PANORAMA

Analysis of PSMA expressioN in prOstate cancer and its Relationship with the presence of nodAl MetastAses

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GLOSSARY OF ABREVIATIONS

BAUS	British Association of Urological Surgeons
CaCTUS	Cancer Clinical Trials Unit, Scotland
CI	Chief Investigator
CT	Computed Tomography
CRF	Case Report Form
EAU	European Association of Urology
ePLND	Extended Pelvic Lymphadenectomy
GCP	Good Clinical Practice
HE	Haematoxylin and Eosin
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ISUP	International Society of Urological Pathologists
LN	Lymph Node
LNI	Lymph Node Invasion
LNM	Lymph Node Metastases
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCITA	National Cancer Imaging Translational Accelerator
NPV	Negative Predictive Value
PET-CT	Positron Emission Tomography – computed tomography
PHS	Public Health Scotland
PSMA	Prostate-specific membrane antigen
PSMA-PET	PSMA Positron Emission Tomography
PSA	Prostate-specific Antigen
RC Path	UK Royal College of Pathologists
RCT	Randomised Control Trial
RP	Radical Prostatectomy
RT	Radiation Therapy
SCTRU	Scottish Clinical Trials Research Unit
SDV	Source Data Verification
SUV max	Max Standardised Uptake Values
TMG	Trial Management Group
TNM	TNM Classification of Malignant Tumours
TSC	Trial Steering Committee

TRIAL SUMMARY

Protocol ID	In vivo PSMA Expression Analysis
Protocol Title	Analysis of PSMA expression in prostate cancer and its relationship with the presence of nodal metastases
Development Phase	Feasibility Study
Aims	1. To determine the relationship of PSMA expression at the primary tumour and the risk of pelvic nodal metastases. 2. To develop relevant protocols and standardised procedures for future imaging studies in a surgical prostate cancer cohort. 3. To develop a platform to support multi-centre prospective study to evaluate PSMA expression in prostate cancer *in vivo*.
Primary Outcomes	1. To establish whether prostate tumours with high PSMA expression have enhanced risk of pelvic nodal metastasis. 2. To establish best practice and optimise protocols for multi-centre application of PSMA PET/CT imaging.
Secondary Outcomes	1. To evaluate the feasibility of a future large scale randomised controlled trial (RCT), and develop quality assurance measures across the study team/network 2. To develop a platform to carry out RCT to study the usefulness of novel imaging/biomarkers for evidence-based treatment decisions in patients at risk of pelvic nodal prostate cancer.
Study Design	To study 60 patients with high risk prostate cancer opting for surgical intervention. Eligible patients will be managed with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND).
Patient Accrual	60 patients will be recruited over 6 months from 4 UK sites.

1. INTRODUCTION

1.1. Background

Surgery and radiation therapy are treatment options for patients with curable prostate cancer at the time of diagnosis. For those patients opting for surgery, radical prostatectomy (RP) and extended pelvic lymphadenectomy (ePLND) is recommended for tumours within the intermediate to high risk category, as judged by clinical parameters such as PSA levels, tumour Gleason score and TNM stage based on cross sectional imaging (e.g. CT or multi-parametric MRI) and isotope bone scans.

The decision to carry out a formal ePLND at the time of RP is widely debated. The guideline from the European Association of Urology recommends RP and ePLND to be performed when a ≥ 5% risk of nodal disease is calculated based on a predictive tool such as the Briganti nomogram [1] (derived from a large cohort of surgical patients with histologic data). For those patients undergoing radiation therapy (RT), there is also significant uncertainty as to the consensus indication for extending the radiation field to include the entire pelvis, in addition to the prostatic bed. Again, there are developed predictive models like the Roach formula [2] to aid decision-making regarding nodal-coverage.

The current practice for both surgical and radiation intervention varies widely with regards to the coverage of the pelvic lymph nodes, dependent on clinician preference and local facilities/expertise. Hence, there is an urgent unmet need for additional tools to support patient stratification according to their respective risks of pelvic lymph node metastasis, in order to reduce the number/proportion of men undergoing ePLND that are later confirmed to have no histological evidence of nodal disease. Improved stratification of patients based on their need for ePLND dissection or not would reduce both costs and operating time in patients at “low-risk” of having metastatic nodal disease, as well as minimising unnecessary surgery related morbidities in terms of lymphocele formation, thromboembolic events, neurovascular and ureteric injury.

