A phase II/III trial of Primary radiothErapy for Androgen sensitive pRostate cancer patients with Lymph nodeS

FINAL PROTOCOL
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Funders:	Cancer Research UK
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

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The PEARLS study has been approved by
Cancer Research UK's Clinical Research Committee (CRC) and is part of the
National Institute for Health Research Clinical Research Network Trial Portfolio

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Dr Julia Murray (Chief Investigator)		24.05.2022
Professor Emma Hall (ICR-CTSU Scientific Lead)		24.05.2022

This protocol describes the PEARLS trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
Version 1.0 dated 07.01.21	Original approved version
Version 2.0 dated 06.07.2021	ISRCTN/REC reference added. Correction of typographical errors. Increase in amount of blood needed for Immune Cell Repertoire sub-study. Additional eligibility required for PSMA-PET sub-study.
Version 3.0 dated 24.05.2022	PSMA PET-CT and/or PSMA PET-MRI acceptable added to the inclusion criteria. Clarification pelvic lymph node cohort criteria.

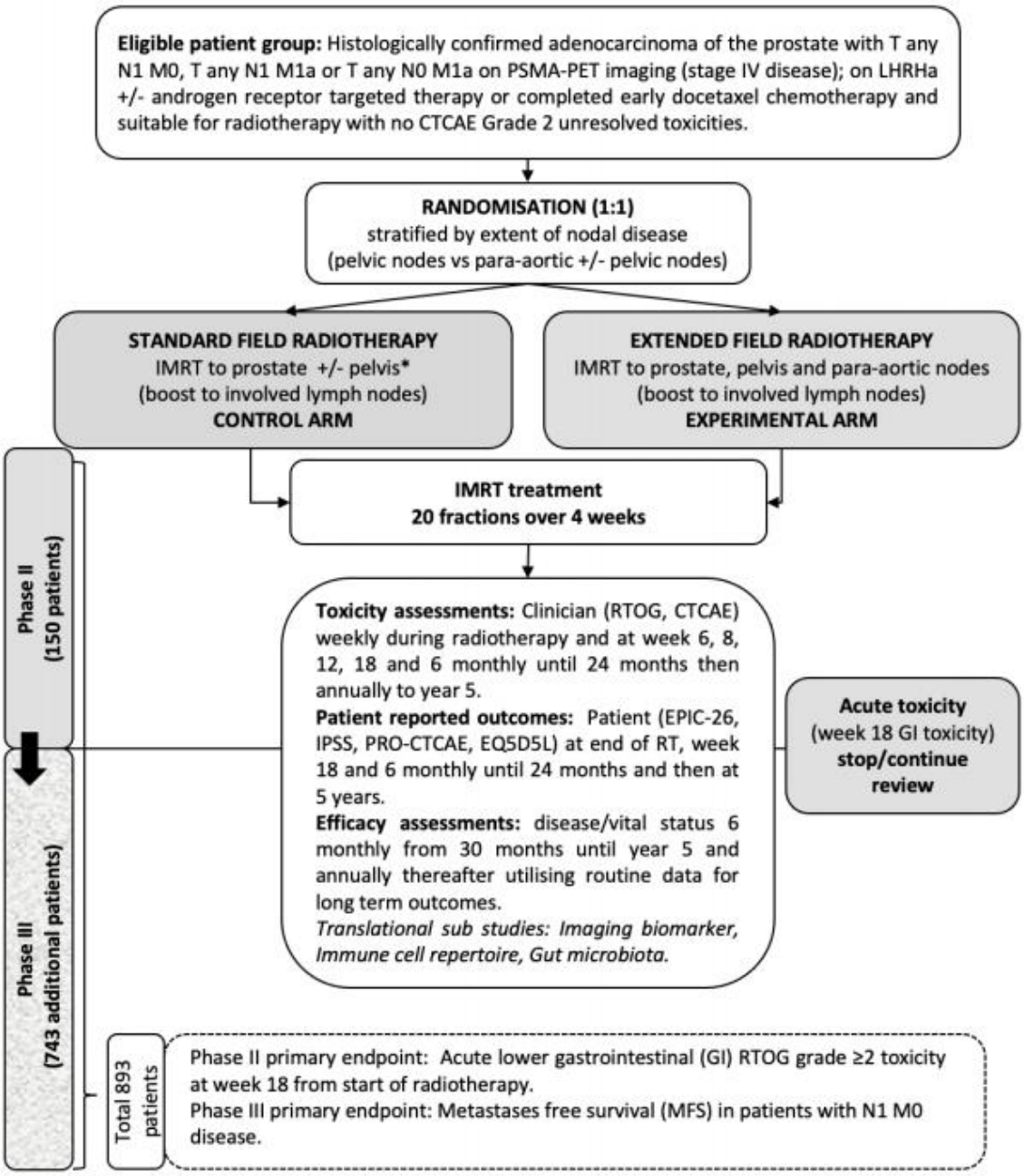
CONTENTS

PEARLS TRIAL SUMMARY

PROTOCOL TITLE	PEARLS: A phase II/III trial of Primary radiothErapy for Androgen sensitive pRostate cancer patients with Lymph nodeS
TRIAL POPULATION	Men receiving radical radiotherapy for node positive prostate cancer.
TARGET DISEASE	Histologically confirmed adenocarcinoma of the prostate with either • any T stage, N1, M0 or • any T stage, N1, M1a* or • any T stage, N0, M1a* confirmed on PSMA PET-CT imaging (stage IV disease). *limited to para-aortic region, defined as below the level of the renal vessels (L1/L2 vertebral interspace).
TRIAL OBJECTIVES	Phase II: To determine whether moderately fractionated extended field intensity modulated radiotherapy (IMRT) is safe in node positive prostate cancer. Phase III: To determine whether extended field IMRT improves metastasis-free survival (MFS) compared to standard field IMRT in patients with N1 M0 disease.
TRIAL DESIGN	Multi-stage randomised controlled trial.
RECRUITMENT TARGET	893 (150 phase II, 743 phase III)
TRIAL TREATMENT	Participants will be stratified by extent of lymph node disease into two cohorts: pelvic nodes or para-aortic +/- pelvic nodes and randomised to receive either: • Control arm – **standard field IMRT**: 60 gray (Gy) to the prostate (and 44Gy to the pelvis with integrated boost of 51Gy to the involved lymph nodes in 20 fractions for patients with pelvic-node disease only). • Experimental arm – **extended field IMRT**: 60Gy to prostate and 44Gy to pelvis and para-aortic region with integrated boost of 51Gy to the involved lymph nodes in 20 fractions.
PRIMARY ENDPOINT	Phase II: Acute lower gastrointestinal (GI) RTOG grade ≥2 toxicity at week 18 from start of radiotherapy. Phase III: Metastasis-free survival (MFS) in patients with N1 M0 disease.
SECONDARY ENDPOINTS	Phase II • Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC) up to 18 week follow up. • Ability to deliver 44Gy in 20 fractions to the pelvic and para-aortic lymph nodes with an integrated boost to the involved lymph nodes of 51Gy in 20 fractions within organ at risk dose constraints using the varying radiotherapy planning techniques and delivery systems at participating centres. • Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy and week 18 follow-up and month 6, 12, 18, 24. • Late RTOG and CTCAE v5 GI, GU at 6, 12, 18 and 24 months. Phase III

	• Acute toxicity RTOG, CTCAE v5 GI, GU, FBC at 18 week follow up. • Late RTOG and CTCAE v5 GI, GU, FBC at 6, 12, 18 and 24 months and then annually for 5 years (excluding FBC after 24 months). • Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy, week 18, and month 6, 12, 18, 24 and 60. • Time to biochemical progression (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment). • Time to and pattern of radiographic progression. • Failure-free survival (FFS). • Overall survival.
EXPLORATORY ENDPOINTS	• Out of radiotherapy field MFS (para-aortic cohort only). • Time to first symptomatic skeletal events. • Time to castration resistance. • Dosimetric and volumetric assessment of prostate, seminal vesicles, lymph nodes and organs at risk.
TRANSLATIONAL SUB-STUDIES (optional)	<u>Imaging biomarker</u> - participants will be asked to have an additional PSMA PET-CT scan at 6 months and at recurrence. <u>Immune cell repertoire</u> – participants will be asked to provide blood samples at baseline, week 2 and week 4 of radiotherapy treatment and then after radiotherapy treatment at week 18, month 6 and month 12. They will also be asked to donate their archival diagnostic tissue. <u>Gut microbiota</u> – participants will be asked to donate stool samples at baseline, at end of treatment and then following treatment at week 12, month 6, 12 and 24. Full details of the translational studies are given in section 19.
FOLLOW UP	Participants will be followed up at weeks 6, 8, 12, 18 and 6 monthly until year 5 from the start of radiotherapy. Long-term data capture will be pursued through routine data sources.

TRIAL SCHEMA



* Standard field size in the control group is defined by extent of nodal disease: participants with pelvic lymph node disease receive IMRT to the prostate + pelvic lymph nodes; participants with para-aortic node disease receive IMRT to the prostate

1. INTRODUCTION

1.1. Background

1.1.1. *Lymph node positive prostate cancer*

Prostate cancer is the most common male cancer in the United Kingdom with around 47,000 men diagnosed each year [1]. Stage IV prostate cancer includes patients whose cancer has spread to regional lymph nodes (N1) or to non-regional or distant lymph nodes (M1a), or to the bone (M1b) or visceral sites (M1c). In 2016, around 22% of patients diagnosed with prostate cancer in England presented with Stage IV disease [1]. In 2017, 1,973 prostate cancer patients in the UK were diagnosed with N1 disease [2].

According to the UICC 8th edition [3] and AJCC 8th edition cancer staging manual N1 disease is classified as metastases in regional lymph nodes. The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic lymph nodes below the bifurcation of the common iliac arteries. They include the following groups: pelvic, hypogastric, obturator, iliac and sacral [4].

There is a lack of prospective data guiding treatment decisions in patients presenting with node positive (N1 and M1a) prostate cancer. Historically, patients presenting with de novo node positive prostate cancer have not been treated with curative intent. However, they are likely to represent a favourable subgroup within the metastatic cohort who may be curable with aggressive multimodality treatment [5].

1.1.2. *Is there a role for extended field radiotherapy?*

For a long time, patients with pathologically-involved lymph nodes at presentation were considered to harbour a systemic disease and thus palliative androgen deprivation therapy (ADT) was considered as the treatment of choice. More recent randomised phase III data have shown a significant failure-free survival benefit by adding docetaxel or abiraterone to ADT [6,7]. However, several reports have challenged the notion that pelvic lymph node involvement is always a systemic disease by demonstrating a benefit from maximizing local control with radical surgery and adjuvant radiotherapy [8] or ADT and radiotherapy [9].

