GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

A randomised controlled trial comparing the clinical and cost-effectiveness of lymph node removal in patients undergoing curative surgery for localised high-risk Prostate Cancer. (ELIPSE)

ELIPSE

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Funder: National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme
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R&D ref: 8310
REC ref: 24/WS/0075
IRAS ref: 329888
Protocol version number and date:

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1. GENERAL INFORMATION

1.1. Study Summary

Study Title	ELIPSE: A randomised controlled trial comparing the clinical and cost-effectiveness of lymph node removal in patients undergoing curative surgery for localised high-risk Prostate Cancer.
Internal ref. no. / short title	ELIPSE
Rationale	Every year in the UK, nearly 50,000 people are diagnosed with prostate cancer (PCa) and over 10,000 men die from it. PCa that has not spread elsewhere in the body but is at risk of doing so is referred to as high-risk localised PCa. Established treatment options for high-risk PCa are surgery and radiotherapy. In the UK, 4000 patients a year undergo surgery for high-risk PCa. When surgeons operate on men with high-risk PCa, they remove the entire prostate gland and, in some cases, also remove the nearby lymph nodes (an immune tissue that forms the early landing sites for cancer spread) in a surgery called pelvic lymph node dissection (PLND). It is thought that PLND gives better cancer clearance and reduces recurrence, which is seen in 30-50% of men with high-risk disease. However, complications from PLND include pelvic lymphoceles, lymphoedema of the legs, deep vein thrombosis (DVT) and/or life-threatening pulmonary embolus (PE). These complications may reduce quality of life, and along with the increased surgical time required, lymph node surgery in addition to removing the prostate might result in additional costs to the NHS. We surveyed UK surgeons and found variable practice with 35% of eligible patients getting lymph node excision. Surgeons told us the current evidence was not good enough to inform decisions about whether it was beneficial to do a lymph node excision knowing that there

	are potential harms, and a clinical trial comparing lymph node excision to no lymph node excision was urgently required.
Study Design	A two-arm (parallel group) multicentre pragmatic superiority patient randomised controlled trial comparing Radical prostatectomy (RP) with pelvic lymph node dissection (+PLND) to RP alone.
Eligibility criteria	Inclusion criteria: • Adults ≥18 years, • Biopsy proven clinically localised high-risk PCa, • Local multi-disciplinary review identifying those high-risk cases thought suitable for RP with negative staging imaging, • Able and willing to give informed consent to participate and to participate in study procedures. Exclusion criteria: • Hormone therapy within the 3 months prior to consent, • Previous Radical treatment for PCa, • Unsuitable for surgical treatment, • People without capacity.
Interventions	Radical prostatectomy (RP) with Pelvic Lymph node dissection (+PLND) vs RP alone.
Randomisation and blinding	Eligible and consenting participants are randomised using the proven 24-hour web-based randomisation application hosted by CHaRT. Participants will be randomly allocated 1:1 to either RP + PLND or RP alone using a remote central, computer-generated randomisation schedule minimised by centre, Gleason Grade [<4+3 (incorporating 3+3, 3+4) versus ≥4+3 (incorporating 4+3,4+4,4+5,5+4,5+5)], PSA (<20 versus ≥20), and Stage (T1/2 versus t3/4).

	Randomisation will occur as close as feasible to the time of surgery, at the discretion of the recruiting site. Blinding of surgeons is not possible. We are not going to blind participants to the intervention received, as the primary outcome of cancer recurrence is objectively measured.
Planned Sample Size	1080 randomised participants (540 in each arm)
Planned Study Duration & key dates	Each participant will be in the study for 36 months after surgery. The total duration of the trial is 72 months. Funding start: 1 February 2024 Recruitment start: 1 September 2024 End of recruitment: 31 August 2026 End of participant follow-up: 31 August 2029 End of funding: 31 January 2030
Primary Objectives:	Compare RP+ PLND and RP alone in terms of cancer recurrence and cost-effectiveness at 3 years.
Secondary Objectives	Compare the treatments in terms of harms (complications and re-intervention rates), complete excision of primary prostate tumour, metastasis free survival (MFS), and health related quality of life (generic and prostate-cancer specific), time to return to normal activities (post-surgery), indirect costs due to productivity losses, and cost to participants; and model cost-effectiveness over the expected lifetime of participants, based on extrapolation of the trial data and linkage with published evidence to capture the full impact of recurrence.
Statistical Methodology and Analysis	All analyses will be based on the intention-to-treat principle. All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan which will be agreed with Trial Steering and Data Monitoring Committees. There will be one analysis of effectiveness outcomes at the end of the trial after all follow-up is complete. There will be no planned interim analysis for efficacy or futility. Safety data will be monitored throughout the trial by an independent DMC.

Methods for the economic evaluation	The study will include a within trial and model based economic evaluation. Full details of the health economics analyses will be set out in the Health Economics Analysis Plan.

1.2. Plain English Summary of Research

BACKGROUND

Around 50,000 people are diagnosed with prostate cancer annually in the UK, and over 10,000 people die from it. Prostate cancer that has not spread elsewhere in the body but is at risk of doing so is referred to as high-risk localised prostate cancer. In the UK, 4,000 patients a year get surgery for high-risk prostate cancer. The operation involves removal of the entire prostate gland and, in some cases, also the nearby lymph nodes from the pelvis. Lymph nodes are part of the body's immune system, the ones in the pelvis are often where prostate cancer spreads to first. Between 30-50% of men with high-risk disease get recurrence of cancer, which means their cancer returns. Some surgeons think that removing the lymph nodes in the pelvis improves the chance that cancer will not return.

However, complications can occur after removing lymph nodes, in particular injury to nerves and blood vessels, fluid collecting at the operation site and blood clots. Sometimes this can cause pain, infection, swelling of legs, problems passing urine and blood clots in the legs and/or lungs. Rarely, this can result in death.

We surveyed UK surgeons that operate on men with high-risk prostate cancer and found only 35% of eligible patients get lymph node removal. Surgeons told us the current evidence from research on the trade-offs in terms of harms and benefits and costs of lymph node removal was not good enough to help them make decisions. They also said a clinical trial comparing lymph node removal to no lymph node removal was urgently required so that men with high-risk prostate cancer and their surgeons could make informed decisions about their care.

DESIGN AND METHODS

We will ask 1080 men with high-risk prostate cancer to join our study from 25 hospitals across the UK. Everyone that takes part will have an equal chance of either having their lymph nodes removed or not during their prostate cancer surgery. We will compare the two options in terms of being cancer free, complication rates, quality of life and costs to the NHS. Men that join will be in the study for 3 years and get regular cancer follow-up at intervals decided by their local NHS hospital, which involves a blood test to help detect prostate cancer. They will also complete questionnaires at regular intervals about their quality of life.

PATIENT AND PUBLIC INVOLVEMENT

Mr Brendan Boylan, co-applicant, is leading our Patient and Public Involvement. He has lived experience of PCa and surgery. He is an active member of the Project Management Group, attending meetings, contributing to discussion and commenting on documents.

The PAG comprises patients who have undergone surgery with and without removal of lymph nodes. They were involved with the key decision making required from patients considering the design of this study, including the choice of outcome measures. In some cases, they had lived experience of complications and advised on the impact of those on recovery.

Prostate Cancer UK (PCUK) and Prostate Cymru provided invaluable insights into the co-production of this study and will continue to be important in its delivery. Our PPI network (including co-applicant Mr Brendan Boylan, PAG and PCUK) will provide advice about the conduct of the trial from a patient perspective and support the research team in development of patient-facing resources and activities to foster participant connectedness with the study. Mr Brendan Boylan will provide this through his regular attendance at the PMG meetings. Where additional PPI input would be advantageous, we will engage with PCUK and Prostate Cymru. We will also provide updates to PCUK and Prostate Cymru.

ANTICIPATED IMPACT AND DISSEMINATION
We anticipate that the study results have potential to impact over 20,000 men in the UK and 100,000 worldwide every year. Plain English summaries of study results will be shared with patients and families affected by prostate cancer through lay media outlets, social media and charity run patient portals.

Scientific output will be through academic conferences and publications.

1.2 Funding and Support in kind

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme	NIHR152686

1.3 Role of Study Sponsor, Funder and Clinical Trials Unit

The Sponsor of this study is Cardiff and Vale University Health Board (CVUHB). It is the role of the sponsor to confirm that there are proper arrangements to initiate, manage, monitor, and finance a study. The Sponsor will not play a role in the study design, conduct, data analysis and interpretation, manuscript writing, or the dissemination of results; this will be the responsibility of the Chief Investigator, Mr Krishna Narahari, an employee of the sponsor organisation.

The Sponsor has responsibility for overall oversight of the trial. The role of the Sponsor is to ensure the study is run safely and effectively by requiring the following:

- Proportionate peer review
- Provision of all appropriate, valid supporting documentation at the point of application
- Clear definition of roles and responsibilities of organisations and individuals, signed off prior to the study commencing.
- Appropriate level of monitoring and audit.
- A risk assessment process to identify any potential risks to the organisation or the health, safety, and well-being of researchers and research participants.
- Involvement of patients and/or the public in study design, where appropriate.
- The Chief Investigator's suitability to fulfil their role, through relevant experience and appropriate training.
- Dissemination of study findings in an appropriate manner.

The Sponsor, through their Research and Development department, has a veto on overall approval for the study.

The funder's role is to finance the study and to receive a study report.

CHaRT (based in the University of Aberdeen) is the Clinical Trials Unit for this project; the roles and responsibilities are described in a schedule to the agreement between the Sponsor and University of Aberdeen.

1.4 Protocol Contributors

Protocol development group

Chief Investigator: Mr Krishna Narahari

Co-investigators: Professor Rakesh Heer, Dr Ann Henry, Mr Ben Challacombe, Dr Brendan Boylan, Professor Graeme MacLennan, Dr Graham Scotland, Professor

Greg Shaw, Professor James Catto, Mr Jonathan Aning, Dr Lorna Aucott, Professor Philip Cornford, Mr Vishwanath Hanchanale
Trial office: Dr Seonaidh Cotton, Dr Ruth Thomas, Dr Samantha Wileman, Mr Mark Forrest

2. ABBREVIATIONS

AE	Adverse Event
BAUS	British Association of Urological Surgeons
CSS	Cause Specific Survival
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CRF	Case Report Form
CVUHB	Cardiff and Vale University Health Board
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ISF	Investigator Site File
MDT	Multi-disciplinary team
MFS	Metastasis free survival
NHS	National Health Service
NIHR	National Institute for Health and Care Research
OS	Overall survival
PCa	Prostate cancer
PI	Principal Investigator
PIS	Participant Information Sheet
PLND	Pelvic Lymph Node Dissection
PMG	Project Management Group

PSA	Prostate Specific Antigen
QALY	Quality-adjusted life year
R&D	Research &Development Office
REC	Research Ethics Committee
RP	Radical Prostatectomy
SAE	Serious Adverse Event
SMDT	Specialist multi-disciplinary team
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee

3. BACKGROUND AND RATIONALE

3.1. What is the problem being addressed?

Prostate Cancer (PCa) is the most commonly diagnosed cancer in the UK. Annually there are 50,000 new cases and over 10,000 Pca related deaths. About 17,000 people are diagnosed with high-risk localised PCa, of which about 4,000 undergo surgery as their preferred curative treatment (1) This group of patients have up to a 50% chance of needing further cancer treatments (2) as well as higher cancer-related mortality compared to lower risk patients. The increased risk is due to either incomplete removal of cancer (positive surgical margins, seen in about 20%) or because of spread of cancer beyond the prostate to the lymph nodes that is not detectable on routine pre-operative scans. Some surgeons, therefore, use pelvic lymph node dissection (PLND) to potentially increase chances of cure in patients with high-risk PCa. However, PLND increases the risk of complications (lymphoedema causing pain and limiting mobility, lymphoceles needing surgery, thrombo-embolic events such as deep vein thrombosis and pulmonary emboli, blood loss, injury to nerves and blood vessels) as well as resulting in longer operative time and higher healthcare costs. (3)

In summary, the benefits, harms, and costs of PLND compared to no PLND during prostatectomy are not well understood, leading to variation in care received across the UK. A robust trial in an NHS setting is required to reduce this uncertainty and provide men, their families and their healthcare professionals with the vital information required to make an informed decision about PLND as part of their cancer treatment.