1.2. Pre-Clinical Data

Prostate-specific membrane antigen (PSMA) is a cell surface protein with significantly increased expression in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands [3, 4]. Another advantage of PSMA as an imaging target is its transmembrane location with a large extracellular domain. Scintigraphy using ProstaScint® (antibody capromab pendetide) has been limited to the detection of non-viable tumor cells, as it targets the cytoplasmic PSMA domain. Other limitations of antibody-based tumor detection methods include their relatively long circulation time, leading to high background to signal ratios and subsequent reduced detection rates.

Methods have been developed to label PSMA ligands with ^{68}Ga, ^{99}mTc and $^{123/124/131}$I, enabling their use for PET imaging, more scintigraphy options and radioligand therapy. The initial experience with PET/CT using (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga (HBED-CC)] coupled to a binding motif to the extracellular domain of PSMA (referred to as 68Ga-HBED-PSMA thereafter) suggests its ability to detect recurrent prostate cancer as well as metastatic disease [5, 6, 7, 8]**.** The majority of reported literature with the use of PSMA based imaging utilised 68Ga-HBED-PSMA-11 as a highly specific tracer for PSMA. Increasingly 68Ga-HBED-PSMA-11 PET imaging is adopted in staging of patients with high risk primary and recurrent prostate

cancer. However, there is urgent need to obtain robust data from multi-centre prospective patients with intermediate to high risk prostate cancer. Importantly, none of the reported series on the use of PSMA PET incorporate formal benchmarking of a centralised PET reporting reference in their study design.

1.3. Clinical Data

To date, the use of ^{68}Ga-HBED-PSMA-11 has been reported to show widely varying data on sensitivity (33–85%) and specificity (82–100%) for the detection of prostate cancer recurrence and the detection of nodal metastases. A recent report of a retrospective single centre surgical cohort with intermediate to high risk prostate cancer undergoing surgical intervention suggested promising data on the use of PSMA PET/CT imaging [8]. All patients harbored a nomogram-calculated risk of lymph node metastasis (LNMs) >20%. 608 lymph nodes (LNs) containing 53 LNMs were detected during RP. LNMs were present in 12 of 30 patients (40%). ^{68}Ga-PSMA PET/CT scans identified 4 patients (33.3%) as LN true positive and 8 patients (66.7%) as false negative. Median size of ^{68}Ga-PSMA-PET/CT–detected versus undetected LNMs was 13.6 versus 4.3 mm ($p < 0.05$). Overall sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA PET/CT for LNM detection were 33.3%, 100%, 100%, and 69.2%, respectively. Hence, LNM size appeared to impact on the diagnostic accuracy of ^{68}Ga-PSMA PET/CT to detect nodal disease. Similar findings were reported [9] with significantly larger LNs being positive on PSMA imaging than those negative on scan but harboring LNMs: 4.73 mm +/-1.45) and 2.73 mm +/- 1.29, respectively; $P = 0.001$).

These studies confirm the urgent need to further define the detection threshold of LNM size for detection by PSMA as well as additional biomarkers to improve the overall confidence of pelvic nodal staging in patients with high risk disease.

1.4. Trial Rationale

Despite no compelling survival benefit attributed to ePLND, the procedure is recommended by EAU Guidelines for patients' with a ≥5% risk of having lymph node invasion (LNI). ePLND is best considered a staging procedure, as subsequent treatment options may depend on the nodal status by histologic evaluation, i.e. whether the patient will be observed (no LNI), receive adjuvant whole pelvis RT (low volume LNI) or consider adjuvant androgen deprivation therapy (high volume metastasis).

Data from the British Association of Urological Surgeons (BAUS) Radical Prostatectomy audit demonstrates that only 39% of men with high-risk disease received a formal ePLND at the time of surgery[14]. This highlights the urgent need for accurate imaging modalities to allow identification of potential LNI and thus reduce the morbidity of over-treatment.

The proposed multi-centre functional imaging study is designed to test the value of ^{68}Ga-HBED-PSMA-11 radiopharmaceutical in PET/CT as a staging test to identify individuals with pelvic lymph node disease (as well as to identify those without lymph node involvement). If the use of ^{68}Ga-HBED-PSMA-11 shows promising results in this study, a randomised controlled trial can be developed in the future to formally study the impact of PSMA PET/CT in patient selection for treatment (surgery or radiotherapy). In addition, besides PSMA PET/CT, other functional imaging tracers/modalities can be incorporated into the optimised study pipeline as future multi-centre prospective studies.

