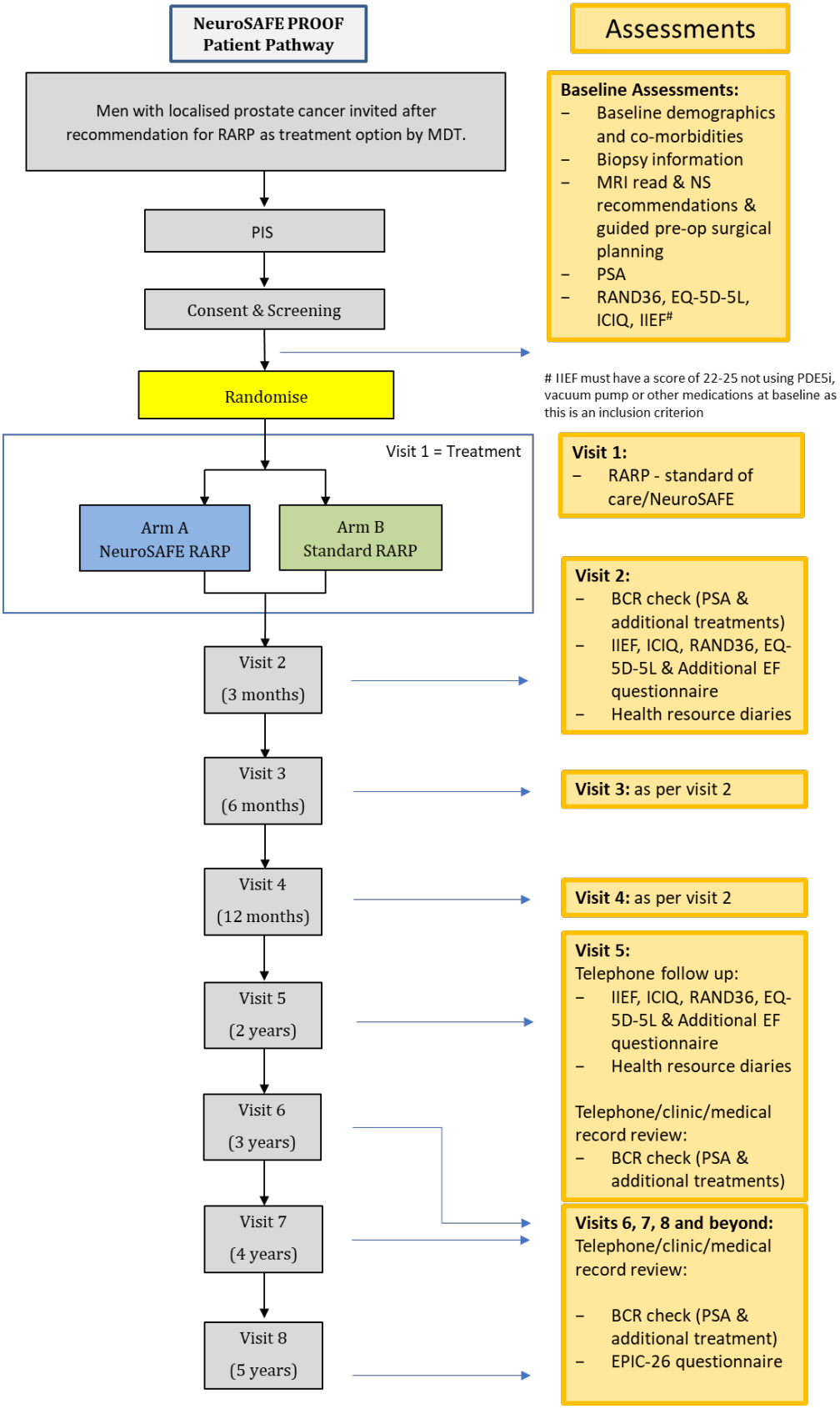
7.2.2.6. Health Economic Analysis

Use of the Health Resource Questionnaires to inform a health cost analysis of NeuroSAFE RARP vs. standard RARP. Please see section 11.3.

- Descriptive analysis by arm

- Economic analysis to assess healthcare resources use by arm and cost analysis to assess:
    - Cost of intervention and control
    - Cost of NHS resource use (medications, physiotherapy
    - Cost of private health care resources (medication, physiotherapy)
    - Other private/societal costs (productivity losses, caregivers costs, out of pocket cost for transport, equipment)

7.3 Trial Schedule



7.4 Table of Assessments

Visit	Screening/ Baseline	Randomisation	Treatment Visit 1	Visit 2 3 months (±6 weeks)	Visit 3 6 months (±6 weeks)	Visit 4 12 months (±6 weeks)	Visit 5[5] 2 years (±6 weeks)	Visit 6 3 years (±6 weeks)	Visit 7 4 years (±6 weeks)	Visit 8 5 years (±6 weeks)	After Visit 8**
Informed consent	x										
Randomisation		x									
Fitness for surgery assessment	x										
PSA	x			x	x	x	x	x	x	x	x
Standard care referral pathway to regional uro-oncology centre	x										
MRI guided pre-op surgical planning			x								
RARP (standard/control or NeuroSAFE/intervention)			x								
Adverse events	x	x	x	x	x	x	x				
EQ-5D-5L – (P/C/E/T)*	x			x	x	x					
ICIQ – (P/C/E/T)*	x			x	x	x					
IIEF-5 – (P/C/E/T*)	x			x	x	x					
RAND36 – (P/C/E/T)*	x			x	x	x					
Additional Erectile Function (EF) questionnaire (P/C/E/T)*				x	x	x					
Additional Treatments Assessment				x	x	x	x	x	x	x	x
Health Resource Diaries data collection				x	x	x	x				
RAND36, IIEF, EQ-5D-5L, ICIQ and Additional EF questionnaire – (P/E/C/T)							x				
EPIC-26 questionnaire (P/E)*								x	x	x	x