Data suggest disease within the para-aortic region due to ascending prostate cancer lymphatic spread from the pelvis into the retroperitoneum in about 75% of cases with pelvic lymph node disease [10]. Data from a single institution series in treated lymph node positive (pN1) patients showed that 24/69 patients had clinical relapse with a median follow up of 60 months. Of these, the para-aortic region was a prevalent position for clinical relapse (6/24 (25%) patients), with no patients having a pelvic lymph node relapse [11]. Therefore, new strategies to further enhance locoregional control, while maintaining an acceptable level of toxicity are possible tools to improve cure rates, as locoregional relapse is linked to metastatic progression [12].

There is currently a non-randomised phase II trial (NCT03079323; n=132) recruiting in Belgium evaluating elective para-aortic radiotherapy for patients who on pelvic lymph node dissection were found to have involved lymph nodes [13], but to our knowledge there are no randomised trials addressing this question.

Extrapolation from non-randomised data of STAMPEDE [6], where 58/71 (82%) N1 patients received radiotherapy to both prostate and pelvis, but not para-aortic nodes, produced evidence of a favourable effect of radiotherapy on failure-free survival (Hazard ratio 0.48; 95% confidence interval: 0.29-0.79) and this forms the basis for one of our hypotheses. We hypothesise that encompassing all radiographically-identified nodal disease within the para-aortic region will also have a favourable effect on metastasis-free survival (MFS). Additionally, ten-year outcomes for pathologic node-positive patients treated in RTOG 75-06, which included prostate, pelvic and para-aortic radiotherapy reported a small fraction (7%) of node positive patients at that time with no evidence of disease [14]. This study was performed in the era before prostate specific antigen (PSA) testing and cross-sectional imaging. Reported toxicity of extended field radiation therapy with non-conformal radiotherapy techniques within RTOG 75-06 [15] showed that 31% of

268 patients had some form of adverse treatment effects, with the majority (over 80%) being mild-moderate (grade 1-2) events. Three patients had complications requiring surgical intervention.

The rationale for including patients with pelvic and/or para-aortic lymphadenopathy is that the experimental radiotherapy field will be the same for both patient groups. There will be a smaller proportion of patients identified with para-aortic +/- pelvic lymphadenopathy relative to those with pelvic lymphadenopathy alone. Nevertheless, this patient group needs randomised evidence to determine best clinical practice and inclusion of the para-aortic nodal group allows added value in an efficient manner [16], for a patient population unlikely to ever have a trial of their own.

We hypothesise that prostate, pelvic, and para-aortic extended field radiotherapy will be safe and tolerable and that this management strategy could offer some node-positive prostate cancer patients a curative treatment and reduce the development of distant metastasis and postpone the time to re-initiation of ADT.

1.1.3. *Why use molecular imaging?*

Patients entering PEARLS will be node-positive with radiologically-defined lymph node disease on molecular (PSMA PET-CT) imaging. Uptake of molecular imaging in recent years outside of the UK has been characterised by early and frequent use outside of clinical trials with lack of prospective evaluation [17]. In the UK, we have an opportunity to prospectively embed these imaging modalities into therapeutic studies to fully quantify their impact [18]. In the proPSMA study, 152 men were randomly assigned to conventional imaging with CT and bone scan and 150 to PSMA PET-CT [19]. This multicentre study has provided evidence that PSMA PET-CT has better accuracy, with consequent management change, fewer equivocal results, and lower radiation exposure compared with imaging using CT and bone scan in men with newly diagnosed prostate cancer. The consequence of more sensitive imaging techniques has seen a change in planned management from that determined by conventional imaging, but we do not know how this impacts on patient outcome. In a series of 108 patients with intermediate or high risk prostate cancer referred for primary staging with PSMA PET-CT, there was a change in planned management due to the PSMA PET-CT findings for 21% of patients, as additional lymph nodes and bone/visceral metastases were detected in 25% and 6% of patients, respectively [20]. Therefore, we expect involved lymph node prostate cancer patients to be more prevalent with the use of molecular imaging. The PEARLS trial will start to address the currently unanswered questions that will be most relevant with the increasing use of more sensitive imaging protocols.

1.1.4. *Can imaging biomarkers support the evaluation of treatment response?*

Assessing therapeutic responses in prostate cancer is a complex issue. Traditionally, the effects of local therapies have been evaluated by MRI, while systemic treatments are evaluated by CT and bone scan. However, these have several limitations with low sensitivity of CT for normal sized lymph nodes and bone lesions. The increasing availability of new imaging techniques and modalities with enhanced diagnostic sensitivity has caused us to question whether molecular imaging markers could better evaluate response and resistance. PSMA PET-CT is currently seen to be one of the most sensitive prostate cancer PET tracers available. A small patient cohort presented in abstract form has shown a strong correlation with complete response on PSMA PET-CT and PSA<0.2ng/ml in hormone sensitive metastatic prostate cancer patients who received upfront chemo-hormonal therapy [21]. As all patients will have diagnostic molecular imaging the PEARLS study provides a framework for assessment of sequential molecular imaging as an intermediate endpoint or biomarker of response in a randomised controlled trial setting.

1.1.5. *Can radiation field size influence the immune cell repertoire?*

Radiotherapy can kill cancer cells through direct and indirect effects. The immune system is increasingly recognised to be important for radiation-induced cell death [22]. The balance between immune-stimulating and immunosuppressive consequences of radiation in a clinical context is not well understood. Historical

studies indicate that radiotherapy has substantial lympho-depleting effects that can last for several months after treatment [23,24]. To our knowledge, the impact of treatment with different sized pelvic radiotherapy fields on the circulating immune cell repertoire has not been investigated. A key current question is whether irradiation of tumour-draining loco-regional lymph nodes compromises the immune-stimulating aspects of radiotherapy treatment. Lymphocytes are highly radiosensitive and we hypothesize that irradiation to the pelvic and para-aortic lymph nodes has immune-depleting consequences. This is because radiotherapy treatment to the pelvic and/or para-aortic lymph nodes encompasses regions containing considerable circulating blood and the pelvic bone marrow, all of which may contribute to immune depletion. With the different field sizes being used, PEARLS provides a unique opportunity to explore the relationship between radiotherapy field size and immune cell repertoire within a single study. In addition, a better understanding of the biology of the immune response in patients being treated with combined radiotherapy and systemic treatment will help identify clinically relevant biomarkers for testing in larger scale prospective studies.

1.1.6. *Does the gut microbiota associate with clinical outcomes of radiotherapy for node positive prostate cancer?*

There is incontrovertible evidence demonstrating that the intestinal microbiota has a profound impact on the host's phenotype. However, there is currently a paucity of data on the potential impact of the microbiota on the outcomes of radiation therapy. Radiation is known to alter the microbiota and there is some evidence from small studies that radiotherapy-associated toxicity can be predetermined based on gut microbiota profile [25]. We have recently conducted a pilot study showing that specific patterns of the microbiota may associate with the development of side-effects, where sequentially collected samples provided the most meaningful results [26]. Moreover, there is growing evidence that the microbiota associates and may predict the outcomes of cancer therapies, including both immunotherapy and cytotoxic therapies [27,28]. Due to the design of PEARLS, with three different radiation field sizes but the same fractionation and dose, a longitudinal evaluation of gut microbiota in patients with acute and late toxicity may lead to novel and inexpensive ways of predicting which patients will experience long term or late side effects, one of the NCRI UK Top 10 living with and beyond cancer research priorities. Moreover, exploratory analyses will allow for unique insights into associations of the microbiota with oncological outcomes. Together, these novel data may allow for further personalisation of treatment and improved quality of life of patients receiving treatment for node positive prostate cancer.

1.2. Known Risks and Benefits of PEARLS

1.2.1. *Potential benefits*

The anticipated benefits for participants include a reduction in nodal recurrences and/or development of metastases hence delaying or negating the need for further systemic therapy with its associated side-effects. Furthermore, quality of life may be maintained and/or improved and additionally, overall survival could also be improved.

1.2.2. *Potential risks*

Extended field radiotherapy may have an increased risk of side effects (loose motions and diarrhoea), because more bowel will be exposed to radiotherapy compared to prostate/pelvic node radiotherapy. Treating larger areas of the body with radiotherapy can have more side effects.

Some participating centres will have limited experience of delivering pelvic and para-aortic lymph node radiotherapy, with an integrated boost to the involved lymph nodes prior to opening PEARLS. However, centres' delivery of treatment techniques will undergo Radiotherapy Trials Quality Assurance (RTTQA) accreditation prior to opening and throughout the trial's duration to maintain a quality standard in accordance with the PEARLS radiotherapy planning and delivery guidelines. It is anticipated that ongoing

central monitoring of safety data throughout the trial will mitigate any potential risks to patients, who may benefit from improvements in disease control by participation in PEARLS.

1.3. Description of Population

PEARLS will recruit newly-diagnosed patients with lymph node positive prostate cancer on PSMA PET-CT who opt to have radiotherapy.

Two cohorts of patients will be recruited: those with lymph node disease limited to the pelvic nodes and those with lymph node disease in the para-aortic region. There is international variation in the classification of regional nodes, with the UICC 8th edition stating the regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. In the updated NRG Oncology international consensus atlas on pelvic lymph node volumes, the superior border is at the aortic bifurcation [29].

For the purposes of PEARLS:

- Patients who have PSMA avid lymph nodes at or inferior to the L4/L5 interspace will be included in the pelvic lymph node cohort. This will encompass the nodes of the true pelvis, which are the pelvic nodes below the bifurcation of the common iliac and the bilateral distal common iliac nodes.
- Patient with PSMA avid lymph nodes superior to the L4/L5 interspace up to the level of renal veins (usually L1/L2 interspace) will be included in the para-aortic lymph node cohort.

1.4. Study Rationale

PEARLS investigates an "orphan" prostate cancer patient group, for which there have been no prospective randomised trials evaluating the effect of radiotherapy. This may, in part, be due to the limited diagnostic performance of conventional imaging. However, with molecular imaging providing a higher detection rate for lymph node disease, we need to now determine the optimal radiotherapy treatment strategy for this patient group. PEARLS complements the completed (CHHiP), currently recruiting (PACE and PIVOTALboost) and soon to open (STAMPEDE Arm M) prostate cancer radiotherapy trials in the UK. PEARLS completes the comprehensive trial portfolio which ensures every newly diagnosed prostate cancer patient in the UK can be offered a UK-led radiotherapy trial.

2. TRIAL OBJECTIVES

2.1. Primary Objectives

Phase II: To determine whether moderately fractionated extended field intensity modulated radiotherapy (IMRT) is safe in patients diagnosed on functional imaging with pelvic and/or para-aortic lymph node positive prostate cancer.