The widely varied range of sensitivity and specificity observed with the use of ^{68}Ga-HBED-PSMA PET/CT imaging is likely multi-factorial, including highly variable patient selection criteria and no pre-defined standard imaging protocol. All published studies so far have tended to "lump" together heterogeneous patient populations or published with small number of patients with no or little attempt for patient stratification. We propose a standardised reporting method with central reviewing and oversight by the NCRI PET core lab at St Thomas' Hospital.

2. TRIAL OBJECTIVES

Aims:

1. To determine the relationship of PSMA expression at the primary tumour and the risk of pelvic nodal metastases.
2. To develop relevant protocols and standard of procedures for future imaging studies in a surgical prostate cancer cohort.
3. To develop a platform to support multi-centre prospective study to evaluate PSMA expression in prostate cancer *in vivo*.

Primary Outcomes:

1. To establish whether prostate tumours with high PSMA expression have enhanced risk of pelvic nodal metastasis.
2. To establish best practice and optimise protocols for multi-centre application of PSMA PET/CT imaging.

Secondary Outcomes:

1. To evaluate the feasibility of a future large scale randomised controlled trial (RCT), and develop quality assurance measures across the study team/network.
2. To develop a platform to carry out RCT to study the usefulness of novel imaging/ biomarkers for evidence-based treatment decisions in patients at risk of pelvic nodal prostate cancer.

3. TRIAL DESIGN

3.1. General Design

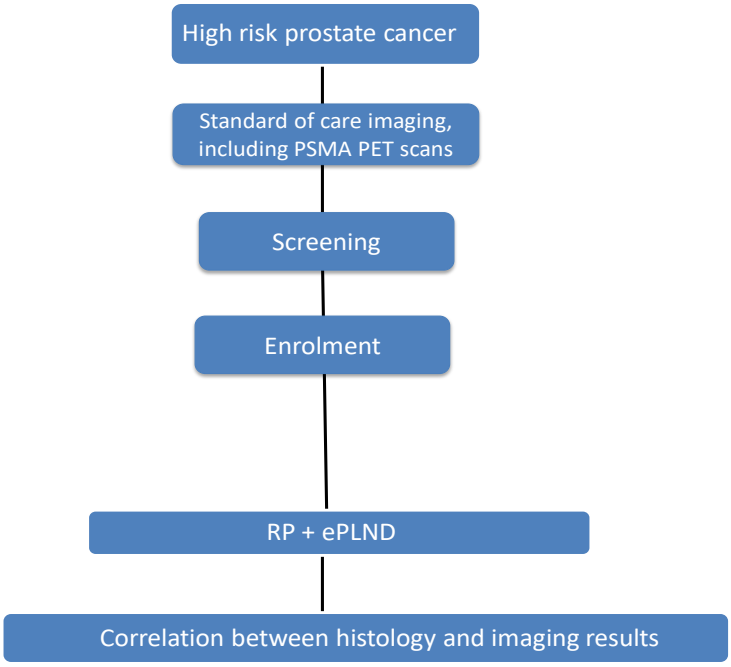
We propose to carry out a PSMA expression feasibility study in a cohort of patients with high risk prostate cancer (in the absence of clinical evidence for distant metastasis) opting for surgical intervention with radical prostatectomy (RP) and extended pelvic lymphadenectomy (ePLND). Sixty patients will be recruited from 4 centres within the United Kingdom, namely Addenbrookes Hospital, Cambridge; Queen Elizabeth University Hospital, Glasgow, University College London Hospital, London and St Bartholomew's Hospital, Barts Health NHS Trust, London. The study will include patients with NCCN (National Comprehensive Cancer Network) high-risk prostate cancer (as defined by one or more of the following: PSA ≥20ug/L, Gleason sum score ≥8, T-stage ≥cT3).

Patients with high risk prostate cancer being considered for radical prostatectomy and pelvic node dissection will have a PSMA PET/CT scan as part of standard of care imaging. Standard of care imaging will be as per local clinical practice (MRI/CT/bone scintigraphy/non-PSMA PET scans), with PSMA PET scan performed in lieu of isotopic bone scan.

Patients who have given signed or verbal informed consent and who have met all eligibility criteria will be enrolled into the trial.

Patients will be recruited from the participating centres within a 6 month period. These patients with high-risk disease will be managed as outlined in Figure 1.

Figure 1. Study outline



Template based extended pelvic lymph node dissection and approach for pathological evaluation of specimens

For patients recruited to this study, an ePLND will be performed at the time of RP, removing lymphatic tissue up to the bifurcation of the common iliac artery, along the external iliac (with the distal limit at the deep circumflex vein and femoral canal), the internal iliac vessels and the obturator fossa, as well as the fossa of Marcille. The lateral limit of the template is at the external iliac vein and the medial limit is the perivesical fat [1, 10]. All specimens will be submitted by the surgeon in separate formalin–filled containers, labelled according to their anatomical location, i.e. left/ right external iliac, left/ right internal iliac, left/ right obturator and left/right fossa of Marcille.

After dissection, specimens from all enrolled patients will be sent for histopathological examination in line with the International Society of Urological Pathology (ISUP) consensus conference [11] and the UK Royal College of Pathologists (RCPath) dataset [12] by designated uropathologists at the study sites. RP specimens will be processed according to routine clinical protocol of the study sites. Lymphatic tissue will be examined by palpation, visual inspection and sectioning at 3 mm intervals, in accordance with a consensus protocol within this study. The transversely sliced lymph nodes (LNs) will be processed, paraffin-embedded and histological sections cut and stained for Haematoxylin and Eosin (H&E). Disease positivity will be defined as the presence of any metastatic deposits of prostate cancer in the LNs examined. For each metastatic LN, both the short axis and largest diameter (expressed in mm) of the metastatic deposits will be recorded. The number of positive nodes and the total number of nodes found will be reported for each of the nodal specimens submitted.

PSMA PET imaging and reporting

Lesions detected by PSMA imaging will be evaluated by their maximum Standardised Uptake Values (SUVmax), which provides an objective quantification of each abnormal lesion, with particular interest for the pelvic lymph nodes, but signals in the prostate, bone and other soft tissue if present will also be assessed. There is a small chance of potential occult distant metastasis being identified in PSMA PET/CT imaging. Regardless of the results of the PSMA PET imaging, ePLND will include clinically recommended anatomical template. Following surgery, the need for additional investigation to clarify the validity of PSMA PET/CT revealed signals will be at the discretion of the clinical team and will not be dictated by the trial. For instance, increased uptake in solid organs or bone may result from Paget's disease or haemangioma, which may require additional correlative imaging.

Images from ^{68}Ga-PSMA PET/CT scanning will be interpreted by two experienced nuclear medicine physicians (one at the local scanning site as well as central reporting by an expert nominated from the PSMA imaging subgroup). All LNs with increased ^{68}Ga-PSMA accumulation will be assigned to their respective anatomical location, measured in the short axis, along with an assigned SUVmax for each affected LN. In addition, visual analysis of the ^{68}Ga-PSMA uptake will included a four-point certainty scoring scale (definitely negative, equivocal probably negative, equivocal probably positive, definitely positive). Although not our primary research focus, PSMA +ve lesions within the prostate will be categorised as either focal or diffuse. Disease involving only one of the four prostatic quadrants will be considered as focal. If prostatic lesions are detected in more than one quadrant, the disease will be classified as diffuse/multifocal (if non-contiguous). Signals that indicate potential distant metastatic sites will also be scored using the four-point certainty scoring scale as described above for pelvic nodes [13].

Attention will be paid to ensure comparable imaging protocols are used across participating sites to ensure data obtained are suitable for objective and robust reporting of PSMA PET/CT across the study. Lesion uptake will be categorised according to a predefined anatomical scoring template.

Image scoring

Interpretation of PET imaging will be performed in accordance with the NCRI PET framework. All positive LNs on ^{68}Ga-PSMA PET/CT will be assigned to the respective anatomical region: left/right external iliac; left/right internal iliac, left/right obturator; left/right fossa of Marcille. Positive matching will be defined as the correlation between PET scan positivity and histological positivity, with histopathological analysis of the LNs considered the reference standard. Positive nodes in each nodal region/chain will be scored individually. These data can then be analysed separately or collectively for each nodal region. Once recruiting sites have satisfied QC evaluation by the UK PET Core Lab, the SUV values will be generated by identical (or very similar) reconstruction algorithms and are expected to be reproducible across the study.

3.2. Inclusion Criteria

1. High risk prostate cancer[1] with no detectable distant metastasis using standard of care imaging (MRI prostate/pelvis, isotope bone scan, CT, non-PSMA PET/CT) undergoing radical prostatectomy and pelvic lymph node dissection.
2. ^{68}Ga-PSMA PET/CT done as part of the staging investigation
3. Histologically proven prostate cancer.
4. No prior prostate cancer treatment including androgen deprivation therapy.
5. Male aged 18 or over.
6. Considered suitable candidate for radical surgery for prostate cancer.
7. Willingness to comply with scheduled visits

3.3. Exclusion Criteria

1. Evidence of demonstrable distant metastasis on standard of care imaging using combination of MRI, CT, isotopic bone scan, non-PSMA PET/CT, or PSMA-PET/CT where undertaken as standard of care.
2. Patients not willing to receive surgical treatment with radical prostatectomy and pelvic node dissection.
3. Patients who are unable or unwilling to give informed consent.

3.4. Withdrawal of Subjects

Patients withdrawing from the study for reasons such as safety, non-compliance or withdrawal of consent etc will continue to be followed up for efficacy and safety as per protocol, unless they are lost to follow up, deceased or withdraw consent to the study.

[1] As defined by with NCCN high-risk prostate cancer, as defined by one or more of the following: PSA ≥20ug/L, Gleason sum score ≥8 or T-stage ≥ c T3

Patients may *withdraw* from the study at any point; this should be indicated on the deviation case report form (CRF).

3.5. Endpoints

Primary Outcomes:

1. To establish whether prostate tumours with high PSMA expression have enhanced risk of pelvic nodal metastasis.
2. To establish best practice and optimise protocols for multi-centre application of PSMA PET/CT imaging.

Secondary Outcomes:

1. To evaluate the feasibility of a future large scale randomised controlled trial (RCT), and develop quality assurance measures across the study team/network.
2. To develop a platform to carry out RCT to study the usefulness of novel imaging/biomarkers for evidence-based treatment decisions in patients at risk of pelvic nodal prostate cancer.

4. TREATMENT

4.1. Treatment Schedule

Patients recruited into the trial will undergo no additional scans, tests or visits other than their normal routine care. Surgery is part of the routine clinical management of these patients and patients will have discussed surgery for their prostate cancer.

4.2. Concomitant Therapy

This study will not be collecting concomitant medications as this study is an imaging study only. Concomitant medications would not have any direct implications to the outcome of PSMA based imaging.

5. ASSESSMENT OF EFFICACY

5.1Treatment and Examination Schedule

Activity	SCREENING/BASELINE[a,]	SURGERY	FOLLOW UP[b] 6 weeks post surgery as per clinical practice
Written or verbal Informed consent	X		
Weight	X		
Eligibility checklist	X		
Study enrolment	X		
Radical Prostatectomy and Lymph Node Dissection		X	
Outcome of surgery			X

[a]Screening/baseline – Prostate Cancer has been diagnosed and confirmed by clinical, radiological and histological investigations pre operatively including relevant standard care.of imaging. Between decision for surgery and pre-operative assessment (to allow patient time for isolation in COVID-19 compliant manner).
[b]Follow up clinic visit 6 weeks post operatively – the patient will receive the outcome of their surgery per routine clinical practice/indication. In current COVID-19 practice, follow up of patients may be via telephone consultation. Per local clinical practice, PSA test may be carried in local GP surgery.

5.2 Schedule of assessments

5.2.1. Screening/Baseline Procedures

Screening procedures.

- Clinical assessment
    - Signed informed consent or verbal consent (for patients who are unable to be seen in clinic prior to surgery
    - Weight

- Histological confirmation of prostate cancer by Prostatic biopsies.

- Laboratory determinations
    - PSA.

- Radiological assessment – confirmation of non-metastatic prostate cancer by
    - MRI prostate/ pelvis
    - CT scan
    - ^{68}Ga-HBED-PSMA-11 PET/CT scan (in lieu of Isotope bone scan)
    - Non- PSMA PET scan [e.g. ^{11}C-Choline PET scan, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) FDG PET scan].

- Eligibility assessment checklist
- Study enrolment

Study Enrolment

The participant's research nurse and/or doctor will screen the participant to ensure that they meet the trial eligibility criteria.

Patients will be enrolled centrally with the Scottish Clinical Trials Research Unit (SCTRU). An eligibility and enrolment checklist must be completed prior to enrolment. Enrolment should take place within 6 weeks prior to the planned surgery.