3.2. Why is this research important in terms of improving the health of patients and care services?

Health/Care need: Currently, a potentially effective procedure is not routinely used in the UK; only a third of men are offered PLND during surgery. (4) We conducted patient and clinician surveys to inform our study design. Our patient group survey (n=57) found that patients regard this as an important question, would be happy to take part in a clinical trial to address this evidence gap and would accept PLND if it was proven to offer a better chance of cancer cure – even if it came with higher risk of complications. Our clinician survey (n=40, representing the breadth of UK centres treating high-risk PCa) found that surgeons do not find the evidence for PLND convincing and are concerned about higher complications. There was equipoise and willingness to take part in a UK study to address this evidence gap. The British

Associations of Urological Surgeons (BAUS) surveyed several study questions across the breadth of Urology and the use of PLND in PCa surgery was ranked top.

Men with high-risk PCa in the UK and worldwide, and their surgeons, lack information to make an informed decision about whether the potential benefits of PLND in terms of cancer outcomes is worth any increased risks and costs. If our trial shows PLND is beneficial, patients would have access to a treatment that improves survival, reduces the need for additional cancer treatments and their side effects, and could save health services the significant cost of additional cancer therapies. If not, then an ineffective over treatment of high-risk PCa can be stopped, reducing significant risks of harm from side effects of PLND, saving the NHS precious theatre resource and time and costs. Furthermore, our PPI groups told us this information was essential to aid decision making for men in the future.

Sustained interest and intent: Updated NICE guidance (1) will lead to a higher proportion of patients diagnosed with clinically significant PCa. This is due to widespread adoption of pre-biopsy MRI as a triage test in PCa diagnosis due its superior specificity and sensitivity in detecting clinically significant PCa.

The role of PLND in this patient group is particularly relevant given the potential for improved survival and reduction in need for additional therapies to control cancer. The findings from our trial will therefore directly influence treatment of future PCa patients.

Capacity to generate knowledge: Systematic reviews and current International Society guidelines (EAU and AUA) recognise the knowledge gap in this area and recommend a well-designed RCT to address this question.(5,6)

Scientific knowledge: This will be the first well-designed RCT assessing the role of PLND in patients with high-risk PCa. It will bridge the gap in evidence and provide a scientific basis to standardise practice in the UK and worldwide.

3.3. Current evidence about PLND in high risk PCa

There are two systematic reviews of the evidence for the role of PLND in high-risk PCa. (3,7) Neither review found RCTs comparing PLND to no PLND. These reviews included 66 observational studies in over 200,000 patients but identified several methodological shortcomings in the current evidence base:

- risk of bias and confounding was high, particular with respect to oncological

outcomes
- conflicting results
- several sources of heterogeneity in definitions of outcomes, complications, health systems, and PCa risk populations of included participants
- limited studies including important outcomes like continence and erectile function
- no studies reporting quality of life.

Both reviews concluded that the evidence base was of low quality and that an adequately powered randomised trial was required to assess the therapeutic benefit of PLND on cancer and other important outcomes.

Although there are no RCTs comparing PLND to no PLND, there are two recent RCTs comparing limited vs extended PLND in in-patients undergoing prostatectomy, irrespective of risk. These studies predominantly comprised of intermediate-risk PCa and compared different degrees of PLND, extended vs limited. Both trials found that extended PLND was no better than limited PLND. (5,6) However, as no PLND is most commonly performed in the UK (35%; BAUS 2019 data), even for those at highest risk of cancer relapse, neither RCT informs our practice about the gains of PLND over no PLND.

Of note, the RCT by Lestingi et al (5), which randomised 300 patients with intermediate or high-risk PCa to receive limited PLND or extended PLND, reported a hazard ratio of 0.91 (95% CI 0.63–1.32, p=0.6) for the primary outcome (biochemical recurrence -free survival). The uncertainty around the hazard ratio does not rule out an important clinical difference in either direction. Although not powered to do so, a subgroup analysis of 69 participants with high-risk PCa suggested a 20% increase in 3-year PSA-free survival in favour of extended PLND.

PLND results in higher complications with 1 in 5 patients receiving PLND developing a complication within 3 months of surgery. (3,8) The most common of these are lymphoceles (10% with PLND vs none for no PLND), injury to nerves of blood vessels, thrombo-embolic events (DVTs, PE) and longer operating times. The clinical community needs to better understand the gains and harms associated with PLND, specifically in high-risk disease. Due to lack of such evidence, NICE makes no recommendation about PLND in high-risk PCa surgery.

3.4 Assessment and management of risk

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and that appropriate expedited and routine reports of adverse events are generated, to a level appropriate to the risk assessment of the study.

Trial participants will be informed of possible benefits and known risks (including known complications) of both interventions in the trial by means of a Participant Information Leaflet (PIL) and discussion with the local Urologists and Research Nurses. Both surgical procedures (Radical Prostatectomy (RP) + Pelvic Lymph Node Dissection (PLND) and RP alone) are routinely used within the NHS. We do not anticipate that participants will run additional risks by participating in the ELIPSE study.

Participants will sign a consent form approved by the Research Ethics Committee. They will give consent to participating in the study, being randomised to RP + PLND or RP alone, and being followed-up within the study. Option elements of consent will include being contacted in the future about this and other research including electronic tracing using NHS data, and data linkage with computerised NHS data sources. Participants who are not able or not willing to give consent or not willing to be randomised will not be recruited.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim

To determine the clinical and cost effectiveness of RP + PLND versus RP alone in patients undergoing surgery for localised high-risk PCa.

Hypothesis

RP + PLND offers better cancer control than RP alone in patients undergoing surgery for high-risk PCa.

Objectives

1. Primary objectives: Compare RP + PLND and RP alone in terms of cancer recurrence and cost-effectiveness at 3 years.

2. Secondary objectives: Compare the treatments in terms of harms (complications and re-intervention rates), complete excision of primary prostate tumour, metastasis free survival (MFS), and health related quality of life (HRQoL; generic and prostate-

cancer specific), time to return to normal activities (post-surgery), indirect costs due to productivity losses and cost to participants; and model cost-effectiveness over the lifetime of participants, based on extrapolation of the trial data and linkage with published evidence to capture the full impact of recurrence.

3. Long term objectives: We will obtain consent from participants to allow future follow-up through efficient means (such as routine data) as part of a separately funded study, allowing correlations with survival (metastasis free survival (MFS), cause specific survival (CSS), overall survival (OS)) at 5 years and beyond.

Table 1: Summary of objectives and outcome measures/endpoints.

Objectives	**Outcome Measures/Endpoints**
Primary Objective Compare RP+PLND and RP alone in terms of cancer recurrence and cost-effectiveness at 3 years.	1. Cancer Recurrence (defined as PSA recurrence/persistence and/or disease progression and/or need for further PCa treatment and/or PCa specific death. 2. Incremental cost per QALY gained at 3 years
Secondary Objectives Compare 1. harms (complications and re-intervention rates), 2. complete excision of primary prostate tumour 3. metastasis free survival 4. health related quality of life (generic and prostate-cancer specific), 5. time to return to normal activities (post surgery), 6. indirect costs due to productivity losses 7. cost to participants	1. Intra-operative complications, Comprehensive Complications Index, further treatment 2. Positive surgical margins 3. Imaging from routine follow-up 4. EPIC-26, EQ-5D-5L 5. Bespoke questions (participant questionnaires) 6. Bespoke questions (participant questionnaires) 7. Adapted version of participant time and travel questionnaire, bespoke

8. model cost effectiveness over the lifetime of participants	questions about directly incurred costs 8. Incremental cost per QALY modelled over expected lifetime of patients

Primary outcome measures:

b. Primary clinical outcome will be cancer recurrence measured by

(i) PSA recurrence/persistence with two consecutive measures ≥0.2ng/ml (American Urological Association-AUA, European urology Association-EAU guidance, Pioneer consortium (1), and/or

(ii) disease progression (e.g. metastatic disease) and/or

(iii) need for further PCa treatment and/or

(iv) PCa specific death.

We will assess blood PSA levels in line with routine local NHS protocols at baseline, and after surgery for the duration of follow-up (in line with NICE guidance and local standard of care) (9). In this cohort of patients with high risk PcPCa, unlike those with low risk disease, PSA recurrence is an excellent, early, objective and easily measurable marker of the need for additional cancer therapy, as well as MFS and potentially OS .(10) Imaging is routinely requested as part of standard NHS care upon PSA recurrence. This will allow us to assess disease progression for metastatic disease detectable on imaging. We acknowledge that in some centres, men with a rising PSA below the conventional threshold 0.2ng/ml may still get cancer treatment for early recurrence (such as those with positive surgical margins and exponential rises in PSA using supersensitive PSA (measuring to the nearest 0.001ng/ml). Our cancer recurrence definition will pick this up.

The vast majority (>95%) of recurrences after surgery for Pca will be biochemical PSA recurrence. Our sample size is based on published PSA recurrence rates, and includes an analysis of over 20,000 patients who underwent surgery for high-risk Pca in 5 US academic institutions.(2) As a small fraction (<5%) may reach the threshold for a diagnosis for recurrence not using PSA, we present a conservative measure of recurrence and sample size.

The primary economic outcome will be incremental cost per quality adjusted life year (QALY) gained (RP + PLND versus RP only) at 3 years post-surgery from the perspective of the NHS. Service resource use will be collected from trial case

report forms and patient questionnaires. Participant level QALYs will be calculated based on responses to the EQ-5D-5L at baseline and 3, 12, 24 and 36 months post- surgery.

Secondary outcomes measures:

(i) Harms

Surgical complications will be captured by Comprehensive Complication Index (CCI) over the peri-operative period (3 months). Most complications for RP +/- PLND occur acutely in the post-operative window. Based on work from our group (as part of a global network), expected rates of significant complications (Clavien-Dindo grade 3 or more) are 5-10 % for RP + PLND and 2-3% for RP only (8,13). Most studies fail to provide information about the cumulative severity of complications, or inform only on the most severe event, ignoring events of lesser severity. The CCI is based on the Clavien-Dindo classification (reporting on the most severe event) and is calculated as the sum of all surgical complications weighted by their severity.(11) This will allow us to compare relative harms more comprehensively–- including all incurred complications and re-intervention rates within 3 months of surgery. This tool is validated in prostate surgery and estimated CCI scores for RP are 5.8 ± 11.7.(11)

(ii) Positive surgical margins

Over 3 years we will capture positive margin rates and their consequence. From current series, positive surgical margin rates of up to 30% are reported. This comes with a burden of increased anxiety for patient, thinking the cancer could come back. In our patient focus groups, being cured of cancer was the main concern. These oncological outcomes will be correlated with HRQoL with a focus on capturing anxiety and cost relating to surveillance/investigation and possibly further treatments.