Phase III: To determine whether extended field IMRT improves metastasis-free survival when compared to standard field radiotherapy in patients with pelvic lymph node only disease.

2.2. Secondary Objectives

Secondary objectives are to assess (and in phase III to compare between extended field and standard field groups):

Phase II

- Acute bowel, bladder and bone marrow toxicity of extended field prostate radiotherapy up to 18 weeks.
- Feasibility of delivery and compliance of randomised treatments at participating centres.

- Patient reported outcomes at 18 weeks.

Phase III

- Acute and late toxicity.
- Patient reported outcomes.
- Time to biochemical progression.
- Time to and pattern of radiographic progression.
- Failure-free survival.
- Overall survival.

2.3. Exploratory Objectives

Exploratory objectives include to assess:

- Out of radiotherapy field MFS.
- Time to symptomatic skeletal event.
- Time to castration resistance.
- Dosimetry of prostate, seminal vesicles, lymph nodes and organs at risk.

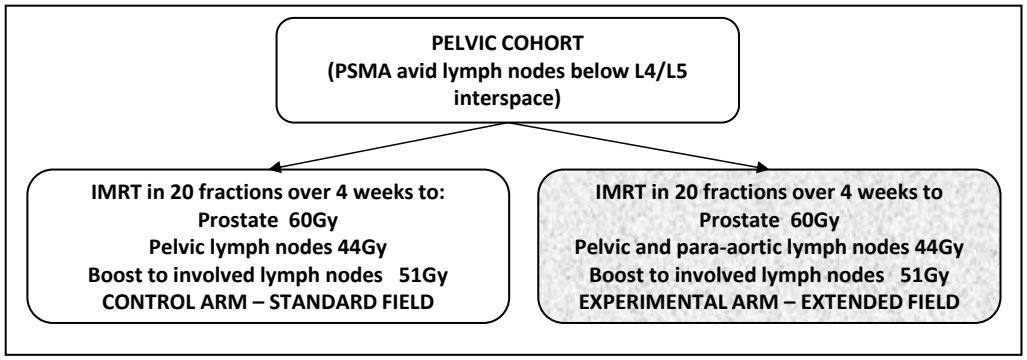
3. TRIAL DESIGN

PEARLS is a multi-stage randomised phase II/III study recruiting patients with lymph node positive prostate cancer.

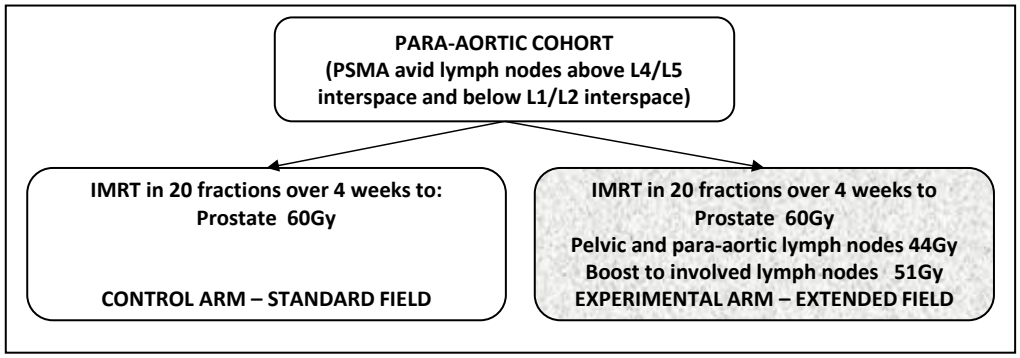
At entry into the study, all patients will be receiving LHRHa (either LHRH agonist or antagonist) +/- androgen receptor targeted therapy or docetaxel chemotherapy in accordance with standard clinical practice at their centre.

All randomised patients will receive IMRT given in 20 fractions over 4 weeks.

Pelvic lymph node cohort randomisation



Para-aortic lymph node cohort randomisation



Radiotherapy field size is determined by minimisation (1:1 allocation ratio).

Patients will be assessed at 6, 8, 12 and 18 weeks and then 6 monthly until year 5 from start of radiotherapy. Long-term data capture will be pursued through routine data sources.

4. STUDY ENDPOINTS

4.1. Primary Endpoints

Phase II: Acute lower gastrointestinal (GI) RTOG grade≥2 toxicity at week 18 from start of radiotherapy.

Phase III: Metastasis-free survival (MFS) defined as the time (in days) from randomisation to the first detection of distant metastasis on imaging or death from any cause, whichever occurs first. Distant metastasis defined as extra-pelvic lymphadenopathy, bone and visceral metastases.

4.2. Secondary Endpoints

Phase II

- Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC) up to 18 week follow up.
- Ability to deliver 44Gy in 20 fractions to the pelvic and para-aortic lymph nodes with an integrated boost to the involved lymph nodes of 51Gy in 20 fractions within organ at risk dose constraints using the varying radiotherapy planning techniques and delivery systems at participating centres.
- Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy and week 18 follow up.
- Late RTOG and CTCAE v5 GI, GU at 6, 12, 18 and 24 months.

Phase III

- Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC).
- Late RTOG and CTCAE v5 GI, GU, blood/bone marrow (FBC) toxicity at 6, 12, 18 and 24 months and then annually for 5 years (excluding blood/bone marrow (FBC) toxicity after 24 months).
- Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy, week 18, month 6, 12, 18, 24 and 60.
- Time to biochemical progression (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment).
- Time to and pattern of radiographic progression.
- Failure-free survival.
- Overall survival.

4.3. Exploratory Endpoints

- Out of radiotherapy field MFS.
- Time to symptomatic skeletal event.
- Time to castration resistance.
- Dosimetric and volumetric assessment of prostate, seminal vesicles, lymph nodes and organs at risk.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 893 participants in total (150 participants in phase II, 743 participants in phase III).

5.2. Source of Participants

Participants will be recruited from participating sites in the UK. Patients will be approached about participation in PEARLS if they are considered (e.g. at multi-disciplinary team meetings) to be fit for radical radiotherapy and fulfil the eligibility criteria. International recruitment from quality assured sites outside the UK may be considered by the Trial Management Group subject to Sponsor and ethics approval and adequate funding.

5.3. Inclusion Criteria

1. Histologically confirmed adenocarcinoma of the prostate (histological confirmation can be based on tissue taken at any time, but a re-biopsy should be considered if the biopsy is more than 12 months old).
2. Any T stage, N1, M0; any T stage, N1, M1a (limited to para-aortic region*); or any T stage, N0, M1a (limited to para-aortic region*) on PSMA PET** imaging done at time of diagnostic staging (stage IV disease).
3. Age at least 18 years.
4. Patient on LHRH analogue therapy.
5. Adequate renal and bone marrow function (clinical decision[+])
6. WHO Performance status of 0-2.
7. Written informed consent.

*defined as below the level of the renal vessels (L1/L2 vertebral interspace).

**PSMA PET-CT and/or PSMA PET-MRI acceptable

[+]*potential parameters:*

Haemoglobin >90, independent of transfusion and/or growth factors.
Platelet count >100, independent of transfusion and/or growth factors.
Creatinine Clearance (CrCl) >30ml/min estimated by Cockcroft-Gault (please use actual weight for calculation unless greater than 30% above ideal body weight then use the adjusted body weight).

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

5.4. Exclusion Criteria

1. Prior radiotherapy to the prostate or pelvis; prior bilateral orchiectomy; radical prostatectomy.

2. For those patients who have received docetaxel chemotherapy or are receiving androgen receptor targeted therapy, there should be no ongoing CTCAE grade 2 or greater GI toxicity relating to this systemic therapy.
3. Medical conditions (non-prostate cancer related) expected to limit life expectancy to <5 years.
4. Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts and would make pelvic node planning more difficult.
5. Medical conditions likely to make radiotherapy inadvisable e.g. inflammatory bowel disease, intractable urinary symptoms, previous colorectal surgery.
6. Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin or small renal masses under surveillance), or if previous malignancy is expected to significantly compromise 5-year survival.
7. Any other contraindication to external beam radiotherapy to the para-aortic and/or pelvic region.

Additional inclusion criteria for patients considering the optional PSMA PET-CT sub-study is that on the diagnostic PSMA PET-CT staging scan they need to have 3 or more PSMA avid lymph nodes.

5.5. Life Style Guidelines

It is highly unlikely that the patient population included in PEARLS will be at risk of fathering a child. However, if this is a possibility for any individual patient, this and sperm banking should be discussed and the patient should be advised to use barrier protection and avoid conception for 12 months after treatment.

Patients within PEARLS will be on long-term androgen deprivation therapy (as part of standard care), therefore bone health needs to be addressed in accordance with local guidelines. If there are no local guidelines, recommendation would be for patients to be prescribed, if no contraindication, alendronic acid 70mg or risedronate 35mg weekly, plus Vitamin D (800 IU/day of cholecalciferol). Calcium supplements are recommended if dietary calcium uptake is inadequate.

6. SCREENING

6.1. Screening Log

All participating sites will be required to keep a log of patients that are potentially eligible for this study i.e. those with node positive prostate cancer on PSMA PET-CT. The information collected on the log will include:

- Date patient identified.
- Screening outcome (patient ineligible/eligible, approached/not approached, accepted/declined participation).
- Reasons for ineligibility, not approaching and declining participation (if available), where possible this should include vertebral level of most superior positive lymph node.
- Trial ID (if applicable).

This information will be used by the Trial Management Group (TMG) to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU at this stage.

6.2. Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with participation. Patients should be given the current ethics approved PEARLS patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

No protocol required assessments should be conducted until the PEARLS consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Patients who consent to PEARLS will be asked to consent to participate in the Translational sub-studies (see section 19 for further details). Patients should be made aware that participation in the Translational sub-studies is entirely voluntary. Refusal to participate in the Translational sub-studies will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff.

6.3. Participation in other Clinical Trials

Participation in other interventional clinical trials will be considered on a case by case basis by the Trial Management Group.

7. RANDOMISATION

All patients must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by emailing ICR-CTSU on:
Randomisation-icrctsu@icr.ac.uk
The randomisation email account is monitored 09.00-17.00 (UK time) Monday to Friday

Radiotherapy treatment should commence as soon as possible and ideally within 8 weeks after randomisation. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant and person registering patient.
- Confirmation that patient has given written informed consent for trial and for any sub-studies.
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist.
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants).
- Date of PSMA PET-CT scan.
- Most superior level of lymph node involvement on PSMA PET-CT.
- Cohort chosen by clinical team (pelvic lymph node cohort **OR** para-aortic lymph node cohort*).
- Prostate cancer related systemic therapies received.