*P – Postal, E – Email, C – Clinic, T - telephone

** after visit 8 data to be collected for a maximum frequency of annually

[5] *Visits after 12 months dependent on future funding*

8 TRIAL ELIGIBILITY

8.1 Number of sites

This trial will be run as a multi-centre, IDEAL stage III trial. There will be a combination of recruiting centres and participant identification centres (PIC sites).

8.2 Inclusion criteria

1. Men opting to undergo RARP for organ confined prostate cancer (including radiological t3a).
2. Potent men (IIEF score of 22-25 not using PDE5i or other medications or devices for first 5 questions at baseline (from baseline PROM or clinical notes)
3. Men who are continent of urine (no self-reported urinary incontinence)
4. Has given written informed consent
5. Ability to read English sufficiently to answer questionnaires and understand PIS

8.3 Exclusion criteria

1. Unable to undergo robotic prostatectomy
2. Known overactive bladder
3. Previous treatment for prostate cancer
4. Previous/current hormone treatment for prostate cancer
5. Nerve sparing deemed futile due to locally advanced disease by surgeon and radiologist

8.4 Withdrawal criteria

1. Unable to perform nerve sparing as planned due to anatomical/technical difficulty during surgery. Intention to treat analysis will be undertaken
2. Patient changes their mind

9 SUBJECT RECRUITMENT

9.1 Identification of trial participant

Patients who potentially meet the eligibility criteria will be identified by the clinical team or during the regional urology cancer MDT team meetings at participating sites. They will be approached by one of the clinical team initially and then the trial team if they are willing to discuss the trial further.

These potential trial patients will be given the ethics committee approved PIS in the form of a physical copy or by email. The patient must be given sufficient time for consideration (without breaching the NHS cancer treatment times) and given the opportunity to ask questions about the trial before deciding whether or not to participate. The right of the patient to refuse to participate in the trial, with or without giving a reason, must be respected. If they are willing to participate in the trial, they will be asked for their informed consent to participate in this trial. PIC sites can issue a PIS only.

9.2 Screening and Consent

After a potential participant has had sufficient time to read the PIS, the enrolment process will follow these steps:

- The purpose of the research and the trial procedure is outlined again to the participant to ensure they understand. If the subject is willing to proceed, the participant will be asked to sign the approved trial consent form. This form may be a hard copy or an electronic consent form sent via an NHS account to the participants email. The original signed consent form will be filed in the investigator site file (ISF) after co-signature by an appropriate member of the research team. A copy will then be given to the participant and a copy filed in the hospital case notes. In the case of an electronic consent form, once signed and sent back to the research team, a fully co-signed copy is sent back to the participant, a copy is printed and stored in the ISF and a copy is stored in the hospital case notes. Please see section 9.3 for further details on e-consent.
- If the participant is willing to take part in the trial, eligibility to enter the trial is assessed based on inclusion and exclusion criteria. If all trial criteria are met, the screening visit CRF is completed. If a participant declines, this is also recorded in the screening log. A unique screening number will be assigned to participants recorded on the screening log.
- The participant is deemed to be recruited into the trial and the participant's GP is informed. At this point a unique subject trial number is allocated.
- Using the Sealed Envelope randomisation system, the patient is randomised using their allocated trial number and will be assigned to either the control or intervention arm. They will then be informed of their date for surgery.

- The patient will be blinded as to which arm they are randomised to. The surgeon will not be blinded. Unblinding will only be performed if an adverse event occurs where knowledge of allocation is perceived by the PI to be important in determining ongoing management.

9.3 Alternative consenting procedures due to COVID-19

9.3.1 e-consent

In line with the HRA COVID-19 guidance released on 28 May 2020, electronic methods for seeking, confirming and documenting informed consent in research studies can now be designed to minimise patient contact and reduce risk to both patient and healthcare practitioner (https://www.hra.nhs.uk/covid-19-research/seeking-consent-covid-19-research/). This has been implemented via an online consent form mimicking that of the currently approved paper copy.

The e-consent form is built using the Research Data Collection Service (REDCap). Owing to the process collecting patient identifiable data the e-consent forms, resides within the REDCap service hosted behind the UCL Data Safe Haven which conforms to NHS Data Security & Protection Toolkit and ISO 27001 Information Security standards (https://www.ucl.ac.uk/isd/services/file-storage-sharing/data-safe-haven-dsh).

10 TRIAL INTERVENTIONS

10.1 Robot-assisted radical prostatectomy (RARP)

Patients will undergo RARP using the DaVinci surgical system as per standard of care in the NHS, and by a surgeon who has performed a minimum of 100 cases.