(iii) Metastasis free survival (MFS)

MFS is defined as time from surgery to the first detection of distant metastasis on imaging or death from any cause, whichever occurred first. MFS will be captured by absence of demonstrable metastasis on conventional imaging (CT, PET CT, MRI, plain x-ray and/or bone scans) performed within 3 years from surgery. Imaging is routinely requested, as part of standard NHS care, upon PSA recurrence and prior to treatment. We will look at MFS at 3 years from surgery based on review of case report file. We will not mandate a scan (as a

study intervention) at 3 years for the sole purpose of measuring MFS as this is not in keeping with a pragmatic trial design that reflects routine NHS practice, subjects participants to unnecessary radiation exposure, does not impact clinical decision making and will add substantially to trial costs.

(iv) HRQoL
Patient reported outcomes captured by validated EPIC 26 (11) and EQ -5D-5L questionnaires collected at baseline, then 3,12, 24, and 36-months post-surgery.

(v) Time to return to normal activities (post-surgery)
This will be measured using bespoke questions related to the time taken to return to usual work and/or leisure activities following surgery, delivered at 3 months post-surgery.

(vi) Indirect costs
Time lost from productive actives due to ill health or treatment will be monitored throughout the trial follow-up, using tailored questions as part of the patient questionnaire at 3 months and the Work Productivity and Impairment Questionnaire at 12, 24 and 36 months. Time lost from paid and unpaid work will be valued using age specific average gross wage rates or appropriate shadow prices.

(vii) Costs to participants
These will be assessed using an adapted version of our participant time and travel questionnaire (administered at 12 months post-surgery), and questions asking participants about directly incurred costs related to their prostate cancer, its treatment, and/or any associated complications (in patient questionnaires at 12, 24 and 36 months).

(viii) Incremental cost per QALY gained with RP+ PLND versus RP alone modelled over the expected lifetime of patients using trial data linked with published evidence.
An economic decision analytic model will be developed to extrapolate cost-effectiveness over the expected life-time of patients. QALYs are chosen as the standard outcome metric of economic evaluation for informing NHS decision making, capturing the combined effects of interventions on health-related quality of life (benefits and harms) and survival.

(ix) Patient acceptability

Previous trials of limited vs extended PLND have demonstrated recruitment feasibility. Our clinician survey revealed equipoise in offering PLND vs No PLND for high-risk PCa patients undergoing surgery. The survey (n=38) included specialist prostate surgeons and generalists who counsel patients prior to SMDTs and refer on to dedicated surgeons. A series of focus group studies were centred on patients (n=57) who had undergone surgery for PCa. From these exercises, we defined specific trial protocols for which there was equipoise from both clinicians and patients in choosing between PLND and No PLND. Specifically, a willingness of both patients (88%) and clinicians (98%) to randomise between PLND and no PLND was confirmed for our proposed inclusion criteria. Nevertheless, we will monitor patient acceptability via screening logs and checking for pre-operative post-randomisation cross over.

5. STUDY DESIGN

A pragmatic multi-centre patient-randomised controlled, parallel group trial, with internal pilot and embedded economic evaluation comparing RP + PLND versus RP alone.

PLND involves excision of lymph nodes from standard pre-defined anatomical locations in the pelvis such as external iliac, obturator, internal iliac territories and so on. The trial template for PLND is described in detail in section 10.

Usual treatment planning, by MDT, will identify those who are candidates for PPCa surgery and potential randomisation between RP + PLND and RP alone. After surgery (RP + PLND or RP alone) men will be followed up by routine NHS management protocols in each trial centre with data captured from medical records by local study teams, and by study questionnaires administered by the central trial office.

The setting will be 25 UK NHS secondary care, medium and high-volume sites (all doing over 50 cases a year with experienced surgeons beyond the initial learning curve of 50 cases).

6. STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

Chief Investigator

Mr Krishna Narahari

Co-Chief Investigator
Professor Rakesh Heer

Grant Holders

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Professor Graham Scotland, Health Economist, University of Aberdeen g.scotland@abdn.ac.uk	Dr Mintu Nath, Senior Lecturer , University of Aberdeen, mintu.nath@abdn.ac.uk

Trial Office Team

1 Chief Investigator
2 CHaRT Director
3 Trial Manager
4 Data Co-ordinator
5 Senior Trial Manager
6 Senior IT Manager
7 Trial statistician
8 Health economist

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT will take responsibility for the day-to-day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up rates. The data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, database support and economic and statistical analyses. CHaRT SOPs, along with relevant Sponsor SOPs, will be followed.

The Trial Office Team will meet formally at least monthly during the course of the trial to ensure smooth running and troubleshooting.

Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. The PMG will meet/teleconference approximately every 3 months.

The PMG has the expertise to cover the clinical, surgical and methodological aspects of the research.

Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

The membership of this committee comprises independent members along with the Chief Investigator (CI) or a nominated delegate. The other ELIPSE grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details of members of the DMC. This Charter is filed in the TMF.

This committee is comprised of independent members and the trial statistician contributes as appropriate. The CI and / or a delegate may contribute to the open session of the meetings as appropriate.

Role of the Funder

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Trial Steering Committees and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer is used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Patient and Public Involvement (PPI)

Mr Brendan Boylan, co-applicant, is leading our Patient and Public Involvement. He has lived experience of PCa and surgery. He is an active member of the Project Management Group, attending meetings, contributing to discussion and commenting on documents.

The PAG comprises patients who have undergone surgery with and without removal of lymph nodes. They were involved with the key decision making required from patients considering the design of this study. In some cases, they had lived experience of complications and advised on the impact of those on recovery.

During the proposal and protocol development stage, the PAG gave critical insights into priorities in decision making, and we learnt about the strong drivers of cure from cancer, as well as the limiting complications and ongoing morbidity that impact on Quality of Life. This helped design the trial to define scenarios where there would be willingness to randomise (such as acceptable lymph node removal templates and tolerating short-term complications). We also learnt that patients are very much guided by their consultant's recommendations and therefore, clinician equipoise was central to patients' considerations for a potential trial. Hypothetically, there was agreement amongst the 47 patients (>80%) in the focus groups for willingness to randomise to our study design. The focus groups also assessed and advised on outcome measure questionnaires.

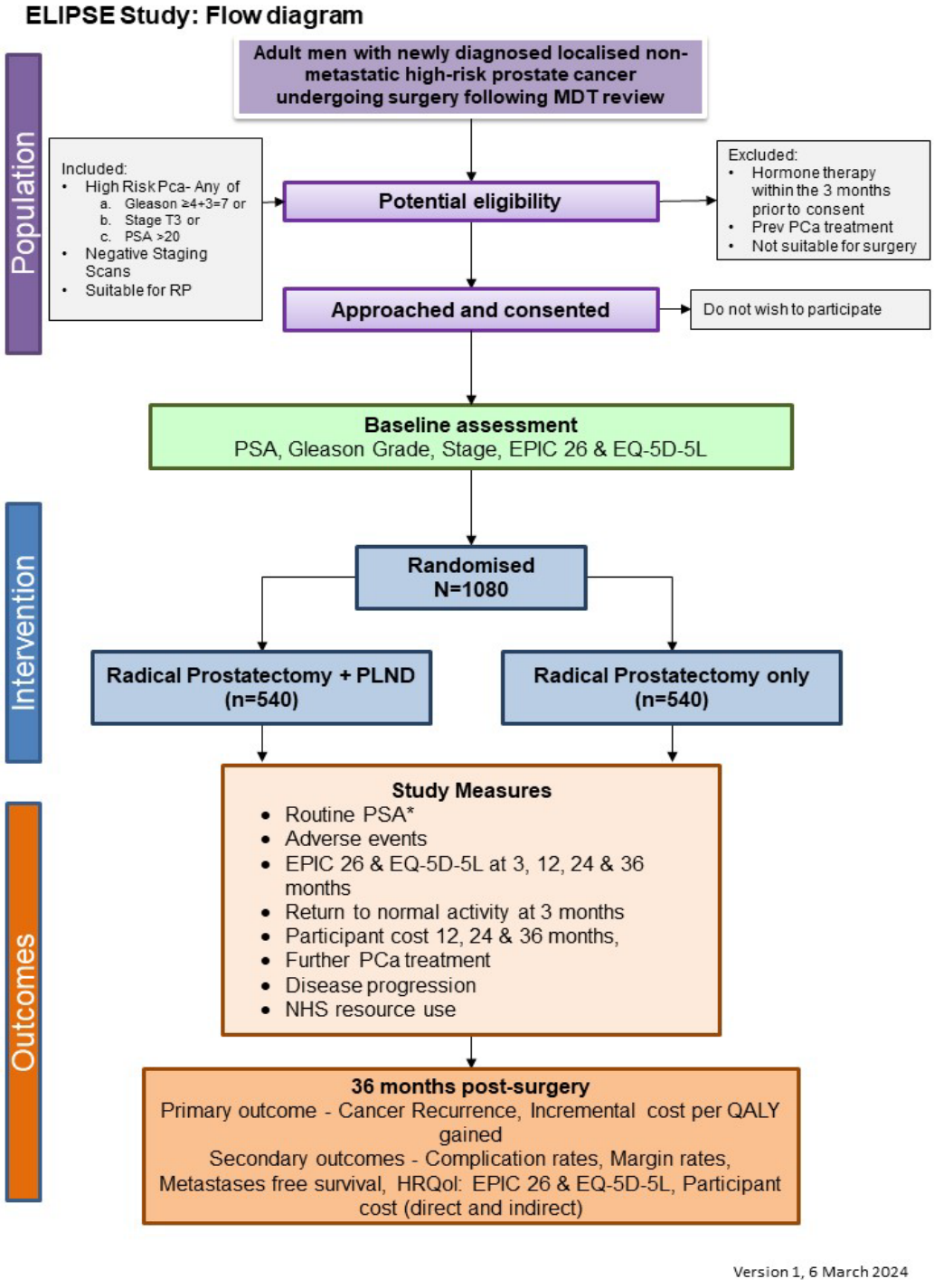
We are also supported by Prostate Cancer UK (PCUK), Prostate Cymru and a national network of patients who also contributed to our focus group discussions. The charity shared infographic and decision-making tools that can be used to support and inform potential participants about the treatment options, the trial itself, and the uncertainties that inform it. This aligned with an ongoing initiative from BAUS Oncology, which we will develop further in this trial, to develop patient decision aids.

On-going contribution: PCUK and Prostate Cymru have provided invaluable insights into the co-production of this application and will continue to be important in its delivery. Our PPI network (including co-applicant Mr Brendan Boylan, PAG and PCUK) will provide advice about the conduct of the trial from a patient perspective and support the research team in development of patient-facing resources and activities to foster participant connectedness with the study. Mr Brendan Boylan will provide this through his regular attendance at the PMG meetings. Where additional PPI input would be advantageous, we will engage with PCUK and Prostate Cymru. We will also provide updates to PCUK and Prostate Cymru.

Results of the study will be distributed to patients and families affected with PCa through bespoke plain English summaries generated in conjunction with our PPI network.

7. STUDY FLOW CHART

Figure 1. Study flow chart



* in line with routine local NHS protocols at baseline, and after surgery for the duration of follow-up (in line with NICE guidance and local standard of care)

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

All adults with clinically localised high-risk PCa with negative staging imaging will be considered through screening in local/regional specialist MDTs (SMDT). PCa treatment in the UK is now centralised to high volume specialist centres via SMDT. Therefore, we will ensure all patients have equitable access to all appropriate options for treatment through referral.