* Patients who have PSMA avid lymph nodes at or inferior to the L4/L5 interspace will be included in the pelvic lymph node cohort. This will encompass the nodes of the true pelvis, which are the pelvic nodes below the bifurcation of the common iliac and the bilateral distal common iliac nodes; patients with PSMA avid lymph nodes superior to the L4/L5 interspace up to the level of renal veins (usually L1/L2 interspace) will be included in the para-aortic lymph node cohort.

The patient will be assigned a unique randomisation number (Trial ID) and treatment allocation will be confirmed (see section 9).

ICR-CTSU will send confirmation to the data management contact at the recruiting site to confirm a patient's entry into the trial.

Radiotherapy treatment should commence as soon as possible, though timing is at clinician discretion, but ideally;

- within 8 weeks after randomisation;
- within 3-6 months of starting hormone therapy if no additional systemic therapy prescribed;
- at least 6 weeks, but not more than 18 weeks after the last docetaxel dose if prescribed;
- between cycle 3 to 7 of the androgen receptor targeted therapy.

Patients may have started the LHRHa therapy up to 3 months prior to commencing docetaxel or androgen receptor targeted therapy.

8. TRIAL ASSESSMENTS

8.1. Screening Assessments

The following assessments should be conducted prior to randomisation unless otherwise indicated:

- Complete medical history.
- DRE and physical examination (both only if clinically indicated).
- PSA test prior to the commencement of ADT.
- Diagnostic PSMA PET-CT to be ideally performed prior to starting ADT or within 4 weeks of commencing bicalutamide/LHRHa therapy.
- Full blood count, biochemistry inclusive of urea & electrolytes, liver function tests, bone ± glucose (within 6 weeks prior to randomisation).
- Assessment of performance status, using WHO scale (see Appendix 1).
- Baseline symptoms will be assessed using RTOG bladder and bowel toxicity scoring and Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5 (within 4 weeks prior to randomisation).
- If the patient has consented to the PRO sub study, completion of the following questionnaires (within 4 weeks prior to randomisation):
    - International Prostate Symptom Score (IPSS)
    - Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire
    - Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).
    - EQ-5D.

8.2. Pre-treatment Assessments

The following assessments should be conducted within 14 days prior to or at radiotherapy planning:

- Assessment of pre-treatment symptoms (RTOG, CTCAE v5).
- PSA and testosterone (2- 4 months after starting ADT).
- FBC *(for patients taking part in T-cell – blood sample collection)* sample to be taken at same time as sub-study blood.

If a patient has a DMSA scan performed because it is clinically indicated, please complete the relevant information in the Case Report Form (CRF).

8.3. On-treatment Assessments

- Acute toxicity assessment (RTOG, CTCAE v5) weekly during radiotherapy treatment.
- Bloods – FBC *(for patients taking part in T-cell – blood sample collection)* sample to be taken at same time as sub-study blood – at end of week 2.
- Bloods – FBC, biochemistry (renal profile ONLY) - at end of week 4.
- Quality of life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L] - at end of week 4 only.

8.4. Post-radiotherapy treatments

8.4.1. *6, 8 and 12 weeks from first external beam radiotherapy fraction*

- Acute toxicity assessment (RTOG, CTCAE v5).

8.4.2. *18 weeks from first external beam radiotherapy fraction*

- Acute toxicity assessment (RTOG, CTCAE v5).
- Quality of life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L].
- Bloods – FBC, biochemistry (renal profile ONLY).
- Bloods – PSA.

8.4.3. *6, 12, 18, 24, 30, 36, 48, 42 and 60 months (from first radiotherapy fraction)*

- Bloods – FBC, biochemistry (renal profile ONLY) **(at month 6, 18 and 24 only).**
- Bloods – FBC *(for patients taking part in T-cell – blood sample collection)* sample to be taken at same time as sub- study blood – at month 12.
- Bloods – PSA.
- Bloods – Testosterone **(at months 48, 60 only).**
- Toxicity Assessment – RTOG and CTCAE (v5).
- Quality of life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L] **(at month 6, 12, 18, 24, 60 only).**

8.5. Procedure at PSA failure or disease recurrence

At PSA failure (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment) or disease recurrence/progression on imaging, participants should be managed and treated according to the local Principal Investigator's clinical judgement. Testosterone level should be taken at this time to determine level of castration. Staging with PSMA PET-CT is strongly recommended at this time, if not available bone scan, CT scan ± MRI should be considered.

If appropriate and/or the patient is considered for local salvage therapies, local control should be assessed by mpMRI imaging, PSMA PET-CT and/or biopsies.

If the patient is on hormone therapy and/or androgen receptor targeting therapy when there is evidence of PSA failure (with evidence of castrate testosterone level) re-staging is advised before changing therapy.

8.6. Discontinuation from Treatment

Participants may discontinue trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease recurrence or PSA failure.
- Unacceptable toxicity.
- Co-morbidities.

Participants who discontinue treatment should continue to be followed up.

8.7. Discontinuation from Follow-up

If a patient withdraws from further follow-up a change in consent status form should be submitted to ICR-CTSU stating whether the patient simply no longer wishes to attend trial follow up visits or whether the patient has withdrawn consent for any further information to be sent to the ICR-CTSU.

8.8. Schedule of Assessments

[1] FBC ONLY at these time-points for patients taking part in the T-cell blood sample collection.

			During RT Treatment				Follow-up (timed from start of radiotherapy)														
Visit/Assessment	Screening (pre-randomisation)	Pre-treatment	End week 1	End week 2	End week 3	End week 4	Week 6	Week 8	Week 12	Week 18	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 60	Year 6-10	Recurrence
Informed consent	X																				
Histological confirmation of prostate cancer	X																				
Complete history and physical examination (physical examination & DRE if clinically indicated).	X																				
Radiological assessment (PSMA PET-CT +/- multi-parametric MRI scan))	X																				
Bloods – full blood count (FBC)	X	X[1]		X[1]		X				X	X	X[1]	X	X							
Bloods - biochemistry (renal profile only)						X				X	X		X	X							
Bloods – biochemistry (glucose, liver function, bone profile, renal profile)	X																				
Bloods - PSA	X	X								X	X	X	X	X	X	X	X	X	X	X	X
Bloods - testosterone		X																X	X		
Toxicity Assessment – RTOG and CTCAE (v5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Quality of Life questionnaire [PRO CTCAE EPIC-26, IPSS, EQ-5D]	X					X				X	X	X	X	X					X		
Optional sub-studies																					
PSMA PET (26 patients)											X										X
T-cell – blood sample collection (**London centres ONLY** – 30 patients) – 6 timepoints		X		X		X				X	X	X									
T-cell – diagnostic tumour collection		X																			
Gut microbiota - stool sample collection (110 patients) – 6 timepoints		X				X			X		X	X		X							

9. TRIAL TREATMENT

Prior to entry into the study, all participants will receive hormone therapy (ADT) +/- androgen receptor targeted therapy or docetaxel chemotherapy in accordance with standard clinical practice at their centre.

9.1. Randomisation options

All patients will undergo PSMA PET-CT imaging prior to randomisation to determine extent of lymph node disease.

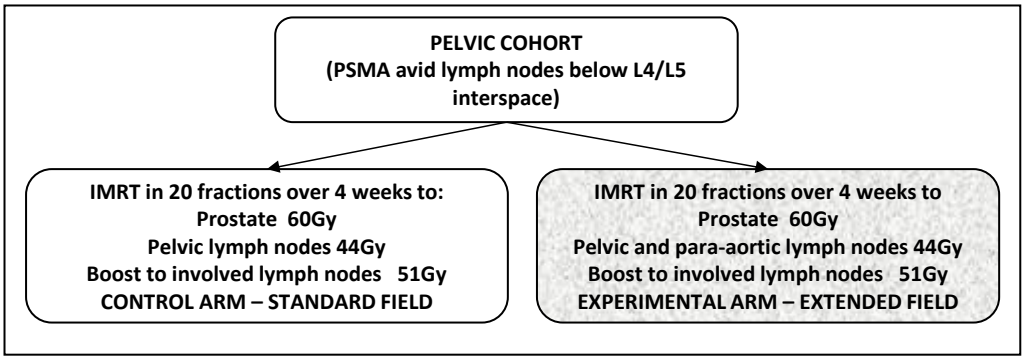
- Patients with lymph-node disease limited to the pelvis will be considered in the *pelvic node cohort*. Patients who have PSMA avid lymph nodes at or inferior to the L4/L5 interspace will be included in the pelvic node cohort. This will encompass the nodes of the true pelvis, which are the pelvic nodes below the bifurcation of the common iliac and the bilateral distal common iliac nodes.

- Patients with lymph node disease extending to the para-aortic nodes (with or without involved pelvic lymph nodes) will be considered in the *para-aortic cohort*. Patients with PSMA avid lymph nodes superior to the L4/L5 interspace up to the level of renal veins (usually L1/L2 interspace) will be included in the para-aortic lymph node cohort.

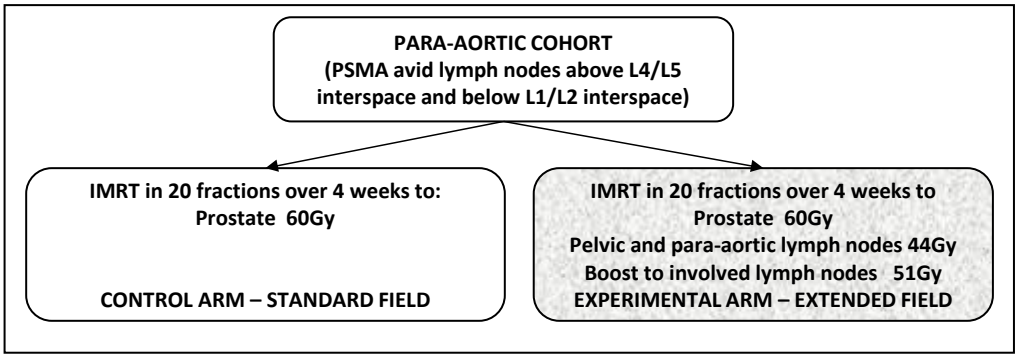
All randomised patients will receive IMRT given in 20 fractions over 4 weeks, to encompass 4 weekends.

Radiotherapy field size is determined by minimisation (1:1 allocation ratio):

Pelvic lymph node cohort randomisation



Para-aortic lymph node cohort randomisation



9.2. Treatment Timelines

Radiotherapy treatment should commence as soon as possible and ideally within 8 weeks after randomisation and ideally within 12-24 weeks of starting hormone therapy if no additional systemic therapy has been prescribed.