10.1.1 Control Arm: Standard RARP

Standard RARP (control arm) is performed as per NHS routine practice at participating regional uro-oncology sites. Pre-operative parameters used to guide surgeon Nerve Spare (NS) decision include mpMRI NS planning sheet prepared in conjunction with a consultant genito-urinary radiologist, prostate biopsy tumour histology information and digital rectal examination under general anaesthesia. Individual surgeons are asked after RARP to grade the quality of NS performed on each side numerically as seen below (25):

- Grade 0 - No nerve spare. Wide excision of lateral pelvic fascia (LPF) and Denonvilliers' fascia.
- Grade 1 - Limited nerve spare, or partial/incremental nerve spare. Incision through outer compartment of LPF.
- Grade 2 – Interfascial nerve spare. LPF is taken just outside the layer of the veins of the prostate capsule. Still largely preserving the large neural trunks (also known as the NVBs).
- Grade 3 – Intrafascial nerve spare. LPF is taken just outside the prostate capsule. Represents greatest possible NS.

NeuroSAFE PROOF collects detailed information on histological surgical margin status for safety and future publication purposes. Descriptions of histological diagnosis can differ between sites due to varying interpretations of histological analyses. In line with quality assurance, we will request anonymised pathology reports to ensure accurate, standardised reporting in the trial database. This will occur across both arms of the trial.

10.1.2 Intervention Arm: NeuroSAFE RARP

NeuroSAFE RARP (intervention arm) will be performed in accordance with previously described methods, initially developed at the Martini Clinik, Hamburg, Germany. All patients in the NeuroSAFE arm will undergo initial bilateral NS where technically possible. The procedure differs from standard RARP in that initial insertion of the robotic camera port is through a modified incision using the Alexis Laparoscopic System (Applied Medical, Rancho Santa Margarita, CA).
Once the specimen is disconnected from its attachments, the specimen can be removed from the patient through the protected incision immediately. Pneumoperitoneum can be re-established quickly by placing the laparoscopic cap back on the Alexis.

The specimen will then be painted by the operating surgeon (sites may differ, but at UCLH; yellow for left and green for right side of the prostate). The painted areas can be sprayed with a fixative spray if site prefers (to prevent ink running). The specimen will be delivered expediently to the pathology laboratory where frozen section analysis of the painted areas will be undertaken. Whilst this 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 result of the frozen section analysis is awaited.

Upon delivery of the prostate gland to the pathology lab, a sharp blade will be used to remove the pre-painted surface of the gland (which had been in contact with the neurovascular bundles). The tissue sample will be snap frozen and embedded in OCT. Using a cryostat, 10-micron thick slices will be placed on slides. The entire length of the area of interest will be sampled in this way generating an average of 5 frozen sections per side and approximately 10 in total. The slides will be stained with H&E and will be examined by a consultant pathologist. As soon as examination is complete the pathologist will telephone the operating surgeon to give the result. On frozen section analysis, presence of cancer cells at the inked surface margin of the specimen constitutes a positive margin and the length of any positive surgical margin will be recorded.

Detailed results of the frozen section examination will be collected and included in the results, including number of sections positive, length of positive margin, grade of cancer cells seen at the margin, identity, and seniority of pathologist. When the frozen section examination demonstrates cancer at the margin of the prostate as per pathology reporting protocol, secondary resection (SR) of the NVB is performed according to one of two ways on each side*:

1. No tissue resected
   or
2. Entire neurovascular bundle resected.

*In the presence of an IFS PSM, the performance of SR of the ipsilateral NVB will be made if any of the following are present:

(1) any PSM on multiple sections on a side,
(2) any Gleason grade 4 or grade 5 adenocarcinoma at the margin.
(3) any single section PSM >2 mm of Gleason Grade Group 1.

If none of the above are present (including up to 2mm of Gleason Grade 3 at the inked margin) no SR will be performed.

Technically during surgery, 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 frozen section.

Detailed times of the beginning of the RARP, the removal of the prostate for specimen painting, arrival of specimen in laboratory, communication of details of fresh frozen section to the surgical team and finishing the RARP are recorded on the day of surgery.

When recording a secondary resection in the database (if applicable), this will be recorded as either:

- No tissue resected (due to none of the above 3 conditions being present)
- Entire bundle resected (due to 1 or more of the above conditions being met)

If the entire bundle is resected, this will automatically be considered as Grade 0, or non-nerve spare, on the side that SR was performed.

10.2 Multiparametric MRI prostate

All patients will have pre-biopsy mpMRI as per the local practice's diagnostic pathway. All radiologists will have at least 2 years of experience in prostate MRI reading. MRI diagnostic tumour detection performance is not formally assessed as all patients enrolling into NeuroSAFE PROOF already have tissue (biopsy) diagnosis of prostate adenocarcinoma and this is not the purpose of the trial. Radiologists are provided with clinical details including PSA, biopsy tumour results, biopsy method, medical history, and any other risk factors such as family history to aid their MRI interpretation. Local tumour staging (according to the PIRADS anatomic division of the prostate at the base, the mid gland and the apex) is graded according to a modified 5 level Likert scale based on the risk scoring system by the European Society of Urological Radiology (ESUR)(26), (1 = No signs of extra-prostatic extension (EPE), 2 = No convincing signs of EPE, 3 = EPE might be present, 4 = EPE is likely, 5 = EPE is highly likely).

Seminal vesicle invasion, lower sphincter invasion, and bladder neck invasion is reported as categorical ancillary reports. Subsequently, the radiologist using the mpMRI makes a NS recommendation for each side of the prostate for each participant regardless of treatment arm allocation. The radiological NS recommendation will be recorded:

- Nerve Sparing: Yes
- Nerve Sparing: No
- Digital rectal examination dependent.