8.2. Inclusion Criteria

- Adults ≥18 years
- Biopsy proven clinically localised high-risk PCa
- Local multi-disciplinary review identifying those high-risk cases thought suitable for RP; with negative staging imaging (as per local standard of care).
- Able and willing to give informed consent to participate and to participate in study procedures.

High-risk PCa is defined as any of

(i) Pre-operative biopsy Gleason grade group ≥ 3 (Gleason score ≥4+3=7), and/or

(ii) PSA >20, and/or

(iii) Radiological, pathological or clinical Stage T3.

These parameters are available as part of routinely collected NHS minimum datasets in PCa diagnostics.

These inclusion criteria are aligned with UK and International (NICE, NCCN-National Comprehensive Cancer Network) definitions of PCa at highest risk of recurrence and progression. These criteria also define the patient cohorts that we used for our power calculations (an analysis of over 20,000 patients who underwent surgery for PCa in five US academic institutions).(2)

8.3. Exclusion Criteria

- Hormone therapy within the three months prior to consent
- Previous radical treatment for PCa (radical treatment includes radical prostatectomy and/or radiotherapy and/or focal therapy [eg *cryotherapy or HIFU]*)

- Unsuitable for surgical treatment
- People without capacity

9. STUDY PROCEDURES

9.1. Screening, eligibility assessment and recruitment

Patients will be identified following review by PCa SMDT at UK hospitals. As part of their routine care, potentially eligible patients may be referred from NHS hospitals to a specialist centre. Such patients may be discussed at SMDT meetings at the specialist centre where their treatment may take place.

Local pathway and procedures at participating hospitals are different and the timing and mode of approach to eligible patients and the consent process may vary to accommodate both the local circumstances and the needs and preferences of the potential participant.

We will provide training at site initiation describing the current evidence base and explaining the need for the trial. We aim to ensure that screened patients appreciate there are choices and uncertainty about treatment and respective treatment outcomes. Irrespective of becoming a participant or not, the study participant information leaflet (PIL) will help provide patients with information about available treatment options. Patients may be given additional (non-study) information or decision support tools that are used in routine care by the treating urologist. Also, the PIL and study protocol will be available at the study website and therefore accessible to potential participants.

Eligible patients will be given or sent a PIL describing the study and will have the opportunity to read this before deciding whether they wish to take part. A member of the clinical team will discuss the surgical options and establish eligibility, and the patient will have opportunity to discuss the study with the clinical team. These consultations may occur face-to-face or virtually using locally accepted NHS platforms. Eligible patients can discuss the study with other members of the local clinical team, research nurses, family and friends and their GP before deciding whether or not to take part in the study. The patient may decide to participate during an initial (or subsequent) consultation with the clinical team, or alternatively at home.

If the potential participant wishes to consider whether or not to participate at home, they will be sent (if the consultation is virtual) or given (if consultation is face-to-face)

the consent form and baseline questionnaire for completion. If the potential participant agrees to be contacted at home, the site Research Nurse will attempt to contact them by telephone to discuss any queries, to ask if they would like to take part in the study, and if so, to take them through the consent process and ask them to also complete the baseline questionnaire and return both of these to the local team at their treating hospital.

Details of the consent discussion, including discussion date, will be recorded in the medical notes and on the trial inclusion form.

Eligibility will be confirmed by the PI, or by a medically qualified delegate at each recruitment site.

A paper screening log will be kept at site, with limited (non-identifiable) information uploaded onto the study website.

All participants who are randomised into the study will be assigned a unique study number.

9.2. Informed Consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. As part of the informed consent process, potential participants will be made aware of all aspects of the trial, including the potential risks and their responsibilities. There is no minimum time that potential participants should be given to decide whether to participate in the trial. Potential participants will be given enough time, as long as they want, to accept or decline involvement, and will be given the opportunity to ask questions and to have these answered before giving consent.

It will be explained that entry into the trial is entirely voluntary, and that treatment and care will not be affected by their decision, and they can withdraw at any time. We will also explain that there are different types of withdrawal, for example they can opt not to receive any further questionnaires but remain in the study for the collection of outcome data from their medical records. In the event of their complete withdrawal from the study (ie no further data collection), it will be explained that their data collected to date cannot be erased and will be used in the final analyses.

Potential participants who cannot give informed consent (e.g. due to their mental state) will not be eligible for participation.

Potential participants who are not able to read or write (but who have capacity and who can speak English sufficiently to understand the information being provided orally) can agree to take part in the trial. In such cases, the trial team will provide them with written literature about the trial. The trial team will read the contents of the participant information leaflet to the potential participant, and discuss this information with them. There should also be a discussion about the support networks that they have to facilitate their participation in the trial (for example help to complete questionnaires). If the potential participant is fully informed and wishes to take part in the trial, a member of the trial team will read out each of the statements on the consent form and the potential participant will be asked to initial or make their mark against each of the statements on the consent form and then to sign or make their mark at the bottom of the consent form. Their agreement to take part in the trial should be witnessed by someone independent from the research team. If a potential participant does not have support to help them complete questionnaires, a member of the trial team can help them by reading the questions to them and recording their responses.

Procedures to seek and gain informed consent from eligible potential participants are agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the NHS National Research Ethics Service.

Where informed consent is received in person, this should be received by an appropriately trained individual who is listed on the delegation log. Consent forms that are returned by post or via e-Consent are checked, signed and dated with the date of receipt by someone who is listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both patient and person receiving consent signatures are present will informed consent be considered to have been obtained. As noted in section 9.1, if the participant completes a hard copy of the consent form at home, they will be asked to return their consent form and baseline questionnaire by post. In such cases, the questionnaire will have been completed before the countersignature on the consent form. However, the data within the baseline questionnaire will only be entered onto the study website after

countersignature is obtained on the consent form. If the participant provides consent via eConsent (section 9.2.1), and has opted to complete the baseline questionnaire directly into the study database (electronic patient reported outcomes ePRO), they will have access to complete baseline questionnaire immediately after completing the eConsent, and so may complete this before the eConsent form is countersigned.

9.2.1 e-Consent

For participants who opt to consent using an e-consent form, they will do this via the secure web-based trial management system provided by CHaRT. If this option is preferred, participants will be asked to provide their email address which will be entered into the secure web-based trial management system. Participants will be sent a verification email with a link to verify their email. Once the email address is verified, participants will be automatically emailed the PIL and a link to the participant e-consent form for their unique study number. The e-consent form will be identical to the approved paper version of consent form, with the approved PIL version number and date automatically populated. The participant will be asked to complete the consent form and provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse. Completed e-consent forms will be checked, and electronically counter-signed by someone listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both participant and person receiving consent signatures are present will informed consent be considered to have been obtained. Participants will be sent a copy of the e-consent form for their own records and a copy will be retained in the ISF and TMF. Should participants who are sent the study information choose not to take part in the study their email address will be deleted (as an automated process) from the trial management system after 3 months. The trial management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made. Database interactions logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

9.2.2 Verbal confirmation of written consent

In some centres, the time between MDT review confirming suitability for RP (one of the inclusion criteria) and listing for surgery is short (around 2 weeks). In some centres, knowledge of the randomisation allocation is required to plan the surgical lists. In these cases, delays in the postal system may preclude men who want to

take part in ELIPSE but complete a hard copy consent form at home, from taking part, because the completed consent form is not received in time to allow the randomisation to take place and plan the surgical list.

In such cases, verbal confirmation of written consent can be used if men wish to use this approach. They will have previously received a copy of the PIL and consent form. A designated member of the ELIPSE site team will contact the potential participant and conduct the consent discussion with them over the phone and ask the participant to initial, sign and date the consent form during the discussion – we are describing this as "verbal confirmation of written consent". The ELIPSE team member will document the discussion in the patient medical notes. The participant will be asked to either return the consent form or to bring the consent form with them when they attend for surgery. During the same phone call the participant will be asked to complete the baseline questionnaire with the team member. The baseline questionnaire must be completed before the participant is randomised and informed about the treatment he will have.

When the consent form is returned, the member of the local site research team with delegated responsibility for consent and who conducted the consent discussion over the phone will countersign and date the consent form. If that person is not available to countersign, then another member of the ELIPSE site team should countersign the consent form. The date of countersignature should not be earlier than the date of the participant signature but may be later. The consent form must be before surgery. If the patient does not send it back or bring it with them when they attend for surgery, there should be a further consent discussion, and a new copy of the consent form should be completed prior to surgery.

Regardless of the method of consent, participants will be given or sent a copy of the completed consent form for their own records and a copy will be retained in the investigator site file (ISF). A copy of the consent form will be placed in their medical records and a copy should be forwarded to the trial office for retention in the Trial Master File (TMF) in the case of a hard copy consent.

9.3. Randomisation, blinding and unblinding

Eligible and consenting participants are randomised using the proven 24-hour web-based randomisation application hosted by CHaRT.

Participants will be randomly allocated 1:1 to either RP + PLND or RP alone using a remote central, computer-generated randomisation schedule minimised by centre, Gleason Grade (<4+3 [*ie incorporating 3+3, 3+4*] versus ≥4+3 [*ie incorporating 4+3, 4+4, 4+5, 5+4, 5+5*]), PSA (<20 versus ≥20), and Stage (T1/2 versus T3/4 .

Randomisation will occur as close as feasible to the time of surgery, at the discretion of the recruiting site.

Participants who are randomised but who do not have RP will be recorded as a post-randomisation exclusion. Randomising as close to surgery as possible should minimise these; however the numbers of post-randomisation exclusions and the reasons for exclusion will be reviewed regularly at trial meetings and we will develop and implement strategies to mitigate this.

Blinding of surgeons is not possible. We are not going to blind participants to the intervention received, as the primary outcome of cancer recurrence is objectively measured (biomarker and imaging) and we do not think there is a threat to internal validity that would require blinding to counter this.

As there is no blinding within the study, emergency unblinding procedures are not required.

9.4. Baseline Assessment

At baseline, the local research team will complete a baseline case report form (CRF), which will capture information to characterise the study population in relation to demographic and clinical factors. We will collect age, ethnicity, Gleason Grade, and stage. As part of standard of care, PSA is routinely measured and this will be captured on the baseline CRF. If multiple PSA have been taken prior to recruitment, the PSA closest to and reviewed at the SMDT where eligibility was confirmed will be recorded in the baseline CRF.

Participants will be asked to complete a baseline questionnaire including EPIC-26 and the EQ-5D-5L. The baseline questionnaire should be completed BEFORE the patient is informed of the randomisation allocation.

Table 1 summarises which outcomes are assessed at each of the timepoints. Further details about collection of outcome data are provided in section 9.6.

Table 1

	Baseline	Surgery	Post- surgery (month)					
			3	6	12	18	24	36
Baseline characteristics	CRF							
PSA*	SoC		SoC	SoC	SoC	SoC	SoC	SoC
Quality of life: EPIC 26, EQ-5D-5L	PQ		PQ		PQ		PQ	PQ
Time to return to normal activities			PQ					
Work productivity and Impairment (Indirect costs)					PQ		PQ	PQ
Participant cost and resource use questionnaire					PQ		PQ	PQ
Participant time and travel					PQ			
Harms (complications, re-intervention rates)			MR, PQ		PQ		PQ	PQ, MR
Recurrence								SoC/MR
Further treatment			PQ		PQ		PQ	PQ, SoC/MR
Surgical details & resource use		MR						MR
Positive surgical margins		MR						
Metastasis free survival (MFS)								MR

CRF case report form completed during baseline assessment; SoC, Standard of Care; PQ, Participant questionnaire; MR, medical records.
For data collected as SoC or recorded in medical records, transcription into study CRF is required.
* Standard of Care PSA tests in line with NICE guidance (9)

9.5. Administration arrangements post recruitment

Following trial entry, the trial office will:

- Notify the GP in writing that a participant has joined the trial.