Radiotherapy treatment should start at least 6 weeks after the last docetaxel dose, but not more than 18 weeks after the last docetaxel dose. If patients are on androgen receptor targeted therapy, radiotherapy treatment should commence ideally between cycles 3 to 7 of the androgen receptor targeted therapy.

Patients may have started the LHRHa therapy up to 12 weeks prior to commencing docetaxel or androgen receptor targeted therapy.

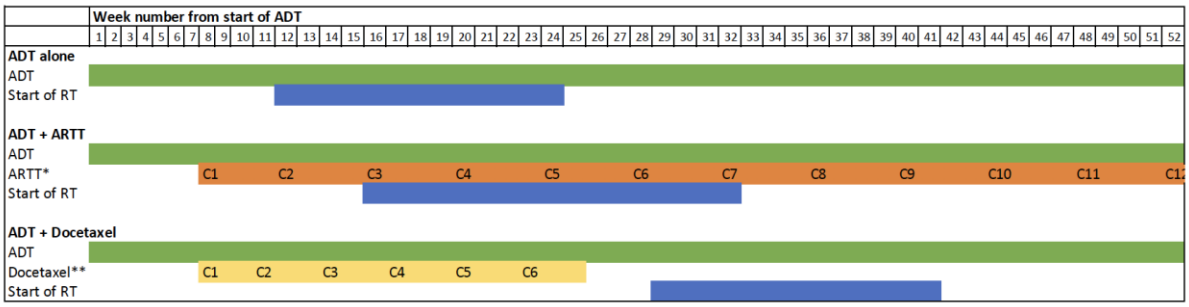


Figure 1: Example of potential treatment timelines. * assumes ARTT commenced 8 weeks from commencement of ADT; ** assumes docetaxel commenced 8 weeks from commencement of ADT and that 6 cycles completed, with no delays.

9.3. Hormone therapy (ADT)

In standard practice, ADT will typically commence after completion of staging investigations. In PEARLS, as PSMA PET-CT scans are used for assessment of disease status, these should wherever possible be arranged prior to commencement of ADT.

LHRH antagonists or LHRH agonists with short-term androgen blockade (i.e. bicalutamide daily or cyproterone acetate given for the initial 1 to 2 weeks to prevent possible 'tumour flare' phenomenon) are usual standard of care. Maximal androgen blockade (bicalutamide and LHRHa therapy) is permitted at clinician discretion. Bicalutamide monotherapy is not permitted.

PEARLS participants will be receiving ADT as part of routine care; therefore drugs will be provided by standard local arrangements.

If the patient is not receiving androgen receptor targeted therapy or docetaxel, radiotherapy planning should ideally take place around 2-6 months after starting ADT so that radiotherapy can start within around 3 to 6 months from the start of ADT.

If the patient is receiving androgen receptor targeted therapy, radiotherapy planning should ideally take place during cycle 2 to cycle 6 for radiotherapy to commence ideally between cycles 3 to 7 of the androgen receptor targeted therapy.

If the patient is receiving docetaxel chemotherapy, radiotherapy planning should ideally take place 1-4 months after the last cycle of docetaxel so that radiotherapy can start a maximum of 12 months from start of ADT.

9.3.1. *Pelvic node cohort*

All participants in the pelvic node cohort (lymph node disease restricted to the pelvic nodes i.e. N1 M0) should receive 2-3 years of ADT in total.

9.3.2. *Para-aortic cohort*

Participants in the para-aortic node cohort (i.e. with nodal disease between L1/L2 interspace and L4/L5 interspace) and allocated prostate radiotherapy (standard field radiotherapy) should receive at least 3 years ADT (indefinite ADT is current standard of care). If participants were to stop ADT at local Principal Investigator's clinical judgement, it is strongly recommended that PSA and testosterone level is subsequently measured at 3 monthly intervals and re-staging advised prior to re-commencing ADT.

Participants in the para-aortic node cohort (i.e. with nodal disease between L1/L2 interspace and L4/L5 interspace) and allocated prostate plus pelvis plus para-aortic region radiotherapy (extended field radiotherapy) should receive 3 years of ADT in total.

9.4. Docetaxel and androgen receptor targeted therapy

Prior to randomisation into PEARLS, patients may have systemic treatment with androgen receptor targeted therapy (e.g. abiraterone, apalutamide, enzalutamide) or docetaxel chemotherapy. This management decision has to be made before randomisation into PEARLS and will be given in accordance with local hospital policy and local funding arrangements.

9.5. Image guided radiotherapy

All patients will receive inverse-planned prostate IMRT delivered in 20 fractions with daily online image-guided radiotherapy (IGRT). Various IMRT delivery techniques are allowed (static field, VMAT, helical tomotherapy, robotic gantry) and all will be referred to as IMRT in the PEARLS Radiotherapy Guidelines unless specifically detailed. At any one participating site the delivery technique should be independent of treatment allocation and is subject to RTTQA approval.

9.6. Radiotherapy Planning and delivery

Radiotherapy planning and outlining should be carried out in accordance with the current version of the PEARLS Radiotherapy treatment planning and delivery guidelines document, available in the PEARLS site investigator file and on request from ICR-CTSU (pearls-icrctsu@icr.ac.uk).

9.7. Treatment Scheduling and Gaps

Treatment can start on any day of the week, except Monday and is given daily, 5 fractions per week; overall duration should be 28-33 days.

A gap of up to 5 days is acceptable in the event of machine service, breakdown or re-planning but further delays should be avoided. Patients should not be started prior to a bank holiday period if this would prolong treatment for more than 7 days. If there is a delay for more than 5 days, please add details including the length of overall treatment time and the reason (radiotherapy toxicity, intercurrent illness, technical issues related to radiotherapy delivery, technical issues related to patient factors e.g. re-planning) on the CRF.

9.8. Supportive Care Guidelines

In the event of patient catheterisation during the course of treatment it is expected that the participant will continue and complete radiotherapy in accordance with their allocated treatment group. As the bladder requires filling prior to treatment delivery, the catheter must be clamped or a flip-valve used.

Participants' symptoms should be managed according to local practice, although the following are suggestions for patient care:

- Slow flow and frequency – tamsulosin or alfuzosin are often helpful.
- Dysuria/frequency – check for evidence of infection and treat if present with appropriate antibiotics, anticholinergics (e.g. oxybutynin, tolterodine, solifenacin), NSAIDs, analgesics.
- Diarrhoea – loperamide or opioid.
- Proctitis – suppository +/- local anaesthetics (e.g. sheriproct, proctosedyl).

9.9. Concomitant Therapy

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication), must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

9.10. Non-permissible Medications/Therapies

Non-permissible concurrent medications/therapies during the radiotherapy include:

- Chemotherapy.
- Radiosensitisers such as methotrexate.

10. RADIOTHERAPY QUALITY ASSURANCE (QA)

PEARLS is an NIHR CRN Portfolio trial and a comprehensive QA programme will therefore be designed and implemented by the Radiotherapy Trials Quality Assurance (RTTQA) Group. This will include pre-trial and on-trial components and full details are provided in the PEARLS Radiotherapy Planning and Delivery Guidelines document. QA will be streamlined for centres that have already completed the QA programme for PIVOTALboost (ISRCTN80146950).

10.1. Pre-trial quality assurance programme

The following will need to be completed by participating centres prior to site activation:

- Facility questionnaire.
- Benchmark outlining case.
- Benchmark planning case.
- Dosimetry audit – centres must have successfully completed a recent external independent audit.

10.2. On-trial quality assurance programme

- Prospective and/or retrospective case reviews.
- Dosimetry site visit (subject to prior RTQA dosimetry accreditation).
- DICOM data collection for all patients.

Further details included in the PEARLS Radiotherapy Guidance document.

11. SAFETY REPORTING

11.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the first study intervention (including fiducial marker insertion) and within 30 days of the last treatment administration and:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- additionally RTOG Grade≥3 acute or late radiation side effects i.e. related to study treatment, occurring within 5 years after radiotherapy treatment will be regarded as an SAE.

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the trial treatment, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Related **Unexpected Serious Adverse** Event
An adverse event that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see section 12.4)

11.2. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of first study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant CRF and submitted to ICR-CTSU.

The severity of AEs should be graded according to the NCI-CTC criteria v5 and RTOG. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

11.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE (except those in section 12.4) that occurs after the first study treatment (including fiducial marker insertion, if applicable) and up to 30 days following the last fraction of radiotherapy must be reported. RTOG grade ≥3 acute or late radiation side effects (except erectile dysfunction) occurring within 5 years after radiotherapy treatment should be reported to ICR-CTSU as described below.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the PEARLS SAE form and emailing to:

The ICR-CTSU safety desk
Email address: sae-icrctsu@icr.ac.uk
For the attention of the PEARLS Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.

11.4. Expected Adverse Events

The following adverse events are considered expected if CTCAE and RTOG grade ≤2 and are exempt from SAE reporting to ICR-CTSU but should be reported using the appropriate CRF:

- Haematuria.
- Dysuria/frequency.

- Nausea/vomiting.
- Prostate spasms or pain.
- Diarrhoea.
- Abdominal pain.
- Urinary tract infection.
- Urinary/clot retention.
- Erectile dysfunction (≤ grade 3).