Once consent has been obtained the participant should be enrolled by emailing the

PANORAMA team at the Scottish Clinical Trials Research Unit:

SCTRU email: PHS.SCTRU@phs.scot

The following information will be required at enrolment:

- Name of hospital, consultant and person enrolling the patient
- Confirmation that the patient has given written or verbal informed consent for trial participation
- Confirmation that the patient is eligible for the trial by completion of the eligibility checklist
- Patients initials, date of birth and study ID number

SCTRU will send sites a Screening Log with a site specific number and sequential study ID numbers. This will be completed by sites as patients are enrolled in the study.

Following written or verbal informed consent being obtained from the patient, the site will inform the respective General Practitioner (GP) of the participant's enrolment.

It may be possible for participants to be recruited into other clinical trials, but this should be discussed with the 0CI via SCTRU before this is considered.

PSMA PET/CT Imaging

PSMA PET/CT scans will be performed in centres accredited by the UK PET Core Lab, based at St Thomas' Hospital, London [*www.ncri-pet.org.uk/*]. Local protocols for scanning preparation, acquisition and quality control processes will have been reviewed to ensure they meet the minimum requirements for participation in the study.
PET scans will be collated by the UK PET Core Lab and technical checks will be undertaken to ensure the image data quality is acceptable and that the PSMA PET/CT scan has been performed to an acceptable standard prior to central review. Any scans not fulfilling these requirements will be flagged to the PI and Clinical PET Expert.
Within each participating NHS site, the study imaging data will remain within the site and stored on NHS computers in keeping with the site's information governance policies. To allow intercomparison of results from different centres, sites will be requested to store the raw image data to allow centralised reprocessing using standard parameters.
All imaging data will be pseudo-anonymised prior to transfer to the UK PET Core Lab (using patient initials and trial number) and sent in DICOM format. Transfer of scan images, raw data and reports will be performed electronically wherever possible. Where sites are unable to send data electronically, use of CDs / DVDs will be used. Electronic transfer from the scaning centres to the UK PET Core Lab will be done using MIMcloud, a cloud-based server located in the EU. Data transfer methods use secure transfer protocols with password protection features and encryption. The pseudo-anonymized data collected will be maintained on university computers and in a secure webhosted environment with password protection features and encryption.

5.2.2 Surgery - Radical Prostatectomy and Pelvic Node Dissection

Pathology

Surgical specimens from radical prostatectomy (RP) and pelvic node dissection will be processed at each of the participating centres for histopathological examination in line with the International Society of Urological Pathology (ISUP) consensus conference [11] and the UK Royal College of Pathologists (RCPath) dataset [12] by designated uropathologists.

Lymphatic tissue will be examined by palpation, visual inspection and sectioning at 3 mm intervals, in accordance with a consensus protocol within this study. The transversely sliced lymph nodes (LNs) will be processed, paraffin-embedded and histological sections cut and stained for Haematoxylin and Eosin (H&E). Disease positivity will be defined as the presence of any metastatic deposits of prostate cancer in the LNs examined. For each metastatic LN, both the short axis and largest diameter (expressed in mm) of the metastatic deposits will be

recorded. The number of positive nodes and the total number of nodes found will be reported for each of the nodal specimens submitted.

5.2.3. Follow up – post surgery

As part of routine clinical care, follow up 6 weeks after surgery.

- Clinical assessment
    - Outcome of surgery
    - Histopathology evaluation of surgical specimens
    - Post-op bloods per routine clinical practice PSA

6. Sub-Studies

Formal translational study and considerations into quality of life and health economics will be developed in a future randomised controlled trial if PSMA PET/CT is shown to be adequately specific and sensitive.

7. PHARMACOVIGILANCE

7.1. Adverse Events

Adverse Events will be not collected as all the treatment is standard patient care and there will be no administration of research treatment. Therefore, there will be no requirement to report Adverse Events or Serious Adverse Events. As there is no research treatment, any serious adverse event cannot be assessed as “related” or “unexpected” and there are no expected outcomes listed in the protocol.

7.2. Pregnancies

N/A

8. DATA MANAGEMENT

All data will be handled, computerised and stored in accordance with the GDPR and Data Protection Legislation and PHS Data Protection Policy.

8.1. Data Collection

Data generated will be collected by SCTRU, who will be responsible for checking the data, entering it on the trial database and validating it. The data collected will include:

- initial clinical details at enrolment
- outcome of surgical procedure
- outcome of histopathology evaluation of surgical specimens
- PSMA PET/CT report

8.2. Record Keeping and Archiving

SCTRU will store study documentation until the end of patient follow up. The documentation will then be archived according to current legislative requirements.