Image-based mpMRI surgical NS planning is aimed to assist surgeons, but NS will still be performed in both control and intervention arm as per the operating surgeon's discretion.

During image based surgical NS planning, all mpMRI scans will be graded as to their quality according to the radiologist who reads the images. Scoring system will be a 1-5 Likert score. Description of criteria on scan required to give a quality score will be based on the following:

1. All three sequences are of insufficient quality to score any lesions.
2. Two out of the three sequences are not diagnostic; therefore, it is not possible to score any lesions.
3. It is possible to score a lesion (rule in) but it is not possible to exclude significant lesions (rule out).
4. One of the sequences is not of sufficient quality. Overall, it is possible to score the lesion (rule in) and rule out lesions in the background.
5. T2, DWI (Diffusion Weighted Imaging) and DCE (Dynamic Contrast Enhanced) are each independently diagnostic quality. The radiologist is able not only to diagnose (rule in) lesions but also to rule out lesions in the background.

10.3 Other prostate evaluation technologies and co-enrolment

Prostate tissue or liquid samples pertaining to prostate cancer research of men enrolled in the NeuroSAFE trial can be used for other intraoperative cytopathological prostate evaluation technologies which will not affect clinical care or performance of treatment as described by this protocol (with their consent). Any 'other' margin evaluation technology assessments at participating sites must have the written approval from the TMG. Any additional prostate specific evaluation technologies will be reflected in the patient PIS and consent forms.

Participating sites considering co-enrolment of NeuroSAFE PROOF patients onto other studies must also have written approval from the TMG.

10.4 UCLH Biobanking

The NeuroSAFE PROOF team works closely with other Prostate Cancer Research teams, including the Molecular Diagnostics and Therapeutics Group at University College London. We understand the research need for successful collaboration in order to maximise the efficient use of research resources. As such, we will invite participants in the NeuroSAFE PROOF trial to consent to the use of their tissue for further translational cancer biology research such as that described in the PEOPLE study.(35) During cut up for intra-operative analysis, tissue from the prostates of participants will be reserved for collection by the Molecular Diagnostics and Therapeutics Group without compromising the performance of the NeuroSAFE technique, the assessment of the prostate specimen for final histological diagnosis, nor elongating the length of the operation/time a man spends under general anaesthetic. The performance of fresh tissue collection from the prostates of men involved will not influence decisions about their clinical care and will only be used for future scientific research studies. It is proposed that matched tumour and benign

prostate tissue will be sampled and collected for local research projects involving biomarkers, diagnostics, and therapeutics for prostate cancer. Methodology of these investigations will include but not be limited to, ex vivo cultures, genomics, and immunohistochemistry. All samples will be pseudonymised and all data will be stored securely within NHS frameworks. All tissue will be stored and tracked in accordance with the Human Tissue Act, with regular internal audits to ensure sample and data security.

Details of the proposed tissue sampling will be described in the REC approved Participant Information Sheet and will be included as an additional 'opt-in' on the Informed Consent Form. A prospective participant may prefer not to consent to tissue sampling for molecular diagnostics and therapeutics and may still consent to being involved in the NeuroSAFE PROOF trial.

11 DATA COLLECTION

Responsibility for data collection will be taken by a nominated individual. Data will be collected in eCRF format. Data will be held according to the Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR). Data will be pseudo-anonymised as necessary. Each participant will be given a trial number, and this will be used on all trial records. This trial number will be known by all NeuroSAFE 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, including the use of secure computer software for video linked proctoring between sites. 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.

11.1 Data transfer (handling, processing and storage)

In the trial, demographic data, clinical end points, surgical, pathology and imaging outcomes, and patient reported outcome data from questionnaires will be collected in accordance with the patient consent form, patient information sheet and various sections of this protocol.

The pseudo-anonymised trial data will be appropriately sent to the trial statistician, please see the trial summary for statistician's contact details, for statistical analysis. UCL as the sponsor, will act as the data controller.

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.

Data entered electronically (e-CRFs) will be stored on secure servers hosted by an approved UCL sub-contractor - AIMES Management Services. AIMES exceed NHS security standards and are:

- Cyber Essentials Accredited
- Health and Social Care Network Access Compliant
- NHS Data Security and Protection Toolkit Compliant (Standards Exceeded)
- ISO27001:2013 Accredited

UCL will remain the data controller.

11.2 Video Collection

Video recordings of all NeuroSAFE operations will be anonymised and linked to each patient's unique trial NRS number. These videos will be stored on an encrypted external hard drive at each site in a locked filing cabinet until the end of the trial before being uploaded and stored in UCL's data safe haven. These recordings are collected to allow for quality control review.

11.3 Health Economics Analysis

A cost-utility analysis of the NeuroSAFE RARP compared to standard RARP will be undertaken using accepted methods. We will analyse cost-effectiveness using a short-run time horizon of 12 months and 2 years (within the trial period - all participants will be followed for at least 2 years). Costs will be assessed from the perspective of the NHS and PSS. Cost components included in the analysis will be the cost of the intervention (standard RARP and NeuroSAFE RARP); NHS costs (inpatient and outpatient visits, diagnostic tests, medications). Resource use data will be collected retrospectively from patients using questionnaires (resource use diary) at 3 months, 6 months 12 months and 2 years. Unit costs will be taken from standard sources.

The cost-effectiveness measures in the short-term model will be the incremental cost per unit of change in the QALY gained. Costs will be measured as described. QALYs will be calculated based on the health-related quality of life (HRQoL) collected using EQ5D5L and RAND36 questionnaires. Patients' utility profiles will be constructed assuming a straight line between each patient's HRQL scores at each follow-up point. The QALYs experienced from 3 months to 2 years will be calculated as the area underneath this profile. Cost-effectiveness will be calculated as the mean cost difference between NeuroSAFE RARP versus RARP divided by the mean difference in outcomes (QALYs) to give the incremental cost-effectiveness ratio (ICER). A sensitivity analysis will be performed to control for input parameters uncertainty.

11.4 Electronic Patient Reported Outcome Measures (e-PROMs)

As a further COVID-19 mitigation strategy, PROM questionnaires will be sent out electronically over email. Clinical research teams at each site will be able to send patients a personalised hyperlink to their NRS number (their trial number) to input their questionnaire answers onto our database. Patients will only have access to their specific NRS profile and for that visit's questionnaires only. These questionnaires contain no patient identifiable data and email addresses for these patients are not stored on the database. Data collected from the patients will be stored using the same company we currently use on a server that conforms to all data protection and HRA requirements. The database will contain no patient

identifiable data and will not be shared with anyone outside of the direct trial management team.

To ease patient burden and for those who may not want to use a computer, hardcopy CRFs can be sent in the post to be filled out and returned. They will then subsequently be entered onto the NeuroSAFE database by the trial team.

12 STATISTICS

12.1 Sample size

As of protocol version 5.0, the NeuroSAFE sample size justification has been updated based on the analysis of 50 patients included in the NeuroSAFE PROOF Feasibility Trial, which was relevant to the original version of this protocol. 25 men were randomly allocated to NeuroSAFE RARP and 25 allocated to standard RARP. They were then followed up to 12-months following treatment. Outcomes related to these men will not be included in main trial analysis.

Based on analysis of the feasibility trial outcomes, the primary outcome was defined as a comparison of erectile function recovery at 12-months between men who underwent NeuroSAFE RARP (intervention) vs. standard RARP (control) with recovery defined as an IIEF-5 score of 21 or above.

The previous recruitment target according to protocol version 4.0 (August 2019) was for 404 men (364 evaluable). This sample size was calculated without the benefit of mature functional (i.e. PROMs/IIEF-15) results related to erectile function recovery.

A new sample size using the newly informed outcome data from the feasibility trial was prepared for protocol 5.0. The sample size is based on a 14% higher proportion of men with IIEF-5 score of 21 and above in the NeuroSAFE RARP (intervention) arm, compared to the control baseline proportion. At 90% power, an alpha of 0.05 and a loss to follow up of 10%, 416 patients (374 evaluable) would be the anticipated recruitment target. This sample size calculation is therefore deemed to be compatible with the sample size calculation submitted and used within protocol version 4.0 (August 2019). Furthermore, the iDMC reviewed the sample size assumptions on 16th Feb 2021 and were unblinded to results from the first 150 men recruited to the main trial. They advised the trial continue recruitment to the original number of 404 men (364 evaluable men). The iDMC will continue to review the recruitment target during the trial.

The secondary outcome #1, the proportion of men regaining continence at 3 months as defined by ICIQ score of 5 or less, is powered at 89% for a 15% increase in the NeuroSAFE RARP (intervention) arm compared to the standard RARP (control) arm at 3 months.

Results of the feasibility trial used for sample size calculation have been redacted from this protocol document, as these are anticipated to be similar to interim results for the full powered ongoing trial, due to the internal design of feasibility trial which shared the same methods and centres as the main trial. The intention of restricted access to these preliminary results, is that these results should not influence recruitment to the main trial, because the feasibility trial was not powered to provide estimates of the primary or secondary outcomes. Full unblinded results

needed for sample size calculation are available in confidence for research ethics review and iDMC.

12.2 Statistical Analysis

A Statistical Analysis Plan (SAP) will be written and locked prior to analysis.

In order for the NeuroSAFE PROOF trial to maintain its recruitment inertia, the NeuroSAFE PROOF trial was transitioned from its feasibility and pilot phases to the fully powered trial (covered in substantial amendment 4.0). As such, all subjects from the 51st patient (inclusive) onwards will be reconsented to the larger RCT. Patients 1-50 were treated as part of the NeuroSAFE PROOF Feasibility Trial, which has reported its primary outcome (recruitment). Full 12-month reports of oncological and functional outcomes from the NeuroSAFE PROOF Feasibility Trial will be analysed as a separate cohort, per the feedback of the NeuroSAFE PROOF Feasibility Trial iDMC. Publication of feasibility trial results will not be before main trial recruitment is completed in order to maintain the equipoise of the clinicians and sites involved in recruitment.

12.2.1 Intent to treat population

The intent to treat (ITT) population, which is the primary population for efficacy, is defined as all men who provide written informed consent to receive the treatment.

12.2.2 Per protocol population

The per protocol (PP) population, which is the secondary population for efficacy, is defined as all ITT subjects who received the intended treatment and had no major protocol deviation or violation that may confound the assessment of efficacy.

12.2.3 Safety population

The safety population is defined as all subjects exposed to the treatment

12.2.4 Statistical methods

Primary outcome: Comparison of the unpaired proportions of men who recover erectile function at 12 months allocated to the NeuroSAFE intervention versus the control arm, based on an IIEF-5 score of 21 or more. Statistical significance will be established using 95% confidence intervals calculated using the Wilson method. P-values will be reported. Further planned subgroup and sensitivity analyses will be conducted as detailed in section 7.2.1
The secondary outcome #1 will use similar methods to the primary outcome.
There will be no adjustment of p-values for secondary outcomes for multiple testing.
STATA statistical software will be used.

Due to interruption the trial due to COVID pandemic, collection of outcomes at particular time points has been affected, with 3- and 6-month time points being less regimented than anticipated. Prior to data lock, the statistical methods will be

reviewed. It is possible that analysis could use survival analysis of time to event analysis up to 12 months for both analyses, if that would make better use of data from multiple time points.
Statistical methods will be reviewed on analysis of a sample of 20% of all data prior to data lock, after data collection and cleaning.

12.2.5 Handling missing data

Multiple imputation will be used for missing data using chained equations in STATA (Multiple imputation using chained equations: Issues and guidance for practice. Ian R. White, Patrick Royston, and Angela M. Wood. Stat Med. 2011 Feb 20;30(4):377-99.)

For the primary outcome, multiple imputation of the ITT population will be based on all time points of outcome measurement as well all relevant participant covariates will be used. Complete case analysis (all available patient data with no imputation) will be reported alongside as a sensitivity analysis to the ITT analysis.

13 DATA MONITORING

13.1 Discontinuation of the trial

13.1.1 Trial Discontinuation by the Sponsor

The Sponsor may terminate the trial at any time if the following occur, and the investigator is unable to take corrective action in any of these cases:

- The investigator is non-compliant with the protocol
- The investigator is non-compliant with the regulatory requirements
- The investigator is non-compliant with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the Research Governance Framework (version 3.3)
- The CRF completion is inadequate

The independent Data Monitoring Committee (iDMC) will perform a quarterly review of the oncological outcomes reported in NeuroSAFE PROOF to ensure participant safety. The iDMC can meet less frequently post recruitment period. The iDMC can advise the Sponsor to terminate the trial early if the 3 monthly BCR safety measure shows an increased incidence in the NeuroSAFE arm (this would be defined as incidences $p<0.01$).

Salvage treatment should only be started after discussion and agreement at SMDT.

13.1.2 Discontinuation of Trial for an Individual Patient

The criteria for discontinuing the trial in the case on individual patients are:

Inter-current illness
Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree

Request by the patient
It is the patients right to request discontinuation of their participation in the trial. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future.

Discontinuation of attendance at an investigating site
Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients no longer attend the participating institution.

13.2 Quality assurance

In order to ensure the quality of the data collected in the trial, the principal investigator will provide means for data monitoring and QC of the database. Data will be handled according to regulatory requirements and be protected according to EU Law Enforcement Directive EU2016/680 (which is now incorporated into UK GDPR) and the Data Protection Act 2018 as well as local data protection requirements.

NeuroSAFE PROOF collects detailed information on histological surgical margin status for safety and future publication purposes. Descriptions of histological diagnosis can differ between sites due to differing interpretations of histological analyses. In order to ensure standard, consistent reporting in line with quality assurance, we will request anonymised pathology reports to ensure accurate, standardised reporting in the trial database. This will occur across both arms of the trial. These reports will be sent electronically in a secure manner (e.g. an NHS.net account) to the NeuroSAFE clinical trial manager at UCL. The reports will be stored in a secure environment that conforms to NHS Digital's data and protection toolkit. The trial manager will de-identify the reports and assign them a unique identifier before sending them for review by a UCLH pathologist. Findings from this quality assurance review will be collated and discussed with all participating pathologists after the last operation (in either arm) has been completed. The reports will be compared to the UCLH pathology reporting standard operating procedure document.

13.3 Assessment of safety

Adverse Event Definitions

Adverse Event

Any untoward medical occurrence in a subject including occurrences, which are not necessarily caused by or related to the intervention

Adverse Reaction

Any untoward and unintended response in a subject, which is related to the intervention

Unexpected Adverse Reaction

An adverse reaction, the nature and severity of which is not consistent with the trial intervention(s)

Serious Adverse Event/Reaction (SAE/SAR)

Any untoward medical occurrence that:

1. Is a life threatening illness or injury
2. Is a permanent impairment to a body structure or function
3. Is a condition requiring hospitalisation or increased length of existing hospitalisation (except hospitalisation for planned admission unrelated to the intervention, urinary retention requiring catheterisation)

4. Is a condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place.
5. Led to foetal distress, foetal death or a congenital abnormality or birth defect
6. Might have led to any of the above

Suspected Unexpected Serious Adverse Reaction
All suspected adverse reactions related to the intervention that is both unexpected and serious.

Adverse Events Classification
The definitions used to describe the relationship between the adverse event and the trial interventions are the following:

Unrelated
An adverse event that is definitely not related to the intervention.

Unlikely
An adverse event for which an alternative explanation is more likely e.g. concurrent drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the intervention. An alternative explanation e.g. concurrent drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the intervention. The relationship in time is suggestive (e.g. confirmed by rechallenge). An alternative explanation is less likely e.g. concurrent drug(s), concomitant disease(s).

Very likely
An adverse event, that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation e.g. concurrent drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by de-challenge and re-challenge).

Un-assessable
It is not possible to assign the reaction to any of the above categories because of insufficient, pending, or contradictory information. Further information is requested in order to lead to an attribution of causality.

13.4 SAE Reporting

All serious adverse events (SAEs) must be reported to the NCITA Clinical Trials Unit within 24 hours of the Investigator's knowledge of the event (except for those that are identified in the protocol as not needing immediate reporting) via the appropriate SAE form. The trials unit will notify the main Research Ethics Committee and sponsor within 15 days of the Chief Investigator becoming aware of the event.

Those events arising will be reported on a three-monthly basis to the TMG and TSC/iDMC in a summary format, to include:

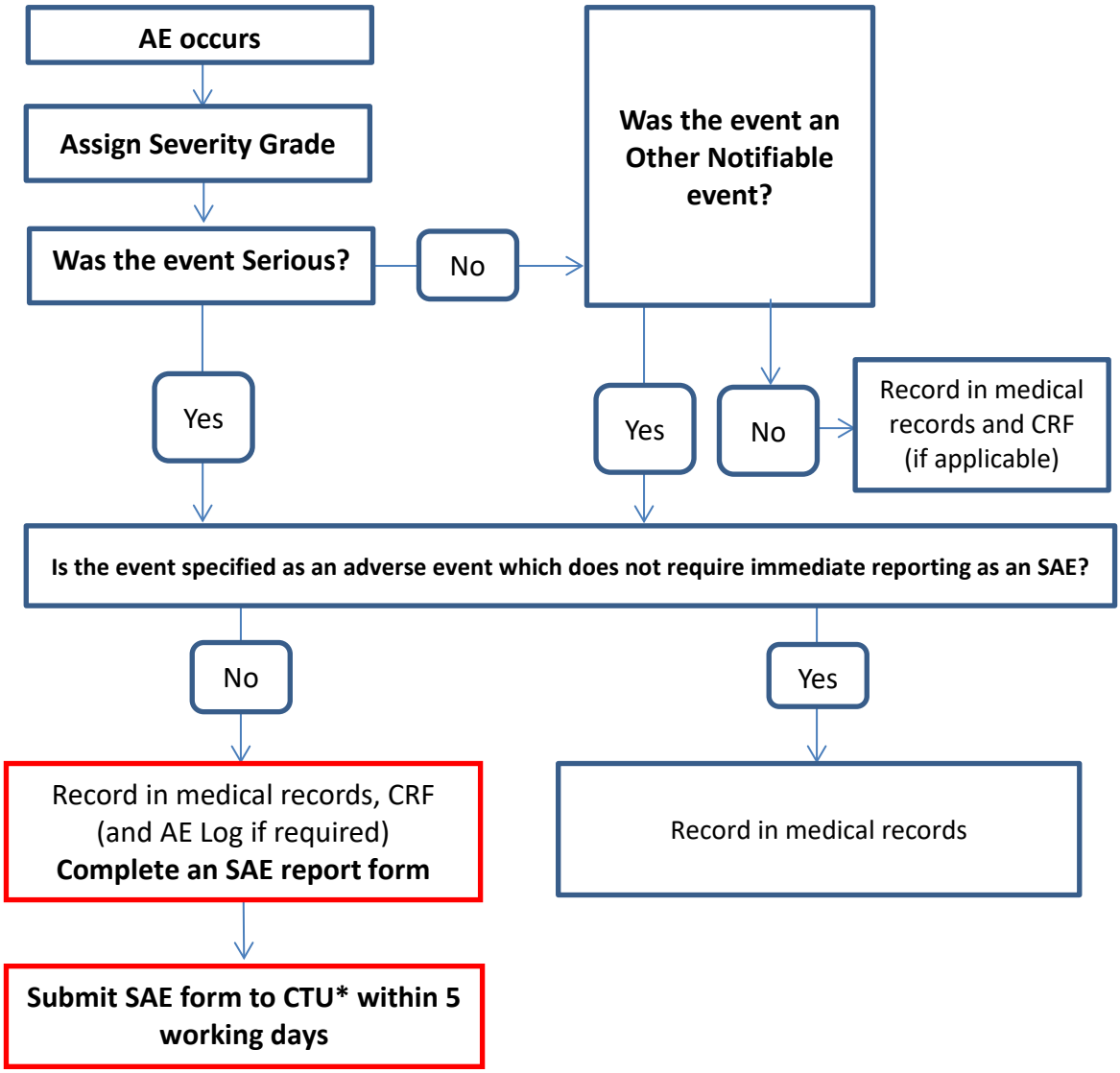
- The number of serious adverse events in a tabular format laying out the percentages of each type of serious events with an indication as to how many of those are thought to be related to the trial intervention.
- The total number of patients recruited during that same 3-month period and in total.
- Clavien-Dindo classified complications of 3 or more will be anonymised and blinded before being submitted to the TMG for central grading and review of site.

13.5 Reporting Requirements

In line with the Health Research Authority guidance on non-CTIMP trials, only reports of SAEs that are listed below will require reporting to the CTU (and subsequently sponsor & ethics):

- **Related** to the trial (i.e. they resulted from the use of the NeuroSAFE technique) and
- **Unexpected** (that is not listed in section 13.7 – Expected Adverse Events)

13.6 Flow of SAE Reporting



*CTU will forward unexpected and related SAEs to REC & Sponsor

SAE Reporting:
Please email the completed SAE form to: uclh.ncita.sae@nhs.net

13.7 Expected Adverse Events

The following are expected adverse events following a radical prostatectomy with their corresponding likelihoods (31-34). 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.