11.5. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 11.5).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

11.6. Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

11.7. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

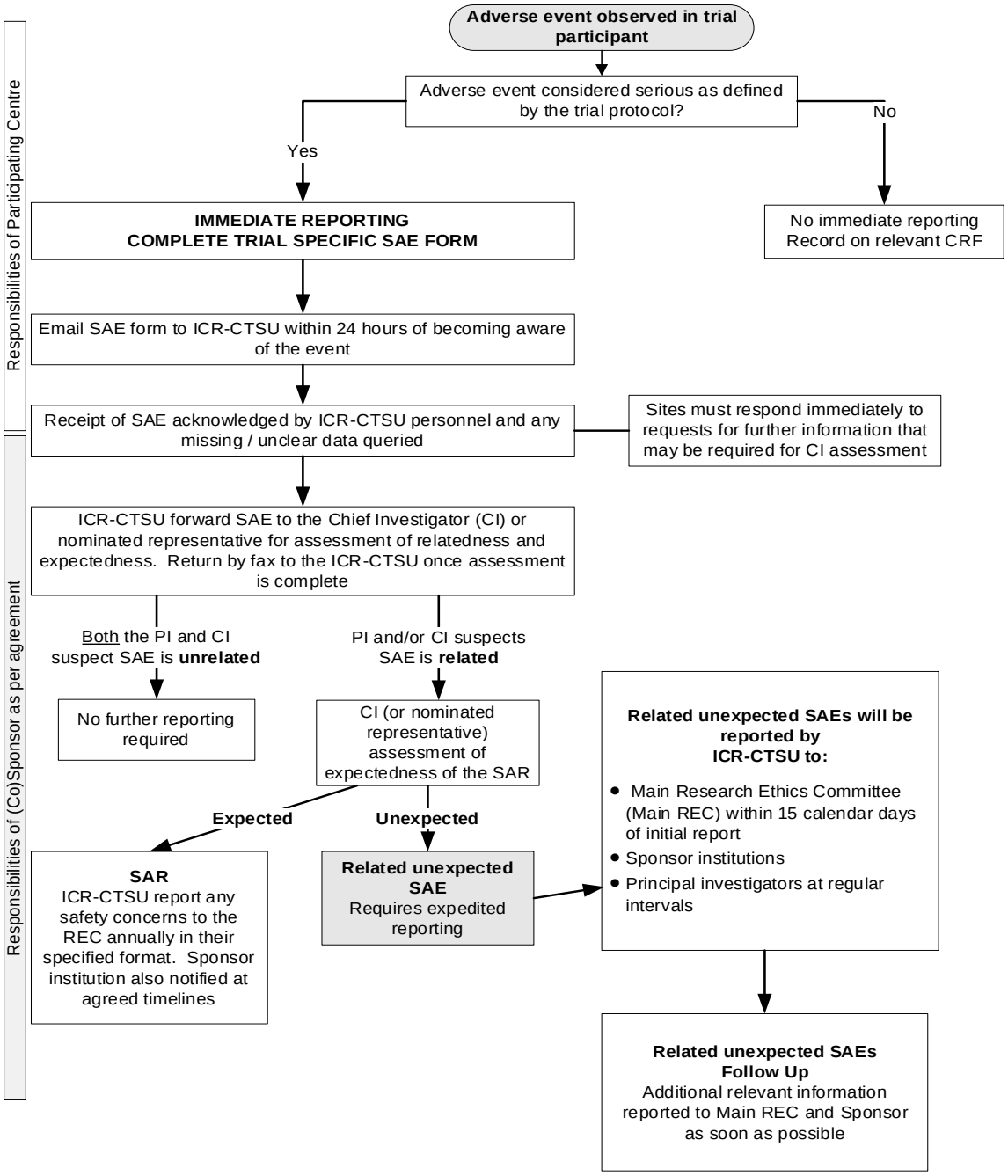
11.8. Annual Safety Reporting

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

11.9. Reporting Pregnancies

If any trial participants' partner becomes pregnant while receiving trial treatment or up to 90 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 2: Flow diagram for SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified above

12. STATISTICAL CONSIDERATIONS

12.1. Statistical Design and Sample Size Justification

PEARLS is a seamless phase II/III trial with separate primary endpoints and sample sizes calculated for each phase. All patients recruited during phase II will contribute to phase III. Recruitment to phase III will continue whilst phase II primary endpoint data mature. On entry to the trial, patients will be stratified by extent of lymph node involvement to give pelvic node and para-aortic node cohorts. Phase II has a toxicity primary endpoint and the principal analysis will combine data from both the pelvic node and para-aortic node cohorts. Phase III is powered to evaluate the primary endpoint of MFS in the pelvic node cohort of patients. It is estimated that the trial will recruit one patient with para-aortic nodal involvement for every four with pelvic only nodal involvement. This estimate is based on a single centre service evaluation (unpublished) and will be monitored throughout the trial.

Phase II

Phase II requires 75 patients to be treated with extended field radiotherapy. With 1:1 treatment allocation ratio the total sample size for phase II is 150 patients. The primary endpoint in phase II is acute lower GI toxicity at 18 weeks from the start of radiotherapy. The RTOG G2+ toxicity-free rate at 18 weeks which if true could imply that the experimental arm does not warrant further investigation is set at 82% i.e. we are looking to rule out a G2+ acute GI toxicity rate of 18% or higher. The RTOG G2+ toxicity-free rate at 18 weeks in the experimental arm is expected to be 92%. Using a Fleming single-stage design (with 5% alpha and 80% power), if at least 68/75 patients receiving extended field IMRT are toxicity-free then this would be considered sufficient to continue to phase III; if 8 or more patients have G2+ GI toxicity at 18 weeks then the toxicity associated with extended field IMRT would be considered too high to continue and the IDMC would be asked to consider whether recruitment should stop or whether amendments to the radiotherapy delivery might be possible to reduce risks to an acceptable level. The phase II stop/continue decision will be based on the combined toxicity experience of both the pelvic node and para-aortic node cohorts as the experimental treatment is the same for both the cohorts. The assessment of toxicity will focus on radiotherapy related events only. The sample size was calculated using the Sample Size Tables for Clinical Studies software.

Phase III

The primary endpoint for phase III is MFS and the time point of primary interest is 5 years. This endpoint was chosen as it is a non-PSA based failure-free survival endpoint and has been found to be predictive of overall survival [30]. The power calculation for phase III is based on the (larger) pelvic node cohort and requires 693 pelvic node patients. It is assumed that the control arm 5-year MFS rate in the pelvic node cohort will be 80%. This is based on extrapolation from two radiotherapy trials [6,7] where patients with known pelvic lymph node disease on conventional imaging were included. The phase III trial has a superiority design and is powered to detect a 7% difference in 5-year MFS from 80% to 87%, corresponding to detecting a hazard ratio of 0.62. This will require a total of 161 events (85% power and a 5% two-sided significance level). The target number of events would be anticipated to accrue in 693 pelvic node patients recruited over 6.5 years of staggered recruitment with a minimum of 5 years follow up on all patients. This assumes that 6% of all patients will be recruited in the first year, 8% in the second year, 12% in the third, 16% in the fourth, 22% in the fifth year, and 36% in the remaining one and a half years. To allow for 3% loss to follow up at the time of the primary endpoint analysis (based on the experience in CHHiP) [31], the target sample size is **714 pelvic node patients** (357 standard field IMRT; 357 extended field IMRT). The sample size is based on the log-rank test using the 'artsurv' command in STATA.

The phase III sample size is driven by the patients (events) required to detect the selected treatment effect in the pelvic node cohort but with concurrent enrolment to the para-aortic node cohort. With the expectation that recruitment of patients with para-aortic disease will be one quarter the rate of patients with pelvic node only disease, we estimate there will be 179 para-aortic patients recruited after 6.5 years giving an estimated **total sample size of 893 patients.**

12.2. Treatment Allocation

Allocation of radiotherapy field size to either standard field IMRT or extended field IMRT uses a 1:1 allocation ratio.

Within each cohort, treatment allocation is by minimisation with a random element. Balancing factors include radiotherapy centre, systemic treatment received (any [including but not limited to docetaxel chemotherapy] vs none) and start of ADT in relation to PSMA PET scan (≤4 weeks vs >4 weeks).

12.3. Endpoint Definitions

12.3.1. *Primary endpoints*

Phase II primary endpoint: Acute lower gastrointestinal (GI) RTOG grade ≥2 toxicity at week 18 from start of radiotherapy.

Phase III primary endpoint: Metastasis-free survival (MFS) defined as the time from randomisation to the first detection of distant metastasis on imaging or death from any cause, whichever occurs first. Distant metastasis defined as extra-pelvic lymphadenopathy, bone and visceral metastases.

12.3.2. *Secondary endpoints*

Phase II

- Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC) up to 18 week follow up.
- Ability to deliver 44Gy in 20 fractions to the pelvic and para-aortic lymph nodes with an integrated boost to the involved lymph nodes of 51Gy in 20 fractions within organ at risk dose constraints using the varying radiotherapy planning techniques and delivery systems at participating centres.
- Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy and week 18 follow up.
- Late RTOG and CTCAE v5 GI, GU at 6, 12, 18 and 24 months.

Phase III

- Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC) up to 18 week follow-up.
- Late RTOG and CTCAE v5 GI, GU, blood/bone marrow (FBC) toxicity at 6, 12, 18 and 24 months and then annually for 5 years (excluding blood/bone marrow (FBC) toxicity from 24 months).
- Patient Reported Outcomes (EPIC-26, IPSS, PRO-CTCAE, EQ-5D-5L) at end of radiotherapy, week 18, month 6, 12, 18, 24 and 60.
- Time to biochemical progression defined as time (in days) from randomisation to 1st biochemical progression (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment). Patients will be censored at the date of their last PSA assessment that does not meet the Phoenix definition of biochemical progression.

- Time to radiographic progression defined as time (in days) from randomisation to radiographic progression. The pattern of radiographic progression will be assessed in differentiating between a) progression within the radiotherapy field, b) progression outside the radiotherapy field but within the trial determined extended field (i.e. up to L1/L2 vertebral interspace) and c) distant progression defined as visceral metastases or nodal metastases superior to L1/L2. Patients will be censored at the latest time-point they were known to be progression-free.
- Failure-free survival defined as the time (in days) from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence, distant metastases or death due to prostate cancer with time to first biochemical failure defined as above.
- Overall survival defined as the time (in days) from randomisation to death from any cause. Patients will be censored at the date of last contact.

12.3.3. *Exploratory endpoints*

- Out of radiotherapy field metastasis-free survival for para-aortic cohort only.
- Symptomatic skeletal events.
- Time to castration resistance.
- Dosimetric and volumetric assessment of prostate, seminal vesicles, lymph nodes and organs at risk.

12.4. Statistical Analysis Plan

Phase II

The phase II safety analysis will be conducted when 75 participants treated with extended field radiotherapy have completed their 18 week assessment. The number and proportion of patients who are RTOG G2+ GI toxicity-free in each group at each time point and specifically at 18 weeks together with the 95% exact confidence intervals will be presented. The safety evaluable population is defined as all patients randomised into the study who received at least one fraction of radiotherapy. Sensitivity analyses may also be conducted using an intention to treat population and/or excluding major protocol violators. Safety data will be presented separately for patients with para-aortic disease but the decision to continue to phase III will be based on RTOG G2+ GI toxicity in all patients receiving experimental extended field radiotherapy. At this stage, formal statistical testing will not be used to compare treatment groups as the focus is on the experimental group and a non-comparative trial design has been used.

The ability to deliver the experimental group radiotherapy will be presented as number and percentage of patients adhering to all mandatory dose constraints. Details will be provided for any patients that did not meet any dose constraints.

PRO scores will be generated using standard algorithms for the questionnaires and presented at end of radiotherapy and week 18. Data will be presented as number/percentage or medians/IQR (mean, SD) for each treatment group as appropriate.

Late toxicity data for individual items will be tabulated at each time point and displayed graphically using stacked bar charts and/or prevalence graphs. It is acknowledged that there will be limited late toxicity data for patients at the time the primary endpoint data are mature for phase II.