The site research team should:

- File a copy of the consent form in the hospital medical notes along with information about the trial.
- Document the eligibility and informed consent process in the notes.
- File a copy of the GP letter into the hospital notes (if required by the site).
- Enter trial data regarding the participant into the bespoke trial website.
- Ensure participant is added to the appropriate surgical list.
- Maintain trial documentation at site.
- Return a copy of the signed consent form to the Trial Office in Aberdeen.

9.6. Follow up

Surgery

The local research team will collect information about the surgical procedure either from medical records or in real time. The surgical CRF will be completed with information about specific surgical details, PLND template adherence, time taken for the operation, techniques of surgery and any specific intra-operative complications.

Discharge and Pathology

Around the time of discharge, time in hospital will be recorded, along with any time spent in ICU or HDU. Pathology and positive surgical margins will also be recorded when this information is available.

PSA

In patients who are having radical treatment for PCa NICE guidance (9) recommends one blood PSA level measurement to be taken no earlier than six weeks after surgery, at least every six months for the first two years and then at least once a year after that.

The results of **all post-surgery PSA tests up to three years** and the date of the test will be recorded by the site research team from laboratory records. The site research team will be asked to check for PSA test (and record these on the study CRF) at least annually.

The trial office will monitor the accumulating PSA data and ask sites to prioritise measurements in patients who may not be being followed up as per NICE guidance. (9)

Missing PSA measurements will be identifiable within the trial dataset and not recorded as protocol deviations.

Harms

Three months after surgery, the local research team will review the participant's medical notes and information recorded on their 3 month questionnaire and complete the Comprehensive Complication Index (CCI) to record any complications following surgery.

Further treatment

At 36 months post-surgery, the local research team will review the participant's medical notes and information reported on their annual questionnaires (prostate cancer treatments and use of healthcare services) to identify any further treatment and secondary health care resource utilisation related to their prostate cancer that has occurred since randomisation. This will be supplemented with data collected from men via a study follow-up telephone call (made by the local study team) or at a routine follow-up appointment if one is scheduled.

Recurrence

At 36 months post-surgery, the local research team will review the participant's medical notes to identify any recurrence from routine tests up to and including 36 months.

Metastasis free survival (MFS)

At 36 months post-surgery, the local research team will review the participant's medical notes to identify absence of demonstrable metastasis up to and including 36 months.

Patient-reported outcomes

Participants will be asked to complete a questionnaire including the EPIC-26, and the EQ-5D-5L at 3, 12, 24 and 36 months post-surgery.

At 3 months participants will be asked about their "time to return to normal activities". At 12, 24 and 36 months, participants will be asked about work productivity and impairment, directly incurred costs and health care resource use.

At 12 months post-surgery, they will also be asked about their time and travel costs associated with accessing care.

At baseline, participants will be asked for their contact preferences for questionnaires. Those selecting email as their preference will have a link to the questionnaire emailed to them. Those selecting postal as their preference will have the questionnaire posted to them. Those selecting text messaging as their preference will have a link to the questionnaire texted to them. First reminders will be emailed, posted or texted to participants (according to their stated preference). A second reminder (by telephone) will be attempted but if there is no response by telephone, a final postal reminder will be sent.

Questionnaires will be administered to all participants who were randomised in the study, regardless of whether they had the surgery they were randomised to receive (RP + PLND or RP alone), unless they have opted out of questionnaire follow-up or have been recorded as a post-randomisation exclusion.

If questionnaires are returned as non-deliverable, attempts will be made by site staff or staff at the Trial Office to trace the participant.

As noted above (section 9.2) any participants are not able to read or write (but have capacity and can speak English sufficiently) can be supported to complete their questionnaires - a member of the trial team can help them by reading the questions to them over the telephone (or at a routine face-to-face clinic visit if one is scheduled) and recording their responses.

9.7. Discontinuation/Withdrawal of Participants from Study

Participants remain in the trial unless they choose to withdraw consent. Participants are free to withdraw from the trial at any timepoint. All changes in status, with the exception of complete withdrawal of consent and post-randomisation exclusions, means the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason.

Changes of status pertaining to participant death should be reported within 24 hours after the site finds out about the patient death. All outstanding CRFs should be completed before the medical records become inaccessible. This will always include the 36 month CRF, the PSA CRF up to that timepoint and the 3 month CRF if it has not been completed yet.

Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. Identifiable data collected with consent will be retained and used in the study but no further data will be collected or research procedures carried out.

As noted in section 9.3, participants who do not undergo RP will be considered as post-randomisation exclusions and will not be followed up further within the study. However, participants who undergo RP but do not receive their allocated treatment (RP + PLND or RP alone) are not considered withdrawals and will be followed-up for all trial outcomes unless they request otherwise. This is a pragmatic study and we will monitor accruing data on treatment received (ie RP + PLND or RP alone).

Participants who request that no further questionnaires are issued will be followed up for other trial outcomes unless they withdraw from other outcome data collection.

Participants for whom any outcome data are available are included in an intention to treat analysis.

9.8. Study Amendments

The CI will seek advice from the Sponsor (CVUHB R&D office) prior to submission of amendments to the relevant bodies. Sponsor will advise if an amendment is substantial / non-substantial and which review bodies need to receive it. The CI will seek approval for any substantial amendments to the protocol or other study documents from HRA/HCRW and REC (if applicable). Non-substantial amendments should be notified to the HRA/HCRW and REC for information. Depending on the categorisation (A, B, C), site NHS R&D Office(s) may need to be given opportunity to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to appropriate approvals being granted.

9.9. Definition of End of Study

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

9.10. Co-enrolment

There may be satellite studies or sub-studies developed as part of the main ELIPSE trial and participants may be co-enrolled into these (see section 19).

Sites may also be involved in other studies that this patient group may be eligible for. ELIPSE participants will be permitted to take part in other non-interventional studies (e.g. questionnaire studies, studies collecting blood/tissue samples or studies investigating aspects of robotic surgery).

Co-enrolment into other interventional studies will be assessed on a case-by-case basis and discussed by the CIs of both studies to ensure no impact on outcomes for either study. If agreed, co-enrolment in these situations will be permitted.

It would not be ethical to deny access of ELIPSE participants to any clinical trials of adjuvant therapy that open to recruitment during the lifetime of ELIPSE (or to adjuvant therapy if it becomes part of standard of care). Equally the ELIPSE trial may suffer from recruitment challenges if in competition with trials of adjuvant therapy. It is likely that only a proportion of participants in the ELIPSE trial would also be eligible for adjuvant therapy, and those who are eligible will be permitted to participate in clinical trials of adjuvant trials subject to appropriate co-enrolment agreements.

Patients will be eligible for inclusion in ELIPSE if they are in the long-term follow-up phase of any other interventional trial.

10. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

Health technologies being assessed

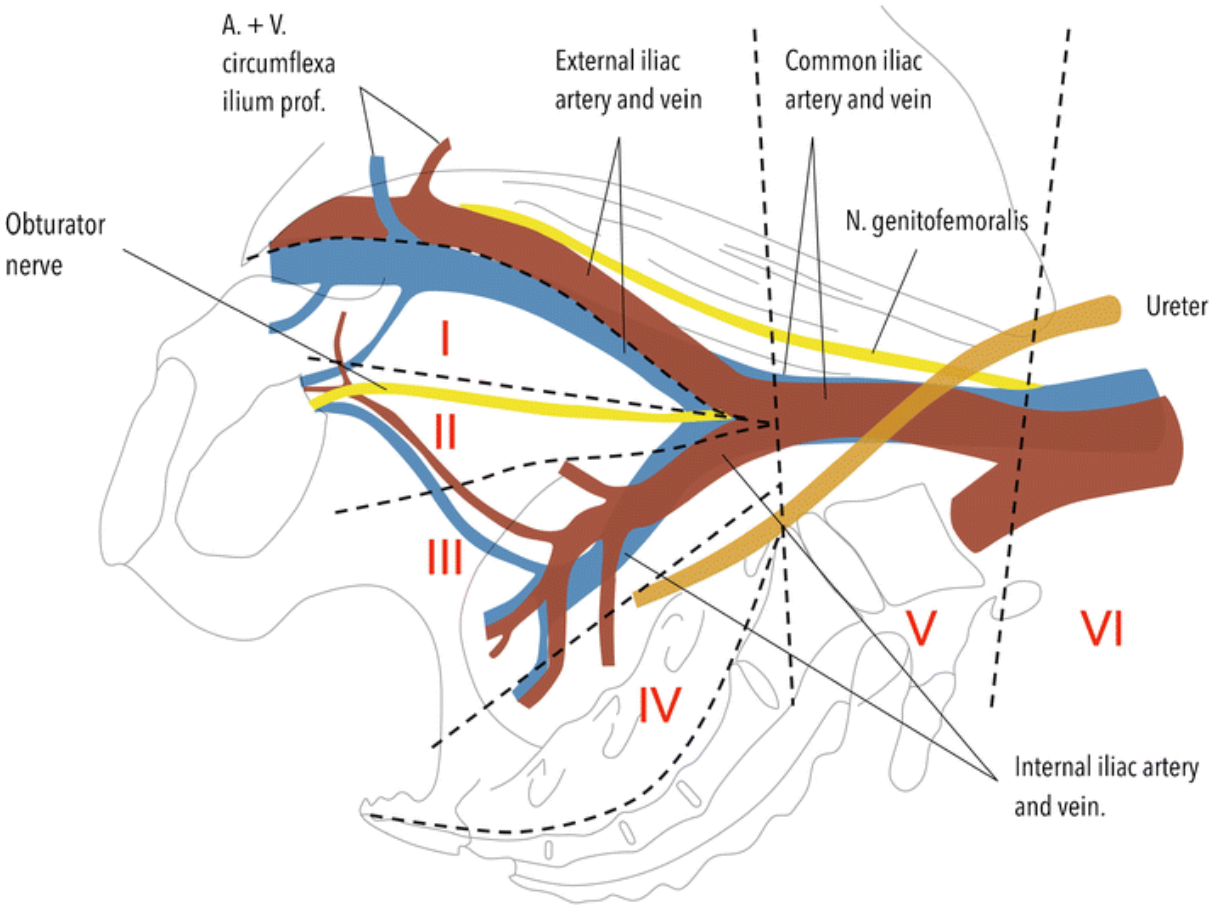
Intervention: Radical prostatectomy with PLND (RP + PLND)

Control: Radical prostatectomy alone (RP alone)

Radical robot assisted laparoscopic prostatectomy is the UK standard care for people undergoing radical prostatectomy surgery for prostate cancer (12) with over 95% of prostate cancer operations carried in high volume centres using this approach. We acknowledge that a very small proportion of people may have open or laparoscopic surgery and we will include these participants in the study, in keeping with the pragmatic nature of the study.

We reviewed an established standard template for PLND with UK wide clinicians (n=38) and confirmed they are willing to adhere to it. This PLND template (see figure 2) involves excision of lymph glands from defined anatomical locations in the pelvis – the external iliac and obturator fossae (zone I and II in figure 2). This template also captures the majority of landing sites for PCa lymph node spread based on mapping studies (13) and is in keeping with the templates used in trials comparing limited to extended PLND. (5,6)

Figure 2: PLND template



(From Colicchia et al, Curr Urol Rep (2017) 18:51) reproduced with permission of RJ Karnes

PLND Quality Assurance- We will adopt a stringent quality assurance process to ensure adherence to the trial PLND template. This will include a surgical video-based demonstration of the PLND template during trial site initiation visit (SIVs) and independent assessment of a surgical image of at least the first five PLNDs in each centre by the trial monitoring group. The surgical images will not carry any identifiable information. As part of routine assessment in line with standardised uropathology guidelines, lymph node packets from specific PLND excision territories will be sent in separate specimen pots to pathology, providing ongoing quality assurance of the extent of PLND.