9. STATISTICS

9.1. Sample Size

If we identify 60 eligible patients we will formally analyse the relationship between PSMA expression in primary tumour and the incidence of pelvic nodal disease.

9.2. Randomisation and Stratification

No randomisation will be performed as this is a single arm study.

9.3. Analysis Plan

A binary logistic regression model will be trained on the SUV values obtained from the PSMA PET/CT imaging to predict whether metastatic disease is present or not. The analysis will be carried out on a (i) per-patient, (ii) bilateral side, (iii) LN-region, and (iv) LN-specific basis (as previously described by Leeuwen et al [9]). Where necessary, a generalized estimating equation model will be used to adjust for correlations within regions of each patient. Performance on unseen data will be assessed using 10-fold cross validation, and calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The "gold standard" assessments to which the model predictions will be compared will be provided by pathology.

Comparison of PSMA PET/CT reporting between local nuclear physician evaluation and review by central experts will be represented in a Bland Altman plot. A consensus will be developed in terms of minimum training required for local nuclear physicians in the review of PSMA PET signals.

9.4. End of Study

This study will end when the following criteria are deemed completed by the sponsor:

- Last patient has attended his last study 'visit' (6 week post-surgery follow up appointment).
- The database has been cleaned and 'locked down' for analysis.

10. ACCESS TO SOURCE DATA/ DOCUMENTS

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the Sponsor, SCTRU or the Coordinating Centre or company supplying the product under investigation, as

well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control will be maintained through adherence to the Principles of ICH GCP (Appendix 2) and the SCTRU or coordinating centre's SOPs. The coordinating centre will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistencies and missing data.

11.1. Monitoring Visits

The trial will be monitored by SCTRU according to SCTRU SOPs. The frequency and objectives of monitoring will be detailed in the Clinical Monitoring Plan, and may include a Site Initiation Visit, Interim Monitoring Visits and a Close out Visit, which will be performed remotely. As a guideline, the frequency and nature of visits will depend on resource, recruitment and site performance. Higher levels of monitoring will be performed, if requested, by the Data Monitoring Committee, or if the investigators, the Trial Management group or Trial Steering Committee identify particular safety issues.

The objectives of the monitoring plan will be to ensure the safety and wellbeing of trial participants, the accuracy, completeness and consistency of data, adherence to the protocol and compliance with Good Clinical Practice. The monitor will have full access to the Case Report Forms and the participant's medical records (as described in section 10), in accordance with the terms of Informed Consent; as well as all trial related files and documents.

11.2. Data Monitoring Committee

An independent Data Monitoring Committee will be established and will meet after 30 patients have been recruited or in the sixth month of the study, whichever comes first. The Data Monitoring Committee will then meet six monthly. The Data Monitoring Committee membership will include independent members with the CI and Trial Coordinator attending the open sessions only. The committee will receive reports from the SCTRU submit its comments and recommendations to the Trial Steering Committee. The Data Monitoring Committee may choose to see the final results and comment on these prior to publication.

11.3. Trial Steering Committee

A trial steering committee will be established to provide overall supervision of the trial, in particular; trial progress, adherence to protocol, patient safety, and consideration of new information. The committee will meet after the first 30 patients have been recruited then again once recruitment has been completed. Additional meetings will be convened if required. The meetings of the committee will be coordinated to follow on from the DMC meetings.

12. ETHICAL CONSIDERATIONS

Ethical approval by a Research Ethics Committee will be secured before the trial can be started. The trial will be carried out according to guidelines of good clinical practice (GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use (Clinical

Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/EC) elsewhere in the European Union and follow the principles of research governance.

12.1. Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (Community Health Index and/or hospital number in Scotland) will be collected to enable tracing through national records. The personal data recorded on all records will be regarded as confidential, and to preserve each patient's anonymity, only their initials will be recorded on CRFs with the exception of the enrolment CRF which will contain the patients date of birth as this is required to check the inclusion criteria. The patients will be identified within the CRFs by the use of a unique trial number allocated to them upon entry into the study.

The Principal Investigator (or designee) at each site must keep a log of patients' trial numbers, names, addresses and hospital numbers. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

SCTRU will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients will only be referred to by Trial Number and Initials in any essential trial related correspondence, including Case Report Forms.

All patient identifiable data will be handled, computerised and stored in accordance with the GDPR and Data Protection Legislation and PHS Data Protection Policy.

12.2. Informed Consent

All patients will be informed of the aims of the study. the procedures and possible hazards to which they will be exposed. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever they want. This will not prejudice the patient's subsequent care.

Documented informed consent must be obtained for all patients included in the study before they are enrolled. This must be done in accordance with the national and local regulatory requirements and must conform to guidelines on Good Clinical Practice.

All Patient Information Sheets & Informed Consent Forms will be version controlled and dated and this information will always be stated in any communication with ethics committees

13. RESEARCH GOVERNANCE

13.1. Institution and Investigator Selection

Chief Investigator – The Chief Investigator will have overall responsibility for the design, co-ordination and management of the study. These include:

- Trial authorisation including responsibility for the protocol and obtaining approvals

- Ensuring that the trial is conducted according to Good Clinical Practice (GCP)

13.2. Trial Organisation

Sponsor – PHS will act as study sponsor. Central study co-ordination, data collection, monitoring and organisation of the data for the statistical analyses will be undertaken by SCTRU, which has processes in place to ensure that the study will not open to recruitment until appropriate approvals and authorisations have been obtained from the independent research ethics committee, and NHS Research and Development departments.

Clinical Trials Unit – The Sponsor has delegated the responsibility for overall project management, data management and monitoring to Scottish Clinical Trials Research Unit, Public Health Scotland. Responsibilities include:

a. Assistance with completion of the IRAS form and REC communication
b. Production of trial specific documentation (i.e. CRFs)
c. Facilitating set up of trial centres
d. Data management
e. Financial Management
f. Monitoring

Statistical Analysis

The final analysis will be carried out once the last patient has been reviewed at the first post-surgery follow up outpatient appointment, and all data deemed 'cleaned' and the database is locked.

Local Project Teams – These will consist of Urological Surgeons and/or Oncologists (responsible for introducing the patient to the study and ensuring eligibility and consent), Research Nurse (responsible for patient recruitment, obtaining consent and co-ordination of all aspects of data collection), Pathologists (responsible for tissue sample analysis), Radiologists and Radiographers (responsible for completing MRI and CT scans to local standard of care protocol). Investigators at the participating centres are responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), the trial agreement and Good Clinical Practice.

Trial Steering Committee (TSC) – The Trial Steering Committee including members of the research team and an independent Chair, will be responsible for the progress and conduct of the study to provide overall supervision of the trial, in particular; trial progress, adherence to protocol, patient safety, and consideration of new information. The committee will meet after the first 30 patients have been recruited then again once recruitment has been completed. Additional meetings will be convened if required. The meetings of the committee will be coordinated to follow on from the DMC meetings.

Trial Management Group (TMG) – A Trial Management Group (TMG) will meet at month three and thereafter at 6 monthly intervals, with additional meetings if deemed necessary.

Data Monitoring Committee (DMC) – A Data Monitoring Committee will meet after 30 patients have been recruited or in the sixth month of the study, whichever comes first. The Data Monitoring Committee will then meet six monthly to review all data. Once all data have been collected, the DMC will meet every three months (or as necessary) to assess model performance

14. FINANCING AND INSURANCE

This study has been developed through multi-centre cross-disciplinary efforts among the CRUK Cancer Imaging Centres Network in collaboration with the study CI, and is funded by CRUK. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

15. PUBLICATION POLICY

All presentations and publications relating to the trial must be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial Management Group representatives from SCTRU and high accruing clinicians. The trials offices and all participating Centers and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

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Appendix 1a – Investigator Statement (SCTRU Copy)

PANORAMA Trial

Analysis of PSMA expression in prostate cancer and its relationship with the presence of nodal metastases

Principal Investigator Declaration

I acknowledge receipt of version 4.0 date 22nd September 2021 of the PSMA Imaging trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please return this copy to: PANORAMA Trial Coordinator
Scottish Clinical Trials Research Unit,
(Partner in CaCTUS - Cancer Clinical Trials Unit Scotland),
Gyle Square,
Area 143A
1 South Gyle Crescent,
Edinburgh,
EH12 9EB

Appendix 1b – Investigator Statement (Investigator Copy)

PANORAMA Trial

Analysis of PSMA expression in prostate cancer and its relationship with the presence of nodal metastases

Principal Investigator Declaration

I acknowledge receipt of version 4.0 date 22nd September 2021 of the PANORAMA trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please retain this copy and file in Investigator Site File.

Appendix 2– The Principles of ICH Good Clinical Practice

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

    This principle applies to all records referenced in this guideline, irrespective of the type of media used.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

    Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.