Phase III

The primary endpoint analysis will include only the pelvic lymph node cohort of patients randomised and will be on an intention-to-treat basis. The primary efficacy analysis will be conducted after 161 events have been observed or, with permission from the IDMC, after all patients randomised to the

pelvic lymph node cohort have completed 5 years follow-up, if this milestone is reached ahead of the target number of events. MFS will be presented as Kaplan-Meier curves by treatment group and MFS point estimates (e.g. at 5 years) will be presented with 95% confidence intervals. Treatment effects will be estimated and tested for significance by the Cox proportional hazards model, adjusted for balancing factors of the minimisation. Further models adjusting for other important known prognostic factors will be fitted. Methods to account for non-proportionality will be used if appropriate.

All secondary endpoints will be stratified by pelvic node only and para-aortic node cohorts.

Acute and late toxicity for individual items will be tabulated at each time point and displayed graphically using stacked bar charts and/or prevalence graphs. Summary scores of worst RTOG/CTCAE grade at each time point will be calculated. For late toxicity, Kaplan-Meier curves (by treatment group) will be presented for time to first Gx+ event; Kaplan Meier point estimates (with 95% confidence intervals) will be reported. Two and five years post randomisation are time points of primary interest. The proportion experiencing G2+ side effects will be presented, comparisons will be made using chi-square or Fishers exact tests.

PRO scores will be generated using standard algorithms for the questionnaires and presented at each time point assessed. Data will be presented as number/percentage or medians/IQR (mean, SD) for each treatment group as appropriate. Graphical presentation will also be used, including investigating changes from pre-radiotherapy assessment to each time point assessed. Emphasis will be given to PRO outcomes at week 18 for acute effects and at 2 and 5 years with analyses that account for the longitudinal nature of the data being conducted.

Efficacy data will be analysed using time-to-event methodology as for the primary MFS endpoint. The time point of primary interest is five years from randomisation. Sensitivity analyses will be conducted with time from start of ADT as the origin for time-to-event outcomes rather than randomisation to account for patients receiving different durations of ADT prior to radiotherapy commencing.

For the para-aortic cohort, who enter the trial with metastatic disease, an exploratory endpoint of out of radiotherapy field metastasis-free survival will be analysed using the same time-to-event methodology as for the primary and secondary efficacy endpoints. Out of radiotherapy field metastasis-free survival is the first detection of metastasis on imaging outside of the radiotherapy field or death from any cause, whichever occurred first. Metastasis are defined as extra-pelvic lymphadenopathy (superior to the L4/L5 interspace), bone and visceral metastases.

Other exploratory endpoints within the para-aortic cohort will include time to symptomatic skeletal event, with an event defined as external beam radiation therapy to relieve skeletal symptoms, a new symptomatic pathologic bone fracture, the occurrence of spinal cord compression or tumour related orthopaedic surgical intervention.

Time to castration resistance will be assessed as a 25% increase from the nadir, with a minimum rise of 2ng/ml, in the context of castrate testosterone values (<50ng/dl) [32].

Dosimetric and volumetric assessment of prostate, seminal vesicles, lymph nodes and organs at risk will be undertaken with dose volume histograms and dose cube information.

Relevant analyses will be adjusted for ADT duration. Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

12.5. Interim Analyses and Stopping Rules

The trial is designed to be a seamless phase II/III trial with stages to assess (i) feasibility and (ii) safety during phase II and (iii) efficacy in phase III. Recruitment will be closely monitored by the Trial Management Group (TMG) and Trial Steering Committee (TSC). An Independent Data Monitoring Committee (IDMC) will review the accumulating data starting approximately six months after the first patient is recruited and then at regular intervals at least annually. Full details of interim analyses and guidance for the IDMC will be in the Statistical Analysis Plan.

Phase II

At each review, the IDMC will review the proposed stopping rule (8 or more patients with G2+ GI toxicity at 18 weeks) with reference to accumulating data in the control group.

A feasibility interim analysis is proposed after approximately half the patients required for the phase II stage (n=75) have been recruited. Recruitment rates, relative recruitment to the extent of disease cohorts, feasibility of delivering radiotherapy and acute toxicity will be reviewed. Recruitment and treatment compliance data including adherence to dose constraints will be shared with the TMG to allow revisions to radiotherapy delivery guidelines if any issues are identified. Toxicity data will not be shared with the TMG at this stage nor prior to the formal analysis of the phase II primary endpoint unless the IDMC advise otherwise.

There will be a formal analysis of the phase II primary endpoint when data are mature, this is expected to be approximately 6 months after the 150th (safety) evaluable patient has been randomised. Recruitment will continue in the phase II centres while data matures for this analysis but no new centres will be opened to recruitment until the IDMC have reviewed the acute toxicity data and confirmed that the trial should continue to the target sample size for phase III. It is intended that the acute toxicity results of the phase II stage will be presented and published, following approval from the IDMC and TSC. Patients entering the trial will be receiving ADT and may have had chemotherapy and/or androgen receptor targeted therapy, the control group will be used to benchmark the expected RTOG GI toxicity in this patient population. The IDMC will be asked to review the proposed stopping rule and advise if thresholds of acceptable toxicity are appropriate to continue with phase III.

The IDMC will also be asked to monitor the toxicity of the 4 week radiotherapy schedule and could advise to switch to a 5 week schedule if acute toxicity was deemed to be unacceptably high. Further details will be provided in the Statistical Analysis Plan.

Phase III

The IDMC will continue to review the accumulating toxicity and efficacy data at least annually. No formal early stopping rule for futility or efficacy for the primary endpoint (MFS) has been planned.

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Clinical Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the

TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

13.2. Trial Steering Committee (TSC)

The PEARLS trial will be overseen by the ICR-CTSU Urological Radiotherapy Trials Steering Committee (TSC) which includes an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. The TSC will meet at regular intervals, and at least annually. The TSC will provide expert independent oversight of the trial on behalf of the sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

13.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chairman and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

14. RESEARCH GOVERNANCE

14.1. Sponsor Responsibilities

The Sponsor of this clinical trial is the Institute of Cancer Research (ICR).

14.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The Principal Investigator is responsible for the trial team and trial conduct at the participating site.

15. TRIAL ADMINISTRATION & LOGISTICS

15.1. Site Activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site

initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

15.2. Investigator Training

Details of any trial specific training other than site initiation.

15.3. Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

15.4. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

15.5. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes, including electronic notes, of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

15.6. Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

15.7. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

16.1. Risk Assessment and Approval

This trial has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

16.2. Public and Patient Involvement

Patient advocate members of the Radiotherapy Focus Group at Royal Marsden, RMH Biomedical Research Centre Consumer group and NCRI Consumer Forum were involved in protocol design including methodology, sample collection, patient information and consent forms and are represented on the TMG.

16.3. Ethics Approvals

The trial will not commence at any participating site until the required approvals are in place. ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee (REC) for multi-centre trials, HRA approval and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

16.4. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the UK Policy Framework for Health and Social Care and the principles of GCP.

16.5. Informed Consent

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki.

Patients should be asked to sign the current ethics approved PEARLS consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved PEARLS patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

16.6. Patient Confidentiality

Patients will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples. Patients who have consented to take part in the Quality of Life study will also consent to ICR-CTSU collecting their home address in order that questionnaire can be posted directly to their home address for completion.

Each investigator should keep a separate log of all participants' Trial IDs, names and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

16.7. Data Protection

All investigators and trials staff must comply with applicable data protection laws at all times.

16.8. Liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

17. FINANCIAL MATTERS

This trial is investigator designed and led. ICR has received funding from Cancer Research UK for the central coordination of the trial. The trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio by virtue of its funding by a NIHR non-commercial partner. NIHR CRN resources should therefore be made available for the trial to cover UK specific research costs

18. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. It is anticipated that the Phase II results will be published separately from the Phase III results. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies. Authorship of all publications will usually be in accordance with ICMJE guidance.

No investigator may present or attempt to publish data relating to the PEARLS trial without prior permission from the TMG.

19. ASSOCIATED STUDIES

19.1. Translational sub-studies

a) Immune cell repertoire

Background

The translational work within PEARLS aims to compare changes in the immune cell repertoire during and after radiotherapy to the prostate gland alone versus radiotherapy to the prostate with pelvic and/or para-aortic LN. Historically, radiotherapy has been shown to cause prolonged lymphodepletion which may be exacerbated by large pelvic/para-aortic fields [33, 34]. More recently radiotherapy has been shown to lead to broadening of the TCR repertoire [35], we hypothesize that this broadening of the TCR repertoire will be compromised if extensive pelvic/para-aortic nodal irradiation is carried out.

This translational study will address two hypotheses:

Hypothesis 1: Radiotherapy to the prostate and pelvic +/- para-aortic nodes will cause 10% more depletion of the circulating CD8+ T cell repertoire compared to radiotherapy to the prostate alone.

Hypothesis 2: Radiotherapy to the prostate alone will cause a broadening of the TCR repertoire which will be compromised in patients receiving additional radiotherapy to the pelvic and/or para-aortic areas.

This sub-study uses two different experimental methods:

1. Flow cytometry to characterise the immune cell repertoire – this will include both quantification of circulating immune cells and assessment of their functionality.
2. TCR profiling to characterise the clonal evolution of the T cell repertoire.

Flow cytometry analysis will be conducted using established immunological panels and a translational platform that is being used routinely in clinical trials led by RMH/ICR.

TCR Sequencing will be conducted in laboratories with extensive experience and expertise in this technique. This biomarker work is hypothesis-driven discovery work. Relevant positive findings would need external validation. Study findings, in particular the timing of radiotherapy-associated lymphodepletion could guide design of future trials including studies of radiotherapy-immunotherapy combinations.

Statistical Analysis

The primary research question is whether the quantity of circulating CD8+ T cells during and after radiotherapy is significantly different in patients treated with prostate radiotherapy versus those treated with prostate plus pelvic/para-aortic radiotherapy. We consider a 10% difference in circulating CD8+ T cells to be clinically significant. Within PEARLS, there are three different radiation fields, and therefore within each, 10 patients will be recruited and two comparisons conducted: prostate radiotherapy (excluding patients who have a boost to involved pelvic lymph nodes) versus prostate + pelvic radiotherapy and prostate radiotherapy versus prostate, pelvic + para-aortic radiotherapy. If significant differences in the immune cell repertoire are seen between groups (>10%), this will serve to support further investigation in a larger cohort of patients (subject to additional funding). The number of patients required for this analysis is based on a pragmatic decision for this discovery work. A formal power calculation would be put together using data generated from this analysis should further investigation be warranted.

Sample collection timing

Peripheral blood samples (30mls) will be collected at baseline (pre-radiotherapy), day 10 (mid-radiotherapy), day 20 (end of radiotherapy), 3, 6 and 12 months following start of radiotherapy in 30 patients in total.