11. SAFETY REPORTING

11.1. Safety-related outcomes collected within ELIPSE

Harms captured by ClassIntra (in the surgery CRF) and the Comprehensive Complication Index (CCI) over the peri- and post-operative periods (up to three

months post-surgery) are an outcome of the ELIPSE study and will be collected as part of the CRF. Participants will be asked to report any later complications of surgery as part of the follow-up questionnaires. We will also collect these from medical records at 36 months post-surgery.

Both surgical procedures (RP + PLND and RP alone) are routinely used within the NHS and safety is well characterised. The ELIPSE study is highly unlikely to reveal any new safety information relating to these procedures. The recording of selected adverse events (AEs) will not impact the safety of participants in the trial, or the integrity of the trial itself.

As such, the following will **not** be classed or reported as AEs or SAEs (but where appropriate, will be recorded as part of the case report form):

- *Intraoperative complications (complication recorded as part of the Surgery CRF)*
- *Surgical complications (any complication recorded as part of the CCI, with or without hospitalisation or prolongation of existing hospitalisation)*
- *Late complications following surgery (for example anastomotic or urethral strictures, foreign body formation from migration of clips, delayed lymphocele or lymphoedema formation, complications arising from treatment for continence or erectile dysfunction and anti-cancer treatments) will be captured in the participant questionnaires and from the review of medical records at 36 months).*
- *Prolonged hospitalisation without an associated adverse event*
- *Additional medication required above that normally expected*
- *Emergency presentations and admissions for prostate related conditions*
- *Routine admissions for pre-planned events*

In addition, any AE that would already be captured as an outcome for the study would not be reported separately as an AE for ELIPSE:

- Positive surgical margins (retreatment/ surgical revision)
- Recurrence or metastasis
- Death (any cause) (a change of status CRF should be completed within 24 hours of the site becoming aware of the death)
- Raised PSA levels
- Outcomes captured as part of EPIC (including problems with urinary function, bowel habits, sexual function other symptoms)

All AEs (except those listed above) that meet the criteria for a Serious Adverse Event (SAE) will be documented from the date protocol defined treatment commenced (entering the anaesthesia suite) until the participant exits from the study (36 months post-surgery or withdraws from collection of data). Any SAEs that are not included in the list above which are assessed to be at least possibly related to the intervention must still be reported in an expedited manner irrespective of how long after intervention the event occurred.

11.2. Adverse Events and Serious Adverse Event definitions

Adverse Event (AE): Any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Serious Adverse Event (SAE): The standard definition of an SAE is any adverse event that:

- Results in death[(a)]
- Is life-threatening[(b)]
- Required hospitalisation or prolongation of existing hospitalisation[(c)]**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition[(d)]

[(a)] In ELIPSE, death is an outcome and will not be recorded as an SAE.

[(b)] The term "life-threatening" in the definition of serious 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.

[(c)] Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

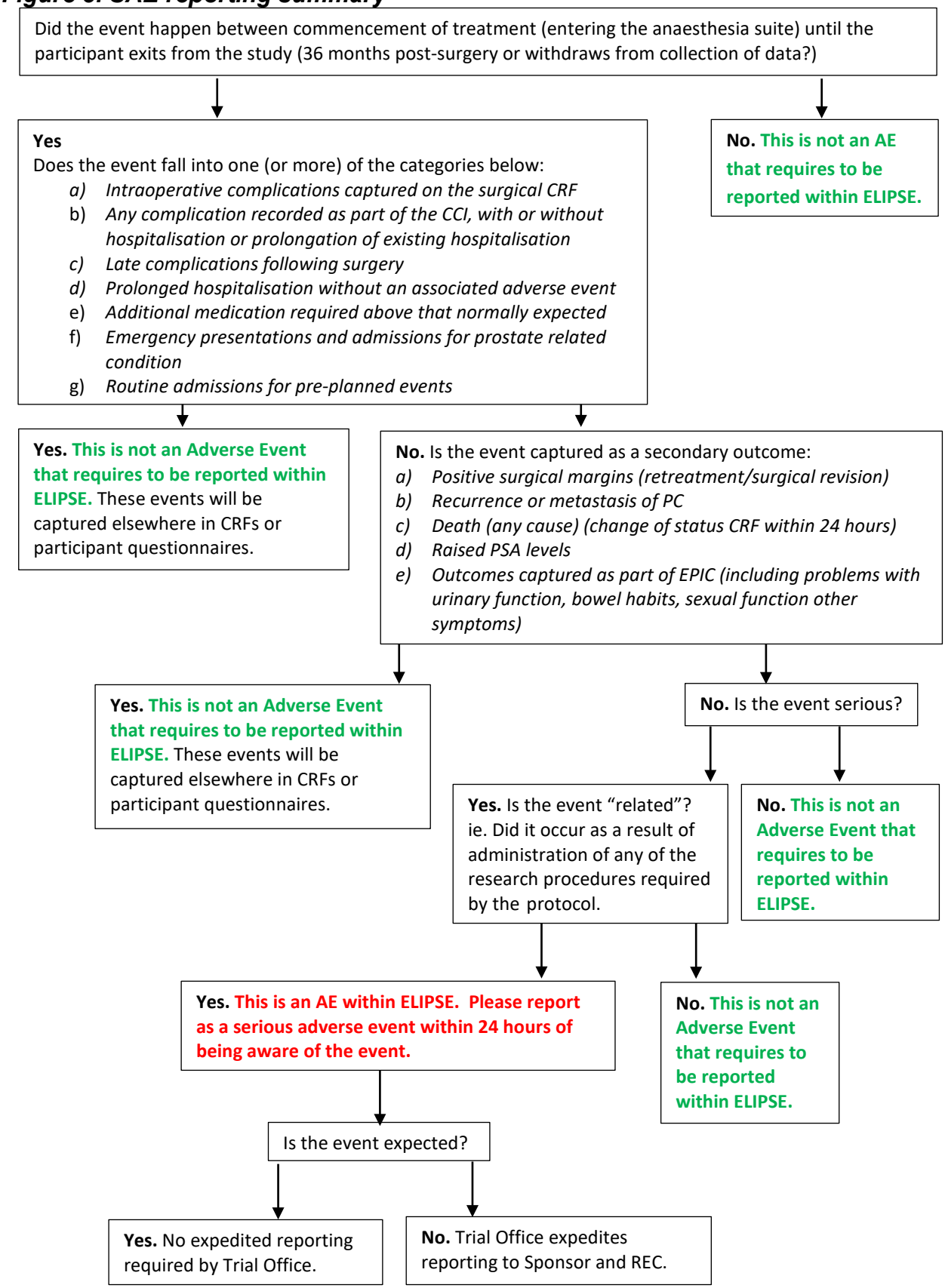
(d) Other events that may not result in death, are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Adverse events are not:

- continuous and persistent disease or symptoms, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied; or
- treatment failure.

Section 11.3 outlines the trial specific considerations in relation to safety reporting (summarised in Figure 3).

Figure 3. SAE reporting summary



11.3. Procedures for detecting, evaluating, recording, & reporting AEs and SAE

11.3.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within the ELIPSE trial (see sections 11.1 - 11.2) are recorded from the date that protocol defined treatment commenced (entering the anaesthesia suite) until the participants exits from the study (36 months post-surgery or withdraws from collection of data). The Investigator asks about the occurrence of relevant AEs/SAEs (i.e. those that meet the criteria for recording within the ELIPSE trial) at every follow-up timepoint, and within follow-up questionnaires.

11.3.2 Evaluating AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event.

Consideration of whether the AE/SAE requires to be recorded within ELIPSE

The investigator should refer to section 11.1 of the protocol and figure 3 to determine whether or not the event requires to be recorded within ELIPSE.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 11.2.

Assessment of Relatedness (causality)

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related:** resulted from administration of any of the research procedures required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.
- **Unrelated**: where an event is not considered to be related to the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

Expectedness will be assessed for events that meet the criteria for serious and related.

11.3.3 Recording SAEs

The Investigator (or delegate) should then record all relevant SAEs on the SAE form.

11.3.4 Reporting SAEs

Reporting responsibilities of sites

Once the Investigator becomes aware that an event has occurred in a trial participant that requires to be recorded as an SAE in ELIPSE, (see figure 3) they must report the information to the Trial Office within 24 hours. The Trial Office will report to the nominated reviewer and the Sponsor within 24 hours of becoming aware of the event.

The SAE form must be completed as thoroughly as possible with all available details of the event and signed by the Investigator or designee.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

To report an SAE to the trial office, site staff can either complete a hard copy of the SAE form and email it to the trial office or create the SAE form directly into the trial website. If the SAE form is created directly onto the trial website, the trial manager will be automatically notified.

Reporting responsibilities of the Trial Office

The Trial Office will report SAEs to the nominated reviewer. The nominated reviewer is Mr Krishna Narahari who may delegate this task to other clinical grant holders if the event is from his recruitment site or if he is unavailable. The nominated reviewer should review the SAE form and comment on the assessment that has been made by the local site. Ideally, this review will be completed within 24 hours.

The nominated reviewer cannot downgrade an assessment from the local site team. Any disparity may be resolved by further discussion between these parties and documented in the TMF. If the disparity cannot be resolved, both assessments are recorded.

If the local site team OR the nominated reviewer considers that the event is *serious, related* (), *and unexpected*, the Trial Office will notify the Sponsor within 24 hours of receiving the assessed SAE.

If the event is *serious but not related*, or *serious, related and expected*, expedited reporting to Sponsor is not required. Rather these events will be summarised and reported to Sponsor, REC, Funder, TSC and DMC in their regular progress reports.

11.3.5 Regulatory reporting requirements

The CI or delegate reports any events that are *serious, related and unexpected* to the REC within 15 days of the CI becoming aware of it using the Non-CTIMP safety report to REC form.

The CI is responsible for submitting annual reports to the REC on the anniversary of the approval.

All related SAEs are summarised and reported to the Funder, the TSC and the DMC in their regular reports.

11.3.6 Follow up procedures

After initially recording and reporting an SAE, the Investigator is required to follow each participant as indicated by clinical practice. Follow up information on an SAE should be reported to the Trial Office as described above in the Section on 'Reporting responsibilities of sites'. The Trial office will notify the Sponsor about any follow-up information.

11.4. Urgent Safety Measures and Serious Breaches of GCP

The CI and PIs may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However, they must alert the sponsor as soon as possible of any such urgent measures by contacting the Cardiff and Vale UHB R&D Office, CI and ELIPSE trial office. The CI will notify the REC of the presenting issue within three days of the urgent measure setting out the reasons for the urgent measure and the plan for further action. If a site PI identifies the presenting issue, he or she should also inform their local R&D department.

In the event that a serious breach of GCP is suspected, this should be reported immediately to the ELIPSE trial office. The ELIPSE trial office will report the

suspected serious breach to the Sponsor and assist with any investigation that the sponsor wishes to undertake. Relevant corrective and preventive actions will be considered by the Sponsor, CI, ELIPSE trial office and site where the event occurred. If appropriate, a protocol amendment will be drafted for approval.

If a serious breach is confirmed, this will be reported to the REC by the ELIPSE trial office.

12. SAMPLE SIZE AND PROPOSED RECRUITMENT PROJECTION

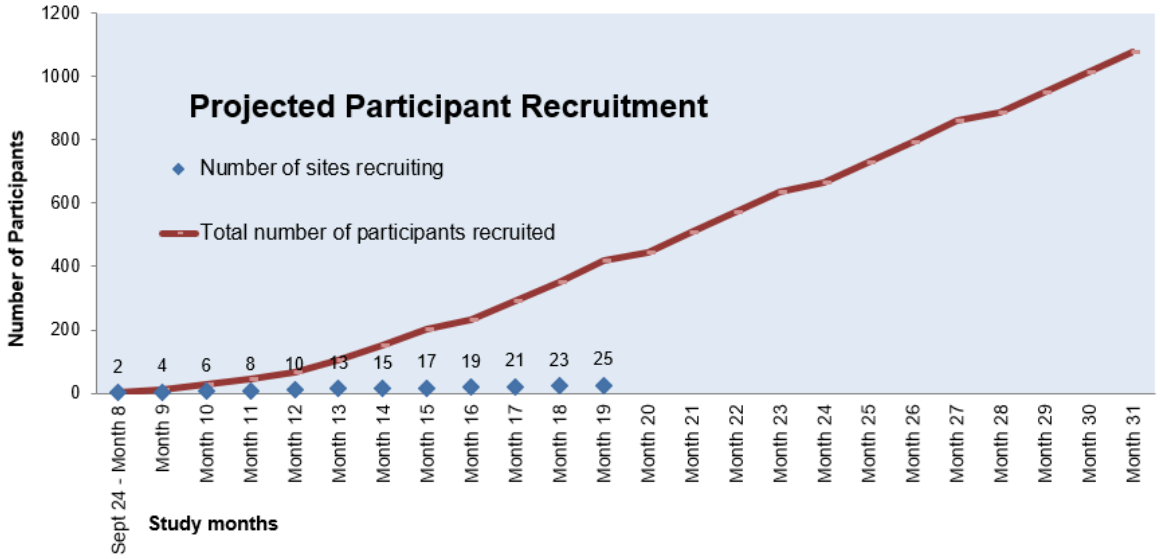
12.1. Sample size

ELIPSE is two-arm superiority trial. The primary outcome is time to cancer recurrence. There is no published data on recurrence rates specifically on those men not undergoing any PLND. However, based on historical data (2) we expect a recurrence-free rate of 67% at three years for those receiving PLND. Urological surgeons told us the recurrence-free rate should be at least 10% higher for PLND for it to be considered clinically superior and lead to routine uptake in clinical practice. This implies a control group event-free rate of approximately 57% at three years, equating to a hazard ratio of 0.71 (RP+PLND versus RP). A subgroup analysis in an RCT of limited vs extended PLND (5) of 69 participants with high-risk PCa similar to the population we will recruit from, suggested a 20% increase in 3-year PSA-free survival in favour of RP + extended PLND. Based on this, we believe a 10% improvement is a realistic and potentially conservative target difference given the comparison to RP only, the uncertainty in the subgroup estimate and our pragmatic design. For 90% power and a two-sided 5% alpha we require 369 events in total, a sample size of 486 in each arm, and a total of 972 participants. Other UK-based trials (MRC RADICALS, NIHR ProtecT) reported attrition rates of less than 5% for capturing post-operative PSA and an overall survival >95% at five years.(14,15) Conservatively, we have inflated our sample size to allow for 10% attrition and require 1080 participants to be randomised in total.(16)

12.2. Recruitment projection

Figure 4 shows the recruitment projection.

Figure 4 – recruitment projection



The project timetable and internal pilot phase is shown in Appendix B.

13. STATISTICAL ANALYSIS

All baseline and outcome data will be described using appropriate summary statistics. All analyses will be based on the intention-to-treat principle. The primary outcome, time to cancer recurrence (time to event), will be analysed using a Cox regression, including a random effect for centre, a fixed effect for treatment, and adjustment for design covariates with death from non-PCa causes censored. As a secondary outcome, PCa free survival will be analysed also using Cox regression with death from non-PCa causes considered as an event. We will also analyse the primary outcome considering death from non-PCa causes as a competing risk. Other secondary outcomes will be analysed using generalised linear models appropriate for the distribution of the outcome. Treatment effects for these models will be estimated at each time-point by time-by-treatment interaction. Treatment effects will be presented with 95% confidence intervals. All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan which will be agreed with TSC and DMC.

Planned subgroup analyses

We will perform subgroup analysis by baseline values of Gleason Grade (<4+3 versus ≥4+3), PSA (<20 versus ≥20), and Stage (T1/2 versusT3/4). Analyses will

follow the plan for the primary outcome but include a treatment-by-subgroup interaction term to test the potential moderating effects of subgroup on outcome.

14. HEALTH ECONOMIC EVALUATION

The economic evaluation will include a within trial cost-effectiveness analysis, comparing costs and outcomes between the randomised treatment groups at three years, and a decision modelling exercise to extrapolate cost-effectiveness over the expected life-time of patients.

Healthcare and resource use incurred throughout the trial will be collected using a combination of trial CRFs and patient questionnaires. Costing of the initial surgical episodes will focus on resource use that differs between the interventions being compared (RP + PLND and RP alone). Trial CRFs for the surgical episode will capture items of resource use that vary between individual patients such as time in theatre, procedures undertaken, grade(s) of surgeon, perioperative complications (and associated further resource use), and date/time of discharge from hospital. A supplementary survey of participating centres will be undertaken to inform any additional items of resource use (e.g. pathology time, specific items of equipment or consumables) that are routinely incurred when PLND is undertaken. The 36 month medical records review will record the routine follow-up of participants, including any tests or investigations, initiation of subsequent PCa treatment due to recurrence, and other secondary health service use required to monitor treatment or manage complications. Patient questionnaires administered at 12, 24 and 36 months will capture patient reported health care resource use and direct costs incurred by patients. The total cost to the health service will be calculated at the individual patient level over the three-year follow-up period of the trial, by combining reported items of resource use with published unit costs data (17-20) or unit prices obtained from centres or manufacturers of relevant equipment and consumables.

Direct costs incurred by participants for accessing health care related to their prostate cancer management will be calculated as a secondary economic outcome. This will be facilitated by a once-off time and travel questionnaire administered to participants at 12 months. Time lost from productive activities when accessing health services, or due to ill-health, will also be captured in the patient questionnaires at 12, 24 and 36 months, and the associated indirect costs to society will be calculated using gross wage rates (21) or appropriate shadow prices.

Generic health related quality of life will be captured at baseline and 3,12, 24 and 36-months post-surgery using the 5-level version of the EuroQol EQ-5D instrument (EQ-5D-5L). Individual participant quality adjusted life years (QALYs) will be determined by applying the National Institute for Health and Care Excellence (NICE) recommended (22) valuation tariff to individual EQ-5D-5L responses and calculating the area under the curve (assuming linear change in health state utility between observed timepoints).

The mean differences in costs and QALYs between patients treated with RP + PLND versus RP alone will be estimated using appropriately specified regression models (e.g. generalised linear models) adjusted for design covariates and baseline health state utility. The Incremental cost-effectiveness ratio (ICER) will be calculated as the mean difference in costs over the mean difference in QALYs, and the statistical uncertainty surrounding it will be characterised using non-parametric bootstrapping. Results will be presented graphically using cost-effectiveness scatter-plots and cost-effectiveness acceptability curves.(23)

Recognising that a three-year time horizon will not capture all important differences in costs and outcomes between the treatments being compared, and that cost-effectiveness may remain uncertain at this timepoint, we will also develop a decision analytic model to extrapolate the over the lifetime of patients. The model will simulate the progression of a cohort of patients through a series of health states reflecting the clinical progression of PCa. Its development and parameterisation will follow best practice guidelines (24) and the final structure and assumptions will be agreed upon in consultation with clinical experts and patient representatives. Whilst the precise structure is to be decided upon, the recently published economic model based on ten-year follow-up of the ProtecT trial may provide a useful starting point. (22) This model, which compared RP, EBRT and AS for localised prostate cancer, included health states for "stable" following primary treatment, "local progression", "metastatic disease" and death. The transitions probabilities, health state costs and health state utility values were derived, by risk status, from ProtecT trial data.(15) Using a similar model structure, we plan to use parametric survival analysis to extrapolate the rate of recurrence following PLND and no PLND, to determine transition probabilities for local recurrence (requiring further treatment) and metastatic disease (if sufficient observations available). Based on published data informing our sample size calculation we expect the time to recurrence data to be sufficiently mature to allow for reliable extrapolation.(25) However, given the relatively slow nature of localised prostate cancer progression, our model will rely on

external sources of evidence (e.g. the ProtecT trial) to inform subsequent transition probabilities form local progression to metastatic disease, and from metastatic disease to death. Health state costs (accounting for routine follow up, management of complications, and subsequent treatments) will be derived from analysis of our trial data, supplemented with data from the published literature to inform costs incurred in more distal health states. Similarly, health state utilities will be estimated by regression analysis of our EQ-5D data, supplemented with external evidence where required.

Each model input will be incorporated as a probability distribution to reflect parameter uncertainty due to sampling variation, and the model will be run probabilistically to characterise the uncertainty surrounding the expected joint difference in lifetime costs and QALYs. Model output will be presented in terms of the incremental cost-effectiveness ratio, cost-effectiveness scatter-plots, and cost-effectiveness acceptability curves.(26) Extensive sensitivity analysis will be conducted to address other structural uncertainties and assumptions, such as the choice of parametric distribution used to extrapolate time to recurrence. All health economic analyses will be further detailed in a Health Economics Analysis Plan, which will be agreed with the PI and TSC in advance of the final analysis.

15. DATA MANAGEMENT

15.1. Access to Data

All processes relating to participant identification and approach as well as procedures for data storage, processing and management will comply with Cardiff and Vale UHB policies.

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with the relevant data protection legislation.

The study may be subject to inspection and audit by Cardiff and Vale UHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

15.2. Data Recording and Record Keeping

A bespoke study website will be developed in CHaRT. Clinical data will be entered into this database by the designated team members working in each recruitment site,

together with data from the baseline questionnaire completed at site. Follow-up questionnaires returned by post to the trial office will be entered into the same database. Staff in the trial office will work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Each website user will have their own user account and password. These will not be shared. The study website has a full audit trail and every data entry made (or changed) is logged to the specific user.

15.3. Source data

The source of outcome data is summarised in table 3 below:

Table 3: Source data

Outcome	Source
Cancer recurrence (PSA, disease progression, need for further treatment, death)	Medical/laboratory records, participant questionnaires
Harms (complications and re-intervention rates)	Medical/laboratory records, participant questionnaires
Positive surgical margins	Pathology report
Metastasis free survival	Medical records
Health related Quality of life (EPIC-26, EQ-5D-5L) Time to return to normal activities Indirect costs Participant costs and resource use questionnaire Participant time and travel	If the participant completes a paper copy of the questionnaire, the hard copy is the source document. If the participant completes the questionnaire on the ePRO system, the electronic record is the source document. If the participant completes the questionnaire by telephone with the research nurse, the source document is considered to the FIRST place the research nurse records the information (which may be a paper copy of the questionnaire or the electronic record)

The ELIPSE trial inclusion form will be completed as a paper CRF before entering onto the study website. This permits signature from a medical doctor to confirm eligibility of the participant. For other CRFs, site staff can either complete a paper copy of the CRF before entry onto the eCRF on the study website, or bypass the paper CRF and enter the data directly onto the eCRF.

- If hard copy CRFs are completed, these are considered to be the source document. These will then be entered by the local study team onto the study website.
- If the data is entered directly into the study website, the electronic record is considered to be the source document. In order to maintain a copy of the data that is independent from the sponsor copy, sites will be encouraged to print or save a copy of the electronic data. The study website will provide this facility.

For all case report forms, there is an electronic record (as part of the study website) which indicates whether the case report form was completed online (no paper copy) or not. This will allow identification of the source document.

Participants will complete questionnaires at baseline, 3-months post-surgery and yearly to 36 months post-surgery. The hard copy of these questionnaires will be considered the source document. If participants complete the questionnaire online (no paper copy) the online copy is considered the source document.

15.4. Participant Confidentiality and Data Protection

The CI and research team is responsible for the data entry, quality of the data and data analysis. The CI will act as the data custodian for this study. Cardiff and Vale UHB and University of Aberdeen are joint data controllers.

Participant's details are stored on a secure database. Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team. Data may be looked at by individuals from the Sponsor organisation, CHaRT or NHS sites where it is relevant to the participant taking part in this trial.

The CI and trial staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the PIL.

The trial staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate trial staff.

Computers used to collate the data will have limited access measures via usernames and passwords. Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network.

No personal data will be downloaded or stored on local hard drives. All data input/access will be via the VPN and/or secure website.

Published results will not contain any personal data that could allow identification of individual participants.

The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set. Participants are allocated an individual trial number which is used to identify questionnaires and case report forms.

We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

15.5. Record Storage and Retention

Responsibilities for archiving are documented in the CTU and site agreements. All essential data and documents (electronic and hard copy) are retained for a period of at least five years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by University of Aberdeen.

The TMF and ISF containing essential documents will be kept for a minimum of 5 years after completion of study. Documents (paper and electronic) will be retained in a secure location during and after the study has finished. Where this is permitted by local trusts, the medical records of participants should be labelled with a retention period (5 years after completion of the study).

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor

16. QUALITY ASSURANCE PROCEDURES

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations.

The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. The study may be subject to inspection and audit by Cardiff and Vale UHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017. As such, Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

17. ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of GCP and in accordance with all applicable regulatory guidance, including but not limited to the UK Policy Framework for Health and Social Care 2017.

This protocol and related documents (and any subsequent amendments) will be submitted for review to the relevant parties (HRA/HCRW and REC).

Annual progress reports and a final report at the conclusion of the study will be submitted to the relevant parties within the timelines defined if required.

17.1. Review and Approvals

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by West of Scotland Research Ethics Service (Committee 5) Research Ethics Committee REC

17.2. Ethical Approval and HRA/HCRW approval

- Before the start of the study, approval will be sought from HRA/HCRW and REC for the protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- Amendments that require review by HRA/HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments through IRAS. This will automatically submit the amendment to both REC and HRA /HCRW.
- The CI (or delegate) also needs to notify the R&D offices and local research teams the amendment(s). The R&D Office(s) will have 35 days from receipt of the amendment to confirm capacity and capability.
- All correspondence with the REC will be retained in the TMF/ISF

- The CI will notify the REC of the end of the study
- If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC

17.3. Peer Review

The project proposal was independently and formally, peer-reviewed in writing and within NIHR HTA board meetings, for importance, scientific quality and feasibility as this is integral to the funding process of the NIHR HTA.

17.4. Governance Review

The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence at any site until local confirmation of capacity and capability is also received via email by the CI/ PI.

17.5. Reporting

CHaRT, on behalf of the CI, shall submit once a year throughout the study or on request, a progress report to the sponsor. CHaRT shall submit regular progress reports to the funder. In addition, an end of study notification and final report will be submitted to the relevant parties.

17.6. Expenses and Benefits

Participants can opt to receive a voucher (of modest value; £15) as a token of appreciation for participation in the study. If they opt to receive a voucher, this will be sent to them with the 3-year questionnaire. Alternatively, they can opt to have this sum donated to Prostate Cancer UK.

18. INDEMNITY AND FINANCE

18.1. Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

19. SATELLITE STUDIES

It is recognised that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the PMG and, if appropriate, with the TSC. Depending on the nature of the satellite trial, the Sponsor may consider this to be a non-substantial or a substantial amendment to the REC approval for the ELIPSE study, or to require REC approval as a project in its own right. R&D management approval may also be required.

20. PUBLICATION AND REGISTRATION POLICY

Please refer to the Appendix C (authorship policy) for full details on authorship.

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Authors will acknowledge that the study was funded by the NIHR HTA and other contributors will be acknowledged.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG and TSC.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

Other Dissemination

Once the main trial findings have been published, a lay summary of the findings will be sent to participants.

Trial findings will also be disseminated to professionals involved in the trial, including GPs of participants, PIs at sites, site staff, etc.

More detailed plans for this dissemination will be considered and developed with input from PPI partners through the duration of the trial and will be finalised as part of the close-out plans

Trial registration

ELIPSE is registered on the UKCRN database and on the ISCTRN.

21. REFERENCES

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APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1			New version (based on TPL-001-01 v3.0 dated 13 September 2021)
Response to REC Provisional Opinion	2	28 June 2024	Krishna Narahari, Seonaidh Cotton	Additional information about the consent process for potential participants who are not able to read or write, and the support available for the to complete questionnaires (sections 9.2 and 9.6) REC reference (front page) and REC name (section 17.1) added. Signposting to the trial PLND template added (section 5). Clarification on archiving responsibilities added (section 15.5). Correction of typographical error in the minimisation criteria (sections 1.1 and 9.3)
AM 01	3	5 July 2024	Maria Ntessalen	Clarification that the independent assessment of surgical image will be for at least the first five PLNDs in each trial centre (section 10). Revision to the definition of the initial learning curve to 50 cases (section 5).
AM 07	4	16/12/2024	Maria Ntessalen	Clarification that the Change of Status CRF should be completed within 24 hours after the site finds out about a participant's death (Figure 3, section 9.7)

				Alignment of the minimisation variable so they are the same everywhere in the protocol (1.1 Study summary, 13 Statistical analysis) Clarification that the surgical images will not carry any identifiable information (Figure 2-PLND template). Addition of "high-risk" to the inclusion criteria (section 8.2 Inclusion criteria) Addition of "pathological" to the definition of high-risk localised PCa (section 8.2 Inclusion criteria) Addition of verbal confirmation of written consent to the consent process (section 9.2.2 Informed Consent) Addition of e-consent process to the protocol (section 9.2.1 Informed Consent) Change in the way the consent form is returned- more general (section 9.1, section 9.2) Addition to the protocol of information on the CRFs to be completed after a participant's death. Section 9.7 Removal of reference to annual REC report (sections 11.3.5, 17.2. 17.5)

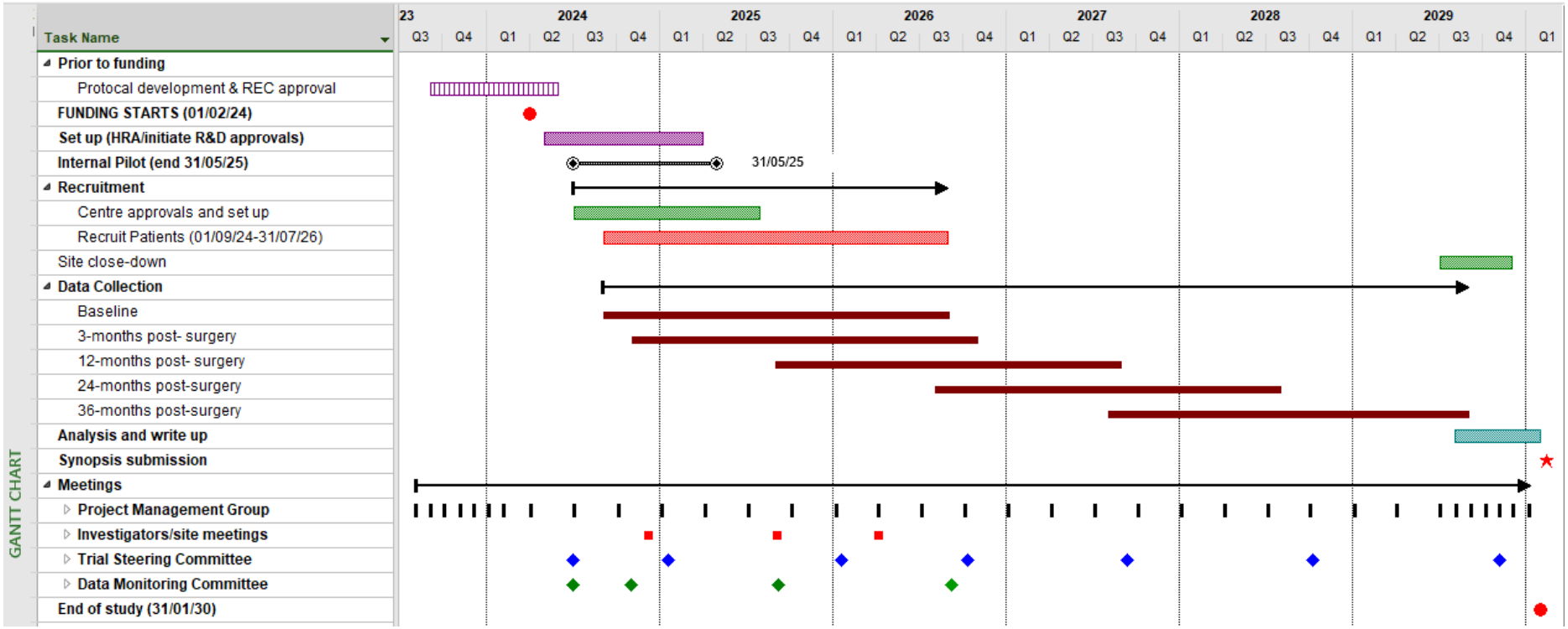
APPENDIX B: PROJECT TIMETABLE AND INTERNAL PILOT PHASE

We plan an internal pilot phase to establish whether recruitment is achievable. We have set two targets: one to assess the opening of centres and the other the recruitment of participants. We propose one decision point at the end of month 9 of the recruitment phase. At the end of month 9 we would expect to have 19 centres set up and 234 participants recruited. The progression criteria are laid out in Table 1 below.

Table 1: Stop/Go criteria at 9 months.

	GREEN	AMBER	RED
Centre recruitment	100% (19 centres)	70-100% (≥ 13 centres)	< 70% (< 13 centres)
Participant recruitment	100% (234 participants) with < 3 of the sites with ≤ 1 participant randomised per month	70-100% (≥ 164 participants but less than 234) ≥ 5/13 sites with ≤ 1 participant randomised per month	< 70% (< 164 participants) > 5 sites with ≤ 1 participant randomised per month
Adherence to intervention	>95%	85% - 94%	<85%
Action	Proceed whist considering opportunities to enhance recruitment from monitoring of screening data and site feedback	Consider recruitment strategies based on monitoring of screening data and site feedback	Discuss urgently with the TSC and funder, considering all options including discontinuation.

Figure X: Project Gantt with milestones



APPENDIX C: AUTHORSHIP POLICY FOR ELIPSE TRIAL

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria.[1]

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-author.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to "The ELIPSE trial group" or "Jane Doe, John Doe, John Smith, Ann Other and the ELIPSE trial group". The article should carry a

footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group')[2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group (PMG). Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

The acknowledgements should also reflect any agreed acknowledgements (for example with suppliers) that were documented in supply agreements (or equivalent).

4. DISCLAIMERS

All papers arising from CHaRT should include any appropriate disclaimers. For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the trial funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the ELIPSE trial, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, should be peer reviewed by the PMG. The PMG will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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