Expected adverse events:

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%

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%

13.7.1 Notification of Death

As with all major surgery there is also a risk of death. The risk of death with either of these surgical interventions is thought to be less than one in a hundred. Any deaths including deaths unrelated to the treatment will be recorded on the CRF/database.

13.7.2 Period of observation

For the purpose of this trial, the period of observation of serious adverse events extends from consent to 90 days post op as it unlikely any SAEs past this point will be related to surgery. This will reduce site reporting workload. Trial follow up should continue according to schedule once the SAE is resolved, if applicable. The trial will, however, continue to collect death SAEs throughout per section 13.7.1.

14 ETHICAL CONSIDERATIONS

The Chief Investigators will take primary responsibility for the conduct of the trial in accordance with the World Medical Association Declaration of Helsinki and subsequent amendments, and the conduct will conform to ICH GCP guidelines and the Research Governance Framework Guidelines.

Subject Information and Informed Consent: The patient's consent to participate in the trial should be obtained after a full explanation has been provided of the procedures to be given. All subjects must sign and personally date an approved informed consent after having received detailed written and verbal information about the reason, nature and possible risks associated with the research program. Patients should be given sufficient time after being given the trial patient information sheet to consider and discuss participation in the trial with family and friends. Patients will always be asked to sign a consent form. One copy will be given to the patient, one copy will be kept with patient's hospital notes and one copy should be kept in the local investigator site file.

The subject must be made aware and agree that personal information may be scrutinized during monitoring and audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to manage the patient however he/she feels fit to suit the best interest of the patient, regardless of the protocol. Similarly, the patient must remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment or the standard of care received.

An Institutional Review Board and/or an Independent Ethics Committee must approve the protocol, the patient information sheet, the content of the informed consent form and any promotional materials used for the recruitment of subjects before the accrual of any patients. If legally required, the protocol and informed consent must be submitted to the country regulatory authorities.

Specific Ethical Issues

None

15 FINANCING AND INSURANCE

University College London holds insurance against claims from participants for injury caused by their participation in the trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the trial. 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 trial 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 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.

The NIHR Research for Patient Benefit, Jon Moulton Charitable Foundation Trust and St. Peters Trust fund this trial.

16 REPORTING 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 upon review by the TMG. Authorship will be determined on a per paper basis. The chief investigator will have final say if agreement cannot be reached.

16.1 Patient and Public Involvement

Patient feedback on the design of the trial was obtained. The PPI events were supported by Macmillan Cancer (Charity no 261017) and Orchid (Charity no 1080540). Participants, patients and their families were asked specifically about the level of blinding, the burden of follow-up appointments and priorities in their recovery from RALP.

Following their feedback, NeuroSAFE PROOF now informs men following surgery of their NS status, though blinding to allocation status (intervention or control) is maintained. Patient representatives sit on both the trial steering committee (TSC) and the Data Monitoring Committee (iDMC) contributing to the oversight of the management of the trial. The trial is also funded by National Institute for Healthcare Research for Patient Benefit (NIHR RfPB) stream, which has patient members on their decision panels.

16.2 NeuroSAFE PhD report

NeuroSAFE PROOF will constitute a substantial part of the PhD research degree for Mr Eoin Dinneen. Mr Dinneen is enrolled at University College London within the Division of Surgery and Interventional Sciences. His supervisors are Professor John Kelly, Professor Shonit Punwani and Mr Greg Shaw (Chief Investigator of NeuroSAFE PROOF). Mr Dinneen anticipates finishing his PhD and submitting his thesis in July 2021. Mr Dinneen has been heavily involved in the design and execution of the both the feasibility and the full-scale NeuroSAFE PROOF trial. Particularly, Mr Dinneen has been influential in the establishment of the NeuroSAFE PROOF feasibility trial, day-to-day running of the trial, designing the full- scale NeuroSAFE PROOF trial, writing protocol versions 2-5, writing and submitting the protocol manuscripts for peer review and publication, co-ordinating PPI on behalf of the NeuroSAFE PROOF team, selecting the primary endpoint, standardisation of reporting of crucial elements of the trial methodologies (such as the role of MRI reporting, the surgical response to the positive NeuroSAFE, statistical handling of the NS status of surgery, and health economics analysis). Mr Dinneen will write his thesis on evaluation of extra-prostatic extension and surgical margin status in men undergoing RARP. This work will rely heavily upon the skills and techniques developed as part of his role in NeuroSAFE

PROOF. Given that the NeuroSAFE PROOF trial will form a significant part of Mr Dinneen's PhD thesis, it is intended that Mr Dinneen be given confidential, unblinded access to data and results of statistical analyses. This will mean that the thesis will be made open access after an embargo period (determined by the CI), to enable first publication of the trial results in a journal.

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18 ROLES AND RESPONSIBILITIES

These membership lists are correct at the time of writing; please see terms of reference documentation in the Trial Master File for current lists.

Protocol contributors

Name	Affiliation	Role
Mr Greg Shaw	UCLH	Chief Investigator and Lead Clinician
Dr Ricardo Almeida Magana	UCLH	Urology clinical fellow
Ms Chris Brew-Graves	UCL	NeuroSAFE co-applicant
Mr Nick Roberts	UCL/UCLH	Trial Manager
Professor Sue Mallett	UCL	Trial Statistician

Trial Team

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Dr Alex Freeman	UCLH	Co-Investigator
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Independent Data Monitoring Committee

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Prof Jane Warwick	Chair/ Independent biostatistician
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