This translational study will only run at sites that are local to the ICR London labs as although blood samples do not need processing on collection, they do need to be transported to ICR labs on the day of collection. Samples need to be sent to the ICR labs in the morning so they can be processed on the same day.

Patients will also be asked to donate their archival diagnostic tissue as the immunological sub-study in PEARLS is looking at change in T cell receptor clones in the blood as a key endpoint. Without also looking at the T cell clones in the tumour we cannot confirm that any changes in the blood match those in the tumour i.e. we need to correlate T cell clones identified by TCR Seq in the blood with T

cells in the tumour. This is important to be able to reliably compare immune changes between the 3 different-sized radiotherapy fields.

b) PSMA PET-CT biomarker imaging response

Background

The primary aim of this substudy is to determine whether PSMA PET-CT can be used as an imaging biomarker in node-positive prostate cancer. We do not know the duration of time after which lesions lose their PSMA-uptake after radiation or whether residual PSMA-uptake is associated with residual tumour viability.

The time point of the scan after radiation has been chosen as 6 months to reduce the risk of false positive PSMA uptake associated with inflammation post radiotherapy. Additionally, there will be a further PSMA PET-CT scan at time of biochemical progression, defined as time (in days) from randomisation to biochemical progression (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment).

There are no specific response evaluation tools for PSMA PET-CT, however, some studies have used PET Response Criteria in Solid Tumours (PERCIST), which was initially developed for systematic and structured assessment of response to therapy with 18F-fluorodeoxyglucose [36]. Therefore, the defined PERCIST categories for response to treatment will be used: treatment response defined as absence of any PSMA uptake in all target lesions on 6 month PSMA PET-CT (complete response, CR) or a decrease in summed SUVmean of ≥30% (partial response, PR). The appearance of a new PSMA-PET/CT-positive lesion or an increase in summed SUVmean of ≥30% (progressive disease, PD). A moderate change in summed SUVmean (between -30% and +30%) without a change in the number of target lesions will be defined as stable disease (SD) [37].

Statistical analysis

Primary endpoint has been defined as: if 90% patients have a complete response according to PERCIST criteria at 6 months post radiotherapy, PSMA PET-CT could be explored as a potential predictive biomarker. Twenty-six patients would allow us to rule <70% of patients having a complete response 6 months, with the expectation it will be 90% of patients (using a Fleming single stage design p0=0.7, p1=0.9, 5% alpha and 80% power).

Additional patient eligibility to that of the main study:

3 or more PSMA avid lymph nodes on diagnostic PSMA PET-CT staging scan.

Scan collection

Baseline and 6 months post radiotherapy and at recurrence. Baseline scan is routine. Six month and scan at recurrence is a research cost which will be paid to sites taking part.

c) Gut microbiome

Background

This translational work within PEARLS is to determine how intestinal microbial populations change during treatment in relation to field size and study associations with bowel toxicity.

Sequential samples from all patients will be obtained and DNA will be extracted in order to permit long-term storage.

DNA will be extracted from faecal samples using the Qiagen Stool Kit (Qiagen. Crawley, UK) according to manufacturer instructions with an additional bead beating step for homogenisation of sample and lysis of bacterial cells. Library preparation and Illumina (MiSeq) sequencing of the V1-2 regions of the 16S-rRNA gene will be performed. Sequences generated from Illumina (MiSeq) sequencing will be analysed with MOTHUR for identification of operational taxonomic units (OTU), taxonomic assignment, community comparison, and data cleaning by adapting its standard operational procedure [38].

Comparisons will be performed at each time point to assess relevant associations between the microbiota and treatment outcomes. Modelling of sequential data will be performed according to methodology developed for a previous pilot study that we have previously developed [24], specifically by using conditional growth models. Although primary analyses will focus on toxicity and target microbial taxa of interest defined in the MARS study, all measurable microbial taxa will be analysed and exploratory analyses will assess relationships between the microbiota and efficacy outcomes. Where relevant, the predictive power of specific bacterial taxa will be assessed using receiver operating characteristic (ROC) curve analysis.

Statistical analysis

Primary endpoint: Differences in bacterial taxa between patients with or without GI side-effects (acute or late).

Secondary endpoints:

- Intra-subject (within the same patient) dissimilarity in bacterial community composition during and after prostate, prostate and pelvic, prostate, pelvic and para-aortic radiotherapy at different timepoints of assessment.
- Differences in bacterial metabolic pathways between patients with and patients without GI side-effects (to infer on differences in microbial function).
- Differences in bacterial diversity between patients with and without GI side-effects.
- Differences in bacterial taxa between patients experiencing recurrence or persistence of disease during follow-up.
- Differences in bacterial diversity between patients experiencing recurrence or persistence of disease during follow-up.
- Differences in bacterial metabolic pathways between patients experiencing recurrence or persistence of disease during follow-up.

The aim is to recruit 110 patients and it is anticipated that approximately 30/110 patients will experience GI side-effects (acute or late). This is based on the assumption that 40% and 20% of patients undergoing radiotherapy for high-risk prostate cancer are expected to develop acute and late GI side effects respectively. With 30 patients expected to have any GI side-effects, a two-tailed t test can detect a standardised effect size of 0.84 or greater (in terms of Cohen's d) with more than 90% statistical power and a standardised effect size of at least 0.75 with more than 80% statistical power. This has been calculated using a comparison of two independent means in G*Power, version 3.1.9.4, assuming an allocation ratio of 3:8 and a significance level of 0.01 (to account for multiple testing, as multiple bacterial taxa will be assessed at each timepoint).

Sample collection

Stool samples will be taken pre-radiotherapy, during the last week of radiotherapy, and at week 12, month 6, 12 and 24 post radiotherapy for microbiome profiling. Samples obtained prior and during radiotherapy will be taken before any bowel preparation procedure (rectal enema), in order to sample each individual's biological status as close to equilibrium (or steady-state) as possible.

19.2. Quality of Life Study

Quality of Life (QoL) is a secondary endpoint in the main trial and will be analysed as described in the statistical analysis plan.

Patient Reported Outcomes will be assessed using the following questionnaires: EPIC-26, IPSS, PRO-CTCAE, and EQ-5D-5L at the following time points; baseline, at end of radiotherapy (week 4), week 18, month 6, 12, 18, 24 and 60.

The EPIC questionnaire [39] (in its version with 26 items) was selected as it best represents typical symptoms after radiotherapy in prostate cancer patients. The EPIC domains for urinary incontinence, urinary irritative/obstructive, bowel and sexual have been advocated within the standard set of patient reported outcomes for men with localised prostate cancer by ICHOM65.

The IPSS questionnaire [40] is a validated diagnostic tool (7 items) and will be used to assess urinary and bowel incontinence.

The NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System [41] was developed to evaluate symptomatic toxicities by self-report in adults, adolescents and children participating in cancer clinical trials. It was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE).

The EQ-5D is one of the most commonly used generic questionnaires to measure health-related QL. The EQ-5D questionnaire consists of a questionnaire and a visual analogue scale (EQ-VAS). The EQVAS is a self-rated health status using a VAS. The EQ-VAS records the subject's perceptions of their own current overall health and can be used to monitor changes with time.

The QL study will be optional for trial participants; however the aim will be to include as many participants as possible to allow full determination of QALYS by treatment arm and to support exploratory analyses. Given the size of the study and the use of focused questionnaires, the introduction of web-based data capture direct from participants will be explored. This may provide opportunities for related trial methodology research e.g. comparison of response rates to paper based and web based completion.

An analysis plan will be developed in consultation with the TMG with key endpoints for each questionnaire. Standard algorithms will be used to derive scores and handle missing data in QL questionnaires. Changes from baseline at each time point will be compared within groups as well as between treatment groups. Analyses to account for the longitudinal nature of the data may be used.

20. REFERENCES

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A1. WHO performance status

Grade	*Performance Status*
0	*Able to carry out all normal activity without restriction.*
1	*Restricted in physically strenuous activity but ambulatory and able to carry out light work.*
2	*Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.*
3	*Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.*
4	*Completely disabled; cannot carry on any self-care; totally confined to bed or chair.*

A2. RTOG Toxicity Scales

Instructions

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused death of the patient.
4. An accurate baseline prior to start of therapy is necessary.

Definitions:

Diarrhoea is defined as a clinical syndrome characterised by frequent loose bowel movements without associated rectal irritation (tenesmus)

Proctitis is defined as a clinical syndrome characterised by rectal irritation or urgency (tenesmus), presence of mucous or blood in the stool and, in some patients, with frequent, sometimes loose bowel movements.

Cystitis is defined as a syndrome characterised by irritative bladder symptoms such as frequency, dysuria and nocturia. Haematuria may or may not be a part of the clinical picture of cystitis.

Acute Toxicity [To be used from baseline to 18 week follow up visit]:

Bladder changes cystitis/frequency:

Grade 0: No symptoms
Grade 1: Frequency of urination or nocturia twice pre-treatment habit/dysuria, urgency not requiring medication.
Grade 2: Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic.
Grade 3: Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/without clot passage.
Grade 4: Haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.
Grade 5: Death directly due to radiation morbidity.

Bowel changes:

Grade 0: No symptoms
Grade 1: Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics.
Grade 2: Diarrhoea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal abdominal pain requiring analgesics.
Grade 3: Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops).
Grade 4: Acute or subacute obstruction, fistula or perforation/GI bleeding requiring transfusion/abdominal pain or tenesmus requiring tube

Late Toxicity [To be used from 6 month follow up visit onwards]:

Grade 0: No symptoms
Grade 1: Minor symptoms requiring no treatment

Grade 2: Symptoms responding to a simple outpatient management, lifestyle (performance status not affected)
Grade 3: Distressing symptoms altering patient's lifestyle (performance status). Hospitalisation for diagnosis or minor surgical intervention (such as urethral dilatation) may be required.
Grade 4: Major surgical intervention (such as laparotomy, colostomy, and cystectomy) or prolonged hospitalisation required.
Grade 5: Fatal complications

A3. GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CI	Chief Investigator
CIS	Carcinoma In Situ
CRF	Case Report Form
DCF	Data Capture Form
DFS	Disease Free Survival
EORTC	European Organisation for Research and Treatment of Cancer
FBC	Full Blood Count
G-CSF	Growth Colony-Stimulating Factors
GFR	Glomerular Filtration Rate
IB	Investigator's Brochure
ICR	The Institute Of Cancer Research
IDMC	Independent Data Monitoring Committee
LFT	Liver Function Test
MDT	Multi-disciplinary team
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PI	Principal Investigator
PIS	Patient Information Sheet
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
U+E	Urea & Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation