REC: 24/EE/0099
IRAS: 327827
ISRCTN: 11089334

POINTER-PC

Pelvis Or Involved Node Treatment: Eradicating Recurrence in Prostate Cancer (POINTER-PC)

A Multicentre Open Label Randomised Phase III Trial Comparing Extended Nodal Irradiation with Stereotactic Body Radiotherapy for oligo-recurrent pelvic nodal prostate cancer

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Version History

Version number	*Edited by*	*Date edit completed*	*Details of editions made*
1.0	N/A. Original Version	**22/01/2024**	N/A. Original Version
2.0	Matthew Carter	**14/05/2024**	Modified archiving period to 5 years.
3.0	Ella Steele, Matthew Carter	**31/10/2024**	○ Updated and clarified how paper and electronic questionnaires will be administered to patients. ○ Following randomisation, a copy of the signed consent form will be sent to CTRU on Secure File Transfer Service (SFTS) instead of by email or post. ○ Paper contact details CRF will not be sent to CTRU on SFTS, it will be entered onto MACRO by RDE by sites. ○ Removal of telephone randomisation and explanation that paper back-up randomisation is available if the randomisation portal is unavailable. ○ Addition of the trial's ISRCTN number. ○ Update to further clarify that the blood sample collection and tissue sample collection is optional. This has been updated in the text and the tables of assessments. ○ Update to the statement of indemnity to reflect the sponsor insurance policy. ○ Update to the table of assessments to include that PSA will be assessed 2 weeks post-RT. This was explained in the text but had not been included in the tables. ○ Minor formatting updates.
4.0	Matthew Carter, Ella Steele, Joanne Copeland, Joanne Webster	**20/03/2025**	○ Updated the CI's title from Dr to Professor. Updated the Joint CI's title to NIHR Advanced Fellow and Honorary Consultant Clinical Oncologist. ○ Included that deprivation score will be collected and provided instructions of how to calculate deprivation score.

			○ Remove PSA being measured at 2 weeks follow-up as this is too early to be an accurate value. ○ Patient contact details for electronic questionnaire administration will be auto inserted into REDCap from Gen24 as it will be collected at the point of randomisation, instead of sites having to enter the data onto the database. As such the F40 contact details case report form is no longer required to be completed at baseline. ○ Clarify that SABR RTQA is required as well as ENI RTQA approval. ○ Explained that the acronyms SABR and SBRT can be used interchangeably, with SBRT being the main acronym used through trial documentation. ○ SABR and RRSAE have been added to the table of abbreviations. ○ Update DMEC meeting frequency to 'at least annually'. ○ Removed non radiotherapy related SAEs as these are not being collected on the trial. ○ Updated the order that ENI-5 and ENI-20 is referenced in the trial summary to have ENI-5 first, keeping it consistent with the rest of the protocol. ○ In the trial summary, updated the secondary endpoint section to have the follow-up timepoints consistent with the rest of the protocol. ○ Added section 8.9 for PIC sites. ○ Added that assessments and QoL at follow-up timepoints can be completed +/- 1 1 week for follow-up time points up to and including 6 months, +/- 1 month for follow-up time points from 12 months onwards. ○ Separated Pre-Randomisation timepoint from Eligibility in schedule of assessments. ○ Baseline PSA moved from Pre-Treatment to Eligibility timepoint ○ Footnote added to schedule of assessments *"Testosterone should be taken after consent but before participants start trial treatment (including ADT)"* ○ Updated the paper questionnaire return to say that completed questionnaires "must be returned either at the next clinic appointment for appointments up to 6 months or posted back to CTRU once the participant commences 6-monthly follow-ups", and

			furthermore for sites to "ensure that they are returned to the CTRU in a timely manner. This may require the research team to call the participant as a reminder to post the questionnaires back". ○ Updated the definition of end of trial to clarify that all participants will be followed up clinically until metastatic disease or until three years post randomisation of the final participant and that post progression, all participants will be followed up for toxicity until three years post randomisation of the final participant. ○ Formatting and grammatical updates.

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Trial Summary

Title	**Pelvis Or Involved Node Treatment: Eradicating Recurrence in Prostate Cancer (POINTER-PC)**
Background	Prostate cancer (PCa) is common, with approximately 50,000 new cases diagnosed each year in the UK. Recurrence may occur in up to half of patients initially treated with curative intent for high-risk localised/ locally advanced PCa. Pelvic nodal recurrence is common and, extrapolating from the primary disease setting, is associated with worse cancer-specific survival. Increased use of positron emission tomography-computed tomography (PET-CT) to investigate elevation of prostate-specific antigen (PSA) after previous curative-intent treatment frequently identifies low volume pelvic nodal recurrence. No clear standard of care exists for these patients, with potential therapeutic approaches including Stereotactic Body Radiotherapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR) to the involved node(s) alone, Extended Nodal Irradiation (ENI) to treat sites of potential micrometastatic spread in addition to involved node(s) or systemic anticancer therapies including androgen deprivation therapy (ADT), docetaxel chemotherapy or second generation androgen receptor antagonists/ androgen biosynthesis inhibitors. SBRT is associated with good local control and minimal toxicities, but there is an absence of phase III evidence regarding its impact on further metastatic progression and overall survival in PCa. In addition, subsequent relapses often occur within the pelvis and repeated SBRT may be infeasible or less effective. Based on observational studies, ENI is associated with promising metastasis-free survival (MFS) compared with SBRT and appears to result in low rates of severe late toxicity. Ultra hypofractionated (i.e. 5-fraction) ENI has been evaluated in phase II trials in the primary disease setting and appears to be associated with low rates of severe toxicity. A randomised controlled trial is now required to investigate the impact on metastatic progression from ENI compared with SBRT in patients with PCa pelvic nodal recurrence and to evaluate the toxicity of 5-fraction ENI compared with a standard 20-fraction schedule.
Population	Adult patients with pelvic nodal recurrence after curative-intent primary treatment for PCa
Design	A UK, multicentre, prospective, open-label three-arm randomised controlled phase III trial of SBRT versus ENI (in 5 or 20 fractions) in patients with PCa pelvic nodal recurrence. Participants will be randomised 2:1:1 to receive: • Arm A. SBRT to involved node(s) (Control arm for the purposes of this study - can be considered standard of care)

	• Arm B. ENI in 5 fractions with SIB to involved node(s) (ENI-5, experimental arm) • Arm C. ENI in 20 fractions with SIB to involved node(s) (ENI-20, experimental arm for the purposes of this study - can be considered standard of care) All participants will receive 12 months of ADT starting up to 1 month before the first day of RT. Additional systemic anticancer therapies (docetaxel/ second generation androgen receptor antagonist or androgen biosynthesis inhibitor) will be allowed post-RT. Testosterone and baseline adverse events will be collected after consent and prior to trial treatment. Clinical and toxicity assessment will be performed at end of treatment and at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months, then annually up to 3 years post randomisation of the final participant or until metastatic progression, as per standard follow up schedules, either in person or by telephone, including measurement of PSA. PSA will not be measured at 2 weeks follow-up. Post progression, toxicity assessments will continue at the above timepoints until 3 years post randomisation of the final participant. Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. Re-staging with PET-CT is mandated. PROM and HRQoL questionnaires will be in an electronic format using REDCap, an online patient specific quality of life data capture system (or paper alternatives) and will be completed at baseline (pre-randomisation) and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT. Please see Table 2, 3 and 4 - Summary of trial assessments for further details.
Objectives	i) To compare ENI (ENI-5 and ENI-20) with SBRT for the endpoint of MFS ii) To compare ENI-5 with ENI-20 for the endpoint of patient reported outcome measure (PROM)-assessed late bowel toxicity at 3 years
Inclusion criteria	• Age ≥18 years. • Histological diagnosis of prostate adenocarcinoma • Previous primary PCa treatment (radical prostatectomy (RP), primary/ post-operative radiotherapy (RT) or brachytherapy without previous pelvic nodal RT).

	• Maximum of 3 PET-CT defined macroscopically-involved pelvic lymph nodes (upper limit of the pelvis is defined as the aortic bifurcation) within 6 months prior to randomisation. • World Health Organisation (WHO) performance status 0-2. • Willing to be randomised to SBRT, ENI-5 or ENI-20. • Patients must be able to provide study-specific written informed consent. • Prepared to participate in follow-up by telephone or in person.
Exclusion criteria	• Previous pelvic nodal RT. • Contraindications to SBRT or ENI (e.g. inflammatory bowel disease). • Contraindications to ADT. • Local recurrence in the prostate gland. • Para-aortic nodal metastases (above the aortic bifurcation). • Mesorectal nodal metastases. • Bone or visceral metastases. • Severe late toxicity relating to primary/ post-operative RT. • Other active malignancy (except non-melanoma skin cancer or other malignancy with a documented disease-free survival of at least 3 years before randomisation). • Castrate-resistant disease.
Sample size	480 participants, recruited from 35-40 UK centres over 4 years.
Randomisation	Three-arm randomisation to SBRT (240 participants), ENI-5 (120 participants) or ENI-20 (120 participants). Randomisation will be performed centrally at University of Leeds (UoL) Clinical Trials Research Unit (CTRU) using a minimisation algorithm including a random element. For the prognostic factors treatment will be balanced for, see section 9.6 Randomisation Process.
Interventions	All participants will be treated with 12 months of ADT, commencing up to 1 month before the first day of RT. RT will be delivered as an outpatient on weekdays. SBRT dose will be 30, 35 or 40 Gy in 5 fractions delivered on alternate days over 2 weeks. ENI-5 dose will be 25 Gy in 5 fractions plus a SIB of 30, 35 or 40 Gy delivered on alternate days over 2 weeks. It is recommended to use 30 Gy for SBRT and for the ENI-5 SIB. However, 30, 35 or 40 Gy in 5 fractions will be permitted, in line with usual departmental practice. ENI-20 dose will be 44 Gy in 20 fractions plus a simultaneous integrated boost (SIB) of 54 Gy to macroscopically involved node(s) delivered daily over 4 weeks. For ENI-20, it is recommended not to start treatment on a Monday to ensure an additional weekend is included in the overall treatment time to reduce toxicity. The trial aims to evaluate the impact of treatment volume rather than dose delivered; therefore the chosen dose

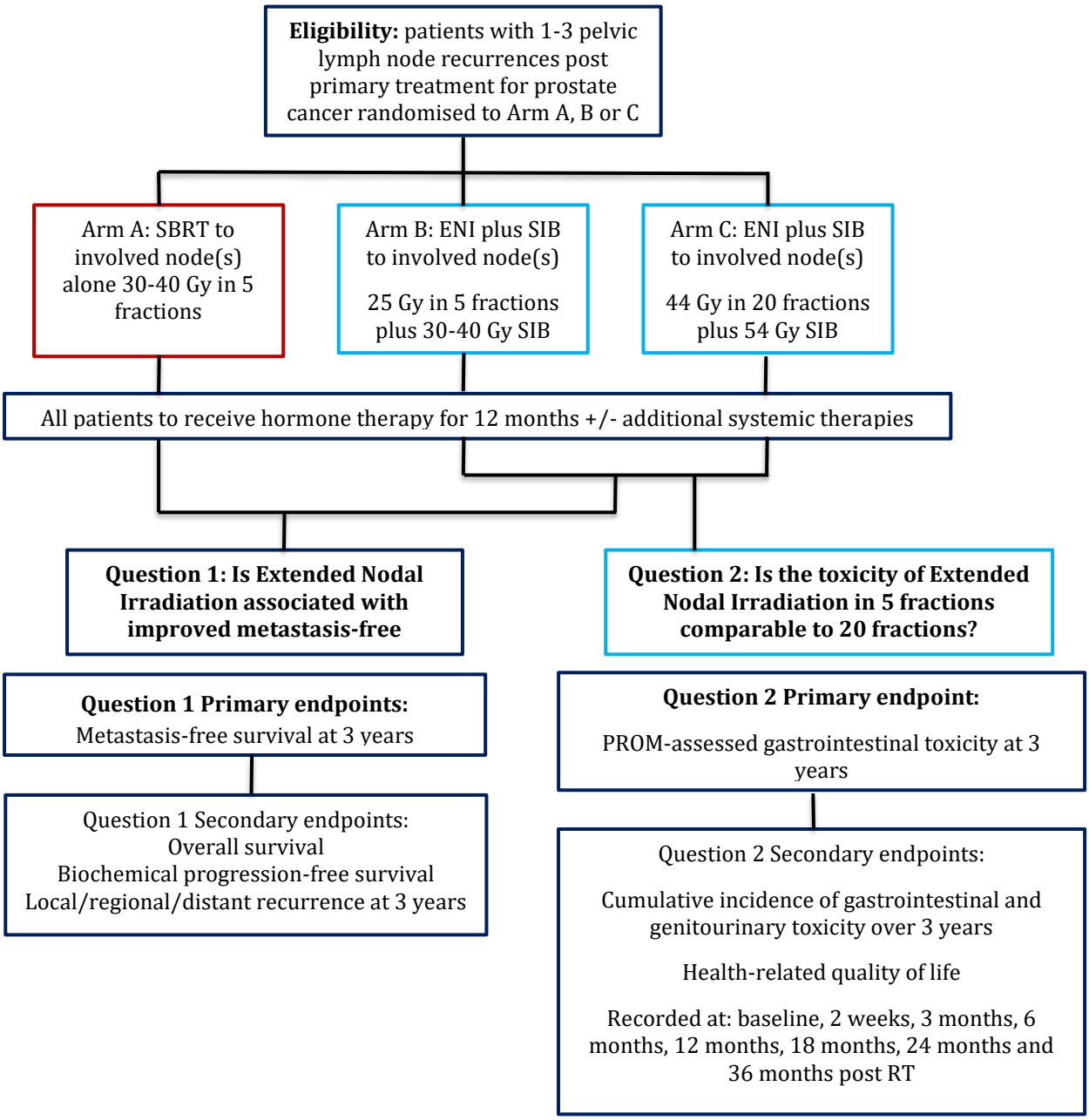
	fractionation schedules are biologically similar when compared using the equivalent dose in 2 Gy fractions (EQD2). Treatments will be delivered with daily online image-guidance. Additional systemic anticancer therapies (docetaxel/ second generation androgen receptor antagonist or androgen biosynthesis inhibitor) will be allowed post-RT.
Follow up	Clinical and toxicity assessment will be performed at end of treatment and at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months post end of treatment, and then annually up to 3 years post randomisation of the final participant or until metastatic progression, as per standard follow up schedules, either in person or by telephone, including measurement of PSA (PSA will not be measured at 2 weeks follow-up). Please note that for telephone follow-up, the PSA blood test will need to be undertaken by the patient's GP prior to the appointment. Post progression, toxicity assessments will continue at the above timepoints until 3 years post randomisation of the last participant. Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. Re-staging with PET-CT is mandated. PROM and HRQoL questionnaires, in electronic format (or paper alternative) will be completed at baseline (pre-randomisation) and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT.
Primary endpoints	• SBRT versus ENI: MFS (defined as time from randomisation to progression of the treated node(s), new nodal, bone or visceral metastatic disease, or death due to PCa). • ENI-5 versus ENI-20: PROM-assessed late bowel toxicity at 3 years, measured using the Expanded Prostate Cancer Index Composite 26-item questionnaire (EPIC-26) bowel function sub-domain.
Secondary endpoints	• Overall survival (OS, defined as time from randomisation to death from any cause). • Biochemical progression-free survival (bPFS, defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT). • Failure-free survival (FFS), defined as time from randomisation to biochemical failure, commencement of further anticancer therapy for PCa, local (prostate/prostate bed) recurrence, progression of the treated node(s), new nodal, bone or visceral metastases or death from PCa. • Patterns of first failure: Local, treated-node(s), other regional/ pelvic lymph node(s), para-aortic lymph node(s), other extra-pelvic

	lymph node(s), bone metastasis, visceral metastasis (liver, lung), other metastasis. • Treatment compliance: treatment duration, number of fractions, total dose received and whether treatment was delivered as planned. • Urinary, bowel, hormonal and sexual toxicities, measured using the relevant EPIC-26 function and other sub-domains at baseline (pre-randomisation) and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT. • HRQoL, measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline (pre-randomisation) and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT. • Clinician-reported toxicity at baseline, end of treatment, 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months post-RT and annually thereafter **until 3 years post randomisation of the final participant** and maximum acute (≤3 months) and late (>3 months) bowel and urinary toxicity measured using Common Toxicity Criteria for Adverse Events (CTCAE) v5.0. • Safety and toxicity overall and at end of treatment and at each follow up timepoint on the basis of Radiotherapy Related Adverse Events (RRAEs), Radiotherapy Related Serious Adverse Events (RRSAEs) and Related and Unexpected Serious Adverse Events (RUSAEs) and measured using CTCAE.

POINTER-PC Trial schema

Figure 1: Trial schema

Trial schema for Objectives i) and ii) are shown in Figure 1 below:



ENI, Extended Nodal Irradiation; PROM, patient-reported outcome measure; SBRT; Stereotactic Body Radiotherapy; SIB, simultaneous integrated boost

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Abbreviations

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse Event
APL	Authorised personnel log
AR	Adverse Reaction
bPFS	Biochemical progression-free survival
cfDNA	Cell-free DNA
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CTC	Circulating tumour cells
CTCAE	Common Toxicity Criteria for Adverse Events
CtE	Commissioning through Evaluation
CTIMP	Clinical Trial of Investigational Medicine Product
CTRU	Clinical Trials Research Unit
CV	Curriculum Vitae
DMEC	Data Monitoring & Ethics Committee
eCRF	Electronic case report form
EDC	Electronic Data Capture
ENI	Extended Nodal Irradiation
ENI-5	Extended Nodal Irradiation in 5 fractions
ENI-20	Extended Nodal Irradiation in 20 fractions
EORTC	European Organisation for Research and Treatment of Cancer
EPIC-26	Expanded Prostate Cancer Index Composite 26 item questionnaire
EQD2	Equivalent dose in 2 Gy fractions
eSIV	Electronic site initiation presentation
FFS	Failure-free survival
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Gy	Dose in units of Gray
HRQoL	Health related quality of life
IMRT	Intensity-modulated radiotherapy
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ISUP	International Society of Urological Pathology
ITT	Intention to treat
MCID	Minimum clinically important difference
MDT	Metastasis-directed therapy
MFS	Metastasis-free survival
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
Non-CTIMP	Non - Clinical Trial of Investigational Medicine Product

OS	Overall survival
PCa	Prostate cancer
pCRF	Paper case report form
PET-CT	Positron-emission tomography-computed tomography
PI	Principle Investigator
PIS	Participant Information Sheet
POINTER-PC	Pelvis Or Involved Node Treatment: Eradicating Recurrence in Prostate Cancer
PROM	Patient-reported outcome measure
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QA	Quality assurance
QLQ-C30	Quality of Life Questionnaire Core 30
RDE	Remote Data Entry
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RRAE	Radiotherapy Related Adverse Event
RRSAE	Radiotherapy Related Serious Adverse Event
RT	Radiotherapy
RTTQA	Radiotherapy Trials Quality Assurance group
RUSAE	Related Unexpected Serious Adverse Event
SABR*	Stereotactic Ablative Radiotherapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT*	Stereotactic Body Radiotherapy
SD	Standard deviation
SFTS	Secure File Transfer Service
SIB	Simultaneous integrated boost
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
UoL	University of Leeds
WHO	World Health Organisation
YCR	Yorkshire Cancer Research

*SABR and SBRT are interchangeable acronyms for the same radiotherapy treatment. SBRT is the main acronym used throughout trial documentation.

1. Background

1.1 Prostate cancer

Prostate Cancer (PCa) is the commonest UK male cancer. In 2018, 49,810 new cases were diagnosed in England[1]. Most present with non-metastatic PCa and can be treated with curative intent by Radical Prostatectomy (RP), external beam radiotherapy (RT) or brachytherapy[2]. Recurrence may occur in up to half of patients initially diagnosed with high-risk PCa (≥T3a N0 M0 disease, prostate specific antigen (PSA) >20 ng/ml and/or International Society of Urological Pathology (ISUP) grade ≥4)[2-4]. Pelvic nodal recurrence is common and, extrapolating from the primary disease setting, is associated with significantly worse cancer-specific survival[5].

1.2 The problem- pelvic nodal recurrence after primary treatment

In recent years, the use of PET-CT to investigate men with elevated PSA following previous curative treatment has become routine and frequently leads to the early diagnosis of low volume PCa pelvic nodal recurrences[6] . Potential treatment options include radiotherapy treatments such as stereotactic body radiotherapy (SBRT) to the involved node(s) alone or extended nodal irradiation (ENI) to treat sites of potential microscopic spread in addition to the involved node(s) and/ or systemic agents (androgen deprivation therapy (ADT), docetaxel chemotherapy, second generation androgen receptor antagonists such as enzalutamide or the androgen biosynthesis inhibitor abiraterone)[2]. SBRT delivers highly targeted radiation to small treatment volumes with a sharp fall-off in dose. It is increasingly used for recurrent pelvic nodal disease as it is convenient, delivered in 3 to 5 treatment visits, with minimal side-effects and is highly effective for local control [7]. National Health Service (NHS) England undertook a SBRT Commissioning through Evaluation (CtE) programme, and more than 500 SBRT treatments for nodal recurrence were performed between 2016-19 across 17 cancer centres, the majority of which were for PCa[7]. The CtE programme demonstrated that SBRT resulted in high levels of local control with minimal toxicity and so SBRT is now commissioned for nodal recurrences by NHS England, despite an absence of phase III evidence to support its survival benefit[7, 8]. ENI is an alternative radiotherapy option, where, as well as targeting involved nodes as identified on PET-CT imaging, treatment volumes encompass adjacent lymph nodes that may harbour microscopic cancer not seen on PET-CT imaging, thereby potentially reducing the risk of developing further lymph node spread[9]. POINTER-PC aims to address the evidence gap in terms of the optimal radiotherapy treatment for pelvic nodal recurrence by comparing SBRT and ENI in a randomised trial. Currently, there are no radiotherapy clinical trials for this patient population in the UK and robust evidence is needed to define the optimal management of pelvic nodal recurrence.

1.3 The evidence for Stereotactic Body Radiotherapy- locally effective but risk of further pelvic recurrence

Two randomised phase II trials of SBRT versus observation for limited PCa recurrence, including pelvic nodal recurrence, have been reported[10, 11]. These suggest that SBRT is well tolerated and may delay further disease progression. Despite these promising

data, there is an absence of high-level phase III randomised trial evidence regarding the impact of SBRT on metastatic progression and OS in PCa. In addition, in observational studies of pelvic nodal SBRT, subsequent relapses often occur within the pelvis. For example, in a multicentre study by Ost et al, 39% of further relapses after pelvic nodal SBRT were located in the pelvis[12]. Repeated SBRT for such relapses may be significantly compromised by the prior treatment and/ or less effective[13]. Overlaps with previously treated areas can make subsequent treatments technically challenging to deliver and risk increased radiation related toxicities[14].

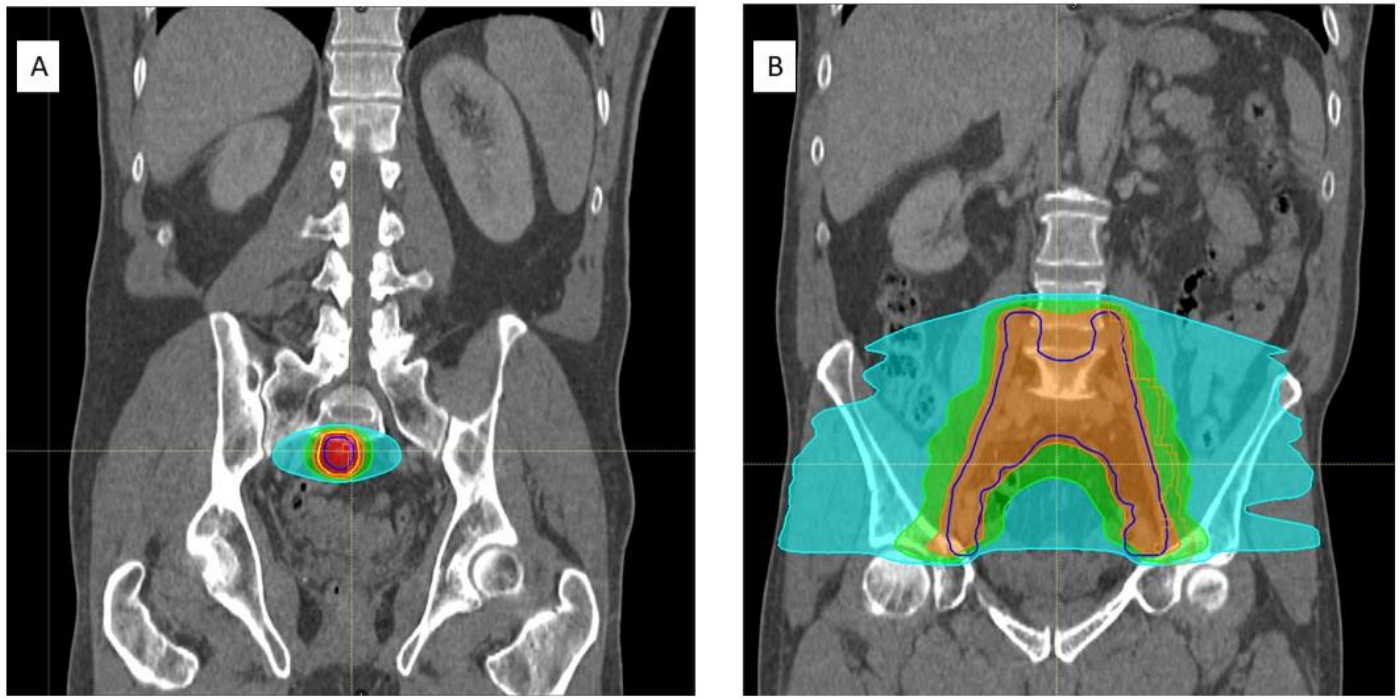
1.4 Extended Nodal Irradiation- a potential solution

ENI for recurrent pelvic nodal PCa has been evaluated in single-arm phase II trials and is associated with promising survival outcomes compared with SBRT in observational studies[9, 15-17]. In a recent multicentre European observational study by De Bleser et al, conventionally fractionated ENI was associated with approximately a 10% improvement in 3-year metastasis-free survival (MFS) compared with SBRT (77% versus 68% for ENI versus SBRT respectively, P=0.01)[9]. Where ENI is delivered for pelvic nodal recurrence after primary/ post-operative prostate bed irradiation, there is the potential for longer term bowel toxicity, specifically late toxicity occurring more than 3 months after completion of treatment. Based on the study by De Bleser et al however, late bowel toxicity rates were low and no greater than grade 2[9].

There is a randomised phase II trial (PEACE V STORM), currently recruiting outside the UK, in the same patient population as POINTER-PC but using metastasis-directed therapy (MDT), defined as local nodal treatment using either radiation (SBRT) or surgery (lymph node dissection)[18]. The PEACE V STORM trial is comparing ENI plus MDT, versus MDT alone (all participants have 6 months of ADT), with the primary endpoint of improved 2-year MFS, with superiority anticipated in the ENI + MDT arm. Our study will not use surgical treatment, consistent with routine NHS practice using RT, as recent studies suggest surgery may be less effective and can be associated with considerable surgery-related toxicities[19]. In addition, PEACE V STORM delivers ENI using daily treatment delivered over 5 weeks while within our study we will test two shorter treatment schedules (20 fractions over 4 weeks or 5 fractions over 2 weeks)[18]. A visual comparison between SBRT and ENI is shown in Figure 2 Coronal CT images.

Figure 2: Coronal CT images

These CT images illustrate the respective radiotherapy target volumes used for SBRT (in A) and ENI (in B) in a patient with a pre-sacral pelvic nodal recurrence after prior post-operative radiotherapy. In A, Gross Tumour Volume (GTV) is indicated by the red outline. In A and B, Planning Target Volume (PTV) is indicated by the dark blue outline. The colourwash illustrates regions receiving higher (red/ orange) and lower (pale blue) radiation isodoses.



1.5 Hypofractionation for Extended Nodal Irradiation

Conventional RT delivers a dose of 1.8-2 Gy per fraction, 5 times per week over several weeks. Hypofractionated RT delivers a higher dose per fraction thus requiring fewer treatment visits over a shorter overall treatment time[20]. When treating primary PCa, the practice of hypofractionated prostate-only RT has been shown to be as effective as longer courses of RT and is now routine[21, 22]. When treating nodal disease, SBRT delivered over 3-5 treatments results in high rates of local control of >70% at 2 years[23]. Extrapolating from this evidence of the effectiveness of hypofractionation in PCa, POINTER-PC will assume the impact of ENI delivered either in 5 or 20 treatments is equivalent in terms of MFS.

When treating larger pelvic volumes, as in ENI, modern technology provides the opportunity to deliver additional radiation dose to the involved nodes (as identified on PET-CT imaging), known as a simultaneous integrated boost (SIB), while also sparing the bowel/ bladder from excessive radiation dose[24]. Hypofractionated ENI delivered in 5 fractions has been investigated in the primary disease setting in early phase and observational studies, frequently with a SIB to prostate/seminal vesicles[25-28]. In these studies, toxicity was acceptable, with ≤5% grade 3 long-term urinary toxicity and no grade 3 long-term bowel toxicity after median follow up of 18-30 months. POINTER-PC will therefore investigate ENI delivered in 5 or 20 fractions in the setting of pelvic nodal recurrence and compare long-term bowel toxicity between ENI delivered over 5 or 20 fractions. The study is designed to address this second toxicity question independent from the comparison of SBRT and ENI on MFS.

1.6 Translational research

There are important questions regarding the optimum combination of additional systemic treatments for this group of patients. There are currently no pre-treatment stratification biomarkers. Identifying patients who are more or less likely to develop distant metastatic disease would allow pre-treatment stratification, facilitating trials investigating systemic treatment escalation and de-escalation.

It is also important to identify patients at particular risk of RT toxicity from re-irradiation and whether there is an association between circulating biomarkers of early normal tissue bowel injury and the clinical manifestation of bowel toxicity. Circulating biomarkers, for example cell-free DNA (cfDNA), DNA methylation patterns, RNA and circulating tumour cells (CTCs), identified from liquid biopsies performed at baseline and following RT have the potential to provide molecular insights regarding tumour response, risk of distant metastatic disease and normal tissue toxicity.

In POINTER-PC we will collect original biopsy +/- prostatectomy samples along with blood samples. Existing tissue samples will be requested at baseline. Blood samples will be taken at 3 time points - prior to, on completion of, and 3 months following RT. Samples will be used to evaluate circulating biomarkers of tumour response, distant metastatic disease and RT bowel toxicity. The CTRU will send a request to sites for the relevant samples when these are needed. Tissue blocks will be stored at

the Manchester Cancer Research Centre before being returned to sites at the end of the trial. For more information on the sample collection process please see the sample collection manual.

Funding for collection of samples has been confirmed, with further funding for analysis being sought at the time of protocol v1.0 going live. Proposed analyses are summarised in section 17.2.5 Translational Statistical Analysis .

2. About the trial

POINTER-PC was developed by a national multidisciplinary team of clinicians, clinical trialists and biostatisticians, with support from National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad) and from the NCRI Prostate Group. Patient representatives have had a key role in shaping the trial design, including from discussions with the Leeds Radiotherapy Patient and Public Involvement Group and with patient representatives from Prostate Cancer UK. The POINTER-PC trial protocol was developed at the EORTC-ESMO-AACR 22nd workshop on Methods in Clinical Cancer Research. The trial is sponsored by University of Leeds and is funded by Yorkshire Cancer Research (YCR). The trial will be conducted in accordance with UK Policy Framework for Health and Social Care Research, National Institute for Health and Care Research (NIHR) Good Clinical Practice (GCP) and the World Medical Association (WMA) Declaration of Helsinki ethical principles for medical research involving human subjects. Ethical approval will be sought through the NHS Health Research Authority (HRA). The trial is registered with International Standard Randomised Controlled Trial Number (ISRCTN) with ISRCTN 11089334.

3. Aims and Objectives

3.1 Aims

i) To determine whether ENI offers superior clinical efficacy in terms of MFS for participants with PCa pelvic nodal recurrence compared to SBRT.

ii) To determine whether ENI can be delivered over a shorter period (5 visits) without significantly impacting patient reported toxicity compared to longer course ENI (20 visits)

3.2 Primary objectives

i) To compare ENI (ENI-5 and ENI-20) with SBRT for the endpoint of MFS

ii) To compare ENI-5 with ENI-20 for the endpoint of patient reported outcome measure (PROM)-assessed late bowel toxicity at 3 years

3.3 Secondary objectives

To assess:

- Overall survival (OS)
- Biochemical progression free survival (bPFS)
- Failure free survival (FFS)
- Patterns of first failure
- Treatment compliance
- Genitourinary (GU), gastrointestinal (GI), hormonal and sexual toxicities (PROM assessed)
- Health Related Quality of Life (HRQOL)
- Acute and late GI and GU toxicities (clinically assessed)
- Safety and toxicity (See Section 15 Endpoints for full definitions of primary and secondary endpoints.)

3.4 Translational objectives

Funding will be sought to explore the following themes:

1. How do levels of CTCs and ctDNA change during and after salvage RT treatment, can these changes in the amount of circulating biomarkers predict response to RT and does this differ by the type of salvage RT treatment?
2. Can CTCs and ctDNA provide molecular insights into patients at greater risk of distant metastatic disease and provide an early indication of tumour response to salvage RT? For example, can detection of pre-treatment ctDNA and/ or CTCs predict response to salvage RT in patients with pelvic nodal recurrent prostate cancer? Can the combination of CTC and ctDNA detection improve sensitivity / specificity for predicting metastatic disease?

3. Can transcriptome signatures identified on archival biopsy/ prostatectomy tissue predict for development of distant metastatic disease following RT for pelvic nodal recurrence?
4. Can biomarkers aid personalisation of salvage RT treatment, based on likelihood of distant metastases and/ or tumour response? For example, can markers identified as prognostic of outcome be combined with clinical prognostic markers to develop personalised treatment prediction models?
5. Can cfDNA released into the blood during normal tissue bowel injury, identified by bowel-specific methylation markers, predict the clinical development of early and late re-irradiation toxicities?

4. Trial design overview

POINTER-PC is a UK, multicentre, prospective, open-label three-arm randomised controlled phase III trial of SBRT versus ENI (in 5 or 20 fractions) in patients with PET-CT defined PCa pelvic nodal recurrence.

The trial will recruit a total of 480 participants over 4 years.

Participants will be randomised 2:1:1 (A:B:C) to receive:

- Arm A. SBRT to involved node(s) (240 participants, control arm for the purposes of this study - can be considered standard of care)
- Arm B. ENI in 5 fractions with SIB to involved node(s) (ENI-5, 120 participants, experimental arm)
- Arm C. ENI in 20 fractions with SIB to involved node(s) (ENI-20, 120 participants, experimental arm for the purposes of this study - but can be also considered standard of care)

All participants will receive 12 months of ADT either starting first day of radiotherapy or up to one month before starting radiotherapy.

It has been confirmed with the UK Medicines and Healthcare products Regulation Agency (MHRA) that POINTER-PC is not a Clinical Trial of Investigational Medicinal Product (CTIMP). Therefore, all safety reporting will follow the requirements of a Clinical Trial that does not use an Investigational Medicinal Product (non-CTIMP).

5. Study population

Adult patients with PET-CT defined PCa pelvic nodal recurrence after previous curative-intent primary treatment for PCa.

6. Eligibility

Patients meeting all the inclusion criteria and none of the exclusion criteria will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted.

6.1 Inclusion criteria

- Age ≥18 years
- Histological diagnosis of prostate adenocarcinoma
- Previous primary PCa treatment (RP, primary/ post-operative radiotherapy (RT) or brachytherapy without previous pelvic nodal RT)
- Maximum of 3 PET-CT (PSMA or choline PET-CT) defined macroscopically-involved pelvic lymph nodes (upper limit of the pelvis is defined as the aortic bifurcation) within 6 months prior to randomisation
- WHO performance status 0-2
- Willing to be randomised to SBRT, ENI-5 or ENI-20
- Patients must be able to provide study-specific written informed consent
- Prepared to participate in follow-up by telephone or in-person

6.2 Exclusion criteria

- Previous pelvic nodal RT
- Contraindications to SBRT or ENI (e.g. inflammatory bowel disease)
- Contraindications to ADT
- Local recurrence in the prostate gland
- Para-aortic nodal metastases (above the aortic bifurcation)
- Mesorectal nodal involvement
- Bone or visceral metastases
- Severe late toxicity relating to primary/ post-operative RT
- Other active malignancy (except non-melanoma skin cancer or other malignancy with a documented disease-free survival for a minimum of at least 3 years before randomisation)
- Castrate-resistant disease

7. Prior and concurrent participation in other clinical trials

Participation in therapeutic clinical trials is not permitted up to the primary endpoint assessment. However, participation in non-therapeutic registry studies or questionnaire-based studies is permitted. Questions about potential clinical trials can be addressed to the Chief Investigator (CI) via UoL CTRU.

8. Participating Sites and Investigators

8.1 Participating sites

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and amendments
- Data collection requirements, including adherence to, paper case report form (pCRF) compliance and electronic case report form (eCRF) submission timelines as per Section 12 Assessments / Section 12.7 Data collection
- Monitoring requirements as outlined in Section 18 Trial Monitoring

8.2 Principal investigators and Co-Investigators

Sites must have an appropriate Principal Investigator (PI) authorised by the site and ethics committee to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating PCa. The trial will be registered with the NIHR Associate PI scheme and resident doctors are encouraged to apply to become an Associate PI for POINTER-PC

(https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm).

8.3 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial-related duties allocated to them, which must be recorded on the site authorised personnel log (APL).

A Curriculum Vitae (CV) for each member of staff must be kept up to date, signed, dated and copies (or statement of their location) held in the electronic Investigator Site File (ISF) held at site. An up to date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation.

NIHR GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation.

8.4 Investigator Site File

The Investigator Site File (ISF) will be provided in an electronic format, which will be sent to sites via Secure Trial Transfer Service (SFTS), the electronic ISF will have all documentation required for sites to deliver all trial related tasks. The trials unit will also supply sites with a skeleton (physical ISF) which will be held at site and store all of forms/logs/contracts which require a wet ink signature, for example: the Authorised Personnel Log (APL), electronic Site Initiation (eSIV) training log, Patient Information Sheet and Informed Consent Form (PISICF) and any other documentation that requires an original wet ink signature. Additionally, sites can also file any other documentation collected at site, pertaining to the POINTER-PC trial, within this skeleton ISF. We can upon request send a complete paper copy of the full ISF if site require this. If so, please email the PointerPC@leeds.ac.uk specific inbox where we shall process this request. Receipt of the ISF must be confirmed before sites can open to recruitment on the trial.

Sites must still keep all the trial documents well organised, including using an ISF contents list/equivalent to help organise.

Sites must ensure it is clear where all the trial documents are stored.

Providing documents electronically does not alter the requirement for wet-ink signatures, sites will need to print applicable forms out for this purpose.

Electronic documents must be stored appropriately securely at sites.

8.5 Radiotherapy quality assurance

A RT quality assurance (QA) programme will be implemented by the NCRI Radiotherapy Trials Quality Assurance (RTTQA) group to ensure treatment is planned and delivered according to the trial protocol. A summary of RTTQA requirements are provided in the **POINTER-PC Radiotherapy contouring, planning, treatment delivery and QA guidelines**.

Achieving both ENI and SABR radiotherapy QA approval is a requirement for sites before they can be opened to recruitment on the trial.

8.6 Site initiation

Before a site is activated, the CTRU trial team will arrange a site initiation. The site initiation will be an electronic process and an audio-visual recorded link with the initiation presentation will be sent to the site.

The audio-visual recorded link will be accompanied by the site initiation training log, which will need to be completed. Best practice would include all related trial specific staff completing the electronic site initiation. As a minimum, the PI, radiotherapy physicist and research radiographer must watch the site initiation video recorded link and slide presentation.

The site initiation audio-visual recorded link and presentation will act as the site initiation and will cover all areas of the trial and management at site.

The following areas will be covered:

- Trial overview and management
- Data collection and process
- Safety reporting
- Essential documentation required for trial

Trial specific staff are required to go through the recorded link and watch the site initiation presentations, then record on the site initiation training log contained within the physical ISF that they have completed the site initiation training. The signed initiation training log must be returned to PointerPC@leeds.ac.uk. A site cannot open to POINTER-PC without the site initiation. Once all documentation is returned, an email confirming that the site initiation has been successful will be issued.

Any questions or queries regarding the trial can also be sent via email to PointerPC@leeds.ac.uk or a meeting can be arranged to discuss any trial specific related queries before confirmation that the site initiation has been successfully completed.

The video recorded site initiation presentation slides can be used as a further training aid for new staff who will work on the study to ensure training standardisation. These staff will need to confirm in the site initiation training log that they have watched the audio-visual recorded site initiation presentation slides.

A copy of the site initiation presentations will be provided for reference in the electronic ISF.

8.7 Essential documentation

The following documentation must be submitted by the site to the CTRU prior to site activation:

- All relevant institutional approvals (e.g. local NHS permissions)
- Completed APL that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed Site Contacts Form (with contact information for the PI, co-investigators, research radiotherapy physics and radiography staff)
- Copy of the PI's current CV that is signed and dated
- Copy of PI's current GCP training certificate
- Signed PI declaration
- ENI and SABR RTQA approval
- Signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution
- Site initiation training log

To minimise additional work in multiple sites opening, centres are asked wherever possible, to make every effort to manage patients for trial purposes on one central site (usually the RT site). Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites, which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

8.8 Site activation

Once the CTRU trial team has received all the required essential documentation, the site has received their electronic ISF and the site has been initiated and the necessary documentation has been sent to the CTRU, a site activation email will be issued to the PI and other research staff by CTRU.

Sites must not approach any potential patients until they have received an activation email from CTRU.

8.9 Participant Identification Centres (PICs)

We plan to use Participant Identification Centres, known as PIC sites. PICs are NHS organisations which identify potential research participants eligible to take part in the trial.

- These are identified via processing personal data and not through normal clinical activity (e.g. through carrying out a search of patient records database to identify individuals that meet a study's eligibility criteria).
- Is following the sponsor(s) instructions in identifying potential research participants;

Directs these potential participants elsewhere without undertaking any further research activity for that study (i.e. the research occurs at another legal entity).

All treatment and research is carried out at non-PIC sites where any patients identified by PICs will be sent to.

PIC sites have less requirements to begin identifying patients that non-PIC sites whilst also enabling patients from other sites to participate in the trial who may not otherwise have done so. POINTER-PC will be utilising PICs to boost recruitment.

9. Consent, Recruitment and Randomisation

9.1 Recruitment setting

Participants will be recruited to the trial from up to 40 UK sites. Research sites will be required to have obtained local management approvals, completed and passed all the required QA checks and undertaken a site initiation with the CTRU prior to the start of recruitment.

9.2 Recruitment and informed consent

Potential participants will be identified through clinic lists and multidisciplinary team meetings and approached for recruitment in outpatient clinics. Suitability will be assessed according to the eligibility criteria for the trial. Attending medical staff (and/ or the trial research team) will provide a verbal explanation of the trial and the appropriate Participant Information Sheet (PIS) for the patient to consider. This will include detailed information about the rationale, design and personal implications of participating in the trial. Following provision of this information, patients will have as long as they need to consider participation and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked to confirm whether they would be willing to take part in the trial.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. Formal assessment of eligibility and informed consent may only be obtained by the PI or an appropriate medically qualified doctor. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. They must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial APL. The PI retains overall responsibility for the informed consent of participants at their research site. This consent process may take place remotely where appropriate, such as during a telephone or video consultation, providing the terms for informed consent as outlined have been met. If remote consent is used site must ensure that no partially signed consent forms are sent to the CTRU as they will not be accepted, only a fully completed copy of the consent form should be sent to the CTRU and the original maintained in the skeleton site file. Please refer to the POINTER-PC Remote Consent Guidance Document for more information on this process. Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial, which are out-with standard routine care at the participating site.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the PIS and consent form are used.
- Checking that information on the consent form is complete and legible.
- Checking that the patient has completed/ initialled all relevant sections and signed and dated the form.

- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient.
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent form signed, etc.).

Following randomisation, site staff are responsible for:

- Adding the participant trial number to the consent form and making sufficient copies and filing the original consent form in the ISF and a copy in the patient's medical notes.
- Giving the patient a copy of their signed consent form and the PIS
- Sending by SFTS a copy of the fully signed consent form to CTRU in line with the terms of the ethically approved consent form.

The participant will be provided with a local contact point where they may obtain further information about the trial.

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki 1996.

The right of the patient to refuse consent without giving reasons will be respected. Consenting participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

The responsibility for prescription and treatment with RT ultimately remains with the PI.

After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated.

9.3 Loss of capacity following informed consent

This is expected to be a very rare occurrence. Any participant who loses physical/ mental capacity would be withdrawn from the trial. Any data collected about the participant up until that point would still be used as part of the trial analysis. This is explained in the PIS.

9.4 Eligibility screening

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements[29], participating research sites will be required to complete a screening log for all patients presenting with PCa pelvic nodal recurrence and screened for eligibility for the POINTER-PC trial. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Anonymised information will be collected including:

- Date screened
- Age
- Ethnicity
- Deprivation Score (see section 9.4.1 & **SSOP06 eCRF Guidance**)
- The reason for non-randomisation:
    - The reason not approached, or
    - The reason not eligible for trial participation, or
    - The reason declined if eligible

However, the right of the patient to refuse consent without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU to capture any and all new applicable data. Once eligibility has been confirmed, participants can then be randomised.

9.4.1 Deprivation Score Collection

Deprivation score is to be collected as part of eligibility screening and reported on the F02 Pre-Randomisation eCRF for any randomised participants. This will require inputting the patient's post code into a website dependent on the patient's home nation. Once a postcode has been input, the website will provide a deprivation score which can then be input onto the screening log for non-recruited patients and recorded on F02 for randomised participants. This will be carried out by staff at site. Further instructions for each region can be found in **SSOP06 eCRF Guidance**.

9.5 Randomisation

Written informed consent for entry into the trial must be obtained and eligibility must be confirmed prior to randomisation.

9.6 Randomisation process

Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by the CTRU. Participants will be randomised on a 2:1:1 basis to receive SBRT, ENI-5 or ENI-20.

A computer-generated minimisation program that incorporates a random element will be used to ensure the treatment groups are well balanced for the following prognostic factors, details of which will be required at randomisation:

- Number of pelvic nodal recurrences (one versus two or three)
- Type of PET-CT at diagnosis of recurrence (PSMA versus other)
- Participant planned for systemic anticancer therapy other than ADT (docetaxel or second generation androgen receptor antagonist or androgen biosynthesis inhibitor versus none)
- Site

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system, which can be accessed via the web. Login details, provided by the CTRU, will be required to access the randomisation system.

The following information will be required at randomisation:

- Site code (assigned by CTRU) of the research site
- Participant details, including initials, date of birth
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (as specified above)
- Participant's preference for completing QoL questionnaires (online or paper) and , if online chosen, the method of receiving online questionnaires (email and/or text message)

Once randomisation is complete, the system will allocate participants a unique 5-digit trial number.

24 hour Randomisation:

Web: https://lictr.leeds.ac.uk/webrand/

Please ensure that the following eCRFs are completed immediately after randomisation:

- Consent Form
- Eligibility Checklist
- Pre-Randomisation
- Randomisation (review of auto-inserted data)

A copy of the consent form should also be sent via the CTRU's secure file transfer service (SFTS)

Once complete, confirmation of randomisation, including details of treatment allocation, will be automatically emailed to the PI and research team.

Please note that in the event that the online randomisation portal is unavailable, you will need to contact the CTRU POINTER-PC team either by telephone or email at POINTERPC@leeds.ac.uk where a paper randomisation will be completed.

10. Interventions

All participants will be treated with 12 months of ADT, commencing on the first day of RT or up to one month before starting radiotherapy. Recommended ADT is LHRH antagonist or LHRH agonist with flare cover. Short-term use of ADT with SBRT/ ENI in this setting is an accepted approach, and this allows the delivery of additional systemic anticancer therapies[9].

RT treatment should commence ideally within one month of randomisation.

RT will be delivered as an outpatient on weekdays. Please see RT guidelines if there are unplanned interruptions in treatment.

SBRT dose will be 30-40 Gy in 5 fractions delivered on alternate days over 2 weeks.

ENI-20 dose will be 44 Gy in 20 fractions plus SIB of 54 Gy to macroscopically involved node(s) delivered daily over 4 weeks.

ENI-5 dose will be 25 Gy in 5 fractions plus SIB of 30-40 Gy delivered on alternate days over 2 weeks.

The trial aims to evaluate the impact of treatment volume rather than dose delivered, therefore the chosen dose fractionation schedules are biologically similar when compared using EQD2 and if the α/β ratio for PCa is assumed to be 1.5 Gy[30], as shown in **Table 1: Planned doses in each arm with EQD2 comparisons using α/β of 1.5 for PCa tumour control.** Using an α/β ratio of 1.5 Gy, the EQD2 of the ENI doses of 44 Gy in 20 fractions and 25 Gy in 5 fractions are 46.5 Gy and 46.4 Gy respectively. The EQD2 of the ENI boost doses of 54 Gy in 20 fractions and 30 Gy in 5 fractions are 64.8 Gy and 64.3 Gy respectively. These doses are also in line with other UK PCa studies either open or in development (PEARLS and PACE-NODES)[31, 32].

Table 1: Planned doses in each arm with EQD2 comparisons using α/β of 1.5 for PCa tumour control.

Arm	*Treatment*	*Number of fractions*	*Total dose*	*EQD2 (α/β=1.5 Gy)*	*Schedule*
A	SBRT	5	30 Gy	64.3 Gy	Alternate days over 2 weeks
			35 Gy	85.0 Gy	
			40 Gy	108.6 Gy	
B	ENI-5	5	25 Gy (pelvis) 30 Gy (SIB)	46.4 Gy (pelvis) 64.3 Gy (SIB)	Alternate days over 2 weeks
			35 Gy (SIB)	85.0 Gy (SIB)	

			40 Gy (SIB)	108.6 Gy (SIB)	
C	ENI-20	20	44 Gy (pelvis) 54 Gy (SIB)	46.5 Gy (pelvis) 64.8 Gy (SIB)	Daily over 4 weeks

ENI-5, Extended Nodal Irradiation in 5 fractions, ENI-20, Extended Nodal Irradiation in 20 fractions; EQD2, Equivalent dose in 2 Gy fractions; SBRT, Stereotactic Body Radiotherapy; SIB, simultaneous integrated boost

Treatments will be delivered using IMRT with daily online image-guidance.

Please see the **POINTER-PC Radiotherapy contouring, planning, treatment delivery and QA guidelines** for full details on immobilisation, planning image acquisition, target volume and organ at risk (OAR) contouring, treatment planning, treatment delivery and QA. Contouring guidance is aligned with other UK PCa trials (PIVOTALboost, PEARLS and PACE-NODES)[31-33]. All centres will complete ENI and SABR RTQA standardisation exercises, consisting of contouring and planning cases, prior to opening to recruitment.

Additional systemic anticancer therapies (docetaxel/ second generation androgen receptor antagonist or androgen biosynthesis inhibitor or any new anti-androgen agent licenced during trial recruitment) will be allowed post-RT. Stratification by the use of additional systemic anticancer therapy has been incorporated into the trial design to account for the potential impact on MFS.

All medication considered necessary for the participants' 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, and if applicable also on the appropriate pages of the CRF.

11. Withdrawal of treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants withdrawn from treatment or prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and eCRFs will continue to be completed.

The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal eCRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

It should be made clear to any participant specifically withdrawing consent for further data collection that further data pertaining to safety will continue to be collected, for example the outcome of an event that was reported prior to withdrawal, and will be included in any safety analysis.

In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available concerning the treatment, they have received in the trial it may be necessary to contact them in the future.

12. Assessments

A summary of the assessment schedule is shown in **Tables 2, 3 and 4: Summary of trial assessments**.

12.1 Prior to approach, consent and randomisation, patients require the following which are used to establish eligibility:

These can be considered standard of care.

- Clinical assessment including history and PSA at recurrence
- Assessment of WHO performance status
- PET-CT (PSMA or choline PET-CT) demonstrating 1-3 PCa pelvic nodal recurrence(s) within 6 months of randomisation

12.2 Performed after consent, prior to randomisation

- Baseline PROM-assessed toxicity using EPIC-26
- Baseline HRQoL assessment using EORTC QLQ-C30
- Deprivation score (**see section 9.4.1 &** SSOP0**6 eCRF** Guidance. **for further information on how to report this)**

12.3 Prior to trial treatment (including ADT)

Prior to trial treatment, patients require:

- Testosterone assessment
- Baseline clinician-assessed toxicity using CTCAE v5.0
- Baseline blood sample for optional translational study

12.4 During radiotherapy

Participants should be reviewed at the end of treatment, including recording of clinician-assessed toxicity using CTCAE v5.0.

End of treatment blood sample for optional translational study.

12.5 During follow up

Clinical and toxicity assessment using CTCAE v5.0 will be performed at **2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months post-RT**, as per standard follow up schedules, either in person or by telephone until metastatic progression. Clinical assessment at each time point includes measurement of PSA (apart from at 2 weeks follow-up), documentation of clinical, biochemical or radiological progression and commencement of any new PCa therapy. Post progression, toxicity assessments will continue at the above timepoints.

After 36 months post-RT, clinical and toxicity assessment will **be undertaken yearly until metastatic progression or 3 years post the last patient being recruited into the trial**, as per standard follow up schedules either in person or by telephone, including measurement of PSA, documentation of clinical, biochemical or radiological progression and commencement of any new PCa therapy. Post progression, yearly toxicity assessments will continue until 3 years post randomisation of the last participant.

Pre-existing symptoms / side effects related to PCa or its primary treatment or that are related to a non-PCa cause that pre-date POINTER-PC trial treatments and remain stable throughout the trial should be recorded on the Pre-Randomisation eCRF and will not be considered as new toxicities.

Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. **Re-staging with PET-CT is mandated.**

PROM-assessed toxicity using EPIC-26 and HRQoL assessment using EORTC QLQ-C30, in electronic format (or paper alternative) will be performed at **2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT.**

12.6 Sample Collection

Please see sample collection manual for full instructions. The sample collection is optional for patients to consent to, and patients can consent to collection of only blood samples, only tissue samples, neither or both.

Blood samples will be taken in Streck tubes at 3 different time points: prior to RT, at the end of RT and 3 months following RT, for the analysis of cfDNA methylation from the plasma and CTCs from the cellular component. These will be used to evaluate circulating biomarkers of tumour response, distant metastatic disease and RT bowel toxicity. Two x 10ml blood samples will be collected at baseline prior to RT, at the end of RT and at 3 months post-RT.

FFPE original biopsy or prostatectomy specimen tissue blocks will be collected at baseline. These will be used to evaluate known prognostic factors for disease recurrence and generate tumour-specific methylation signatures for detection in cfDNA.

The CTRU will send a request to sites for the relevant tissue samples when these are needed. Tissue blocks will be returned to sites at the end of the trial.

Blood samples will be sent to Dr Alex Clipson at Cancer Research UK Manchester Institute. Tissue blocks will be sent to Professor Ananya Choudhury at University of Manchester.

Table 2: Summary of trial assessments – Arm A - SBRT

				Radiotherapy Treatment (RT)[1]		End of Treatment	During follow up (post-radiotherapy treatment)[2]										
	Eligibility	Pre-Randomisation (after consent)	Pre-Treatment	Week 1	Week 2	End of Treatment	2 weeks[3]	6 weeks[3]	3 months[3]	6 months[3]	12 months[3]	18 months[3]	24 months[3]	30 months[3]	36 months[3]	Yearly thereafter (until trial close or metastatic progression)[3]	Yearly thereafter (until trial close)[3]
Clinical assessment	X					X	X	X	X	X	X	X	X	X	X	X	
Performance Status	X																
PSA	X							X	X	X	X	X	X	X	X	X	
Testosterone[4]			X														
Informed consent	X																
**PET-CT* ** **	X																
SBRT				X	X												
CTCAE			X			X	X	X	X	X	X	X	X	X	X		X
Optional Blood Sample Collection[5]			X			X			X								
EPIC-26		X					X		X	X	X		X		X		
EORTC QLQ-C30		X					X		X	X	X		X		X		

CTCAE, Common Toxicity Criteria for Adverse Events; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPIC-26, Expanded Prostate Cancer Index Composite 26-item questionnaire; PET-CT, positron emission tomography-computed tomography; RT, radiotherapy.

[1] ADT, Androgen Deprivation Therapy, all participants will receive a standard of care 12 months of ADT from either the start of radiotherapy or up to one month before starting radiotherapy. Radiotherapy treatment should commence ideally within one month of randomisation. SBRT dose will be 30, 35 or 40 Gy delivered on alternate days over 2 weeks.

[2] Follow-up will be carried out either in person or by telephone.

[3] +/- 1 week for follow-up time points up to and including 6 months, +/- 1 month for follow-up time points from 12 months onwards.

[4] Testosterone should be taken after consent but before participants start trial treatment (including ADT)

[5] The sample collection is optional for patients to consent to, and patients can consent to collection of only blood samples, only tissue samples, neither or both. Blood samples will be collected at site before being sent to Dr Alex Clipson at Manchester. Please see the sample collection manual and section 12.6 for further information.

*PET-CT scans should be completed within 6 months prior to randomisation. ** Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. Re-staging with PET-CT is mandated.

Table 3: Summary of trial assessments – Arm B - ENI-5

				Radiotherapy Treatment[1]		End of Treatment	During follow up (post-radiotherapy treatment)[2]										
	Eligibility	Pre-Randomisation (after consent)	Pre-Treatment	Week 1	Week 2	End of Treatment	2 weeks[3]	6 weeks[3]	3 months[3]	6 months[3]	12 months[3]	18 months[3]	24 months[3]	30 months[3]	36 months[3]	Yearly thereafter (until trial close or metastatic progression)[3]	Yearly thereafter (until trial close[3]
Clinical assessment	X					X	X	X	X	X	X	X	X	X	X	X	
Performance Status	X																
PSA	X							X	X	X	X	X	X	X	X	X	
Testosterone[4]			X														
Informed Consent	X																
**PET-CT* ** **	X																
ENI-5				X	X												
CTCAE			X			X	X	X	X	X	X	X	X	X	X		X
Optional Blood Sample Collection[5]			X			X			X								
EPIC-26		X					X		X	X	X		X		X		
EORTC QLQ-C30		X					X		X	X	X		X		X		

CTCAE, Common Toxicity Criteria for Adverse Events; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPIC-26, Expanded Prostate Cancer Index Composite 26-item questionnaire; PET-CT, positron emission tomography-computed tomography; RT, radiotherapy

[1] ADT, Androgen Deprivation Therapy, all participants will receive a standard of care 12 months of ADT from either the start of radiotherapy or up to one month before starting radiotherapy. Radiotherapy treatment should commence ideally within one month of randomisation. ENI-5 dose will be 25 Gy in 5 fractions plus a SIB of 30, 35 or 40 Gy delivered on alternate days over 2 weeks.

[2] Follow-up will be carried out either in person or by telephone

[3] +/- 1 week for follow-up time points up to and including 6 months, +/- 1 month for follow-up time points from 12 months onwards.

[4] Testosterone should be taken after consent but before participants start trial treatment (including ADT)

[5] The sample collection is optional for patients to consent to, and patients can consent to collection of only blood samples, only tissue samples, neither or both. Blood samples will be collected at site before being sent to Dr Alex Clipson at Manchester. Please see the sample collection manual and section 12.6 for further information

*PET-CT scans should be completed within 6 months prior to randomisation. ** Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. Re-staging with PET-CT is mandated.

Table 4: Summary of trial assessments – Arm C - ENI-20

				Radiotherapy Treatment[1]				End of Treatment	During follow up (post-radiotherapy treatment)[2]										
	Eligibility	Pre-Randomisation (after consent)	Pre-Treatment	Week 1	Week 2	Week 3	Week 4	End of Treatment	2 weeks[3]	6 weeks[3]	3 months[3]	6 months[3]	12 months[3]	18 months[3]	24 months[3]	30 months[3]	36 months[3]	Yearly thereafter (until trial close or metastatic progression)[3]	Yearly thereafter (until trial close[3]
Clinical assessment	X							X	X	X	X	X	X	X	X	X	X	X	
Performance Status	X																		
PSA	X									X	X	X	X	X	X	X	X	X	
Testosterone[4]			X																
Informed consent	X																		
**PET-CT* ** **	X																		
ENI-20				X	X	X	X												
CTCAE			X					X	X	X	X	X	X	X	X	X	X		X
Optional Blood Sample Collection[5]			X					X			X								
EPIC-26		X							X		X	X	X		X		X		
EORTC QLQ-C30		X							X		X	X	X		X		X		

CTCAE, Common Toxicity Criteria for Adverse Events; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPIC-26, Expanded Prostate Cancer Index Composite 26-item questionnaire; PET-CT, positron emission tomography-computed tomography; RT, radiotherapy.

[1] ADT, Androgen Deprivation Therapy, all participants will receive a standard of care 12 months of ADT from either the start of radiotherapy or up to 1 month before starting radiotherapy. Radiotherapy treatment should commence ideally within one month of randomisation. ENI-20 dose will be 44 Gy in 20 fractions plus a simultaneous integrated boost (SIB) of 54 Gy to macroscopically involved node(s) delivered daily over 4 weeks.

[2] Follow-up will be carried out either in person or by telephone.

[3] +/- 1 week for follow-up time points up to and including 6 months, +/- 1 month for follow-up time points from 12 months onwards.

[4] Testosterone should be taken after consent but before participants start trial treatment (including ADT)

[5] The sample collection is optional for patients to consent to, and patients can consent to collection of only blood samples, only tissue samples, neither or both. Blood samples will be collected at site before being sent to Dr Alex Clipson at Manchester. Please see the sample collection manual and section 12.6 for further information.

*PET-CT scans should be completed within 6 months prior to randomisation. ** Re-staging investigations should be prompted by biochemical failure (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT) and/ or symptoms suggestive of recurrence. Re-staging with PET-CT is mandated.

12.7 Death

All deaths occurring from the date of randomisation to the end of follow up must be reported to the CTRU using the Notification of Death eCRF on the POINTER-PC database **within 7 days** of a site becoming aware of the event. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

12.8 End of trial

The end of trial is defined as the date of collection of the last participant's last data item. All participants will be followed up clinically until metastatic progression or until three years post randomisation of the final participant, whichever is sooner. All participants will be followed up for toxicity until 3 years post randomisation of the final participant. In order to collect 3 years post randomisation data, follow up eCRFs will be completed up to 3 years post RT for the final participants).

12.9 Data Collection

Trial participant data will be collected electronically via the CTRU Remote Data Entry (RDE) database.

12.9.1 Questionnaire Data Collection

All baseline questionnaires (EPIC-26 and EORTC QLQ-C30) will initially be completed on paper, however once participants have completed their questionnaire, they can choose whether their subsequent questionnaires are administered on paper in clinic, or electronically via the electronic patient reported outcome software Research Electronic Data Capture (REDCap). Before randomisation, but after consent, the research team will collect the participant's preferred method of paper or electronic administration and, if electronic completion is chosen, their contact details (email address and/or mobile phone number). This information is collected on the randomisation system. The CTRU will be responsible for assigning the participant to the REDCap system if they have chosen electronic administration of the questionnaires. Please make sure to ask the participants their preference for how the link to the QoL questionnaire is delivered, via email and/or text message.

Any subsequent changes to contact details will need to be recorded by RDE into the REDCap database. The research team is responsible for updating all participant contact details.

12.9.2 Paper Questionnaire Administration

Participants who choose paper administration of the questionnaires will receive the questionnaires at their clinic visits. The research team will provide participants with an envelope with the trial name, participant's trial ID and visit timepoint on, for the participant to put their completed questionnaires in. Please ensure that the participant has sealed the envelope to ensure confidentiality. The research team

should then send the questionnaires to the CTRU at the address below as soon as they are completed:

POINTER-PC Trial

Clinical Trials Research Unit

Leeds Institute of Clinical Trials Research

Worsley Building

University of Leeds

Leeds

LS2 9JT

The questionnaires should be completed in clinic wherever possible, however, if the participant is unable to, they can be taken away for completion. These must be returned either at the next clinic appointment for appointments up to 6 months or posted back to CTRU once the participant commences 6-monthly follow-ups. In this instance, the research team should supply already addressed envelopes with prefixed stamp to the participant for the paper questionnaires to be returned to CTRU and ensure that they are returned to the CTRU in a timely manner. This may require the research team to call the participant as a reminder to post the questionnaires back. The envelopes and stamps will be supplied either in the skeleton ISF or you will need to contact the POINTER-PC email POINTERPC@leeds.ac.uk and we will send these to you. Please ensure that you fix the stamp and complete the address for the participant. The research team will need to confirm with the participant at their next clinic visit that they have posted their completed QoL questionnaires back to CTRU.

12.9.3 Paper Questionnaire Administration with Telephone Follow-up Appointment

If the participant has chosen to complete QoL questionnaires via paper with telephone follow-up appointments, the research team will be required to supply the QoL questionnaires in preparation. Dependent upon what the participant specifies, the research team could provide the paper QoL questionnaires in advance to the participant, if they are aware the participant will have telephone follow-up appointments in future. The research team should supply already addressed envelopes with prefixed stamp to the participant for the paper questionnaires to be returned to CTRU. The envelopes and stamps will be supplied either in the skeleton ISF or you will need to contact the POINTER-PC email POINTERPC@leeds.ac.uk and we will send these to you. Please ensure that you fix the stamp and complete the address for the participant when sending out QoL questionnaires. The paper questionnaires should be there at the time the participant has their telephone appointment, to enable the participant to complete and return the questionnaires at that timepoint. The paper questionnaires should be sent to:

POINTER-PC Trial

Clinical Trials Research Unit

Leeds Institute of Clinical Trials Research

Worsley Building

University of Leeds

Leeds

LS2 9JT

12.9.4 Electronic Questionnaire Administration

For participants who choose to complete the questionnaires electronically, SMS and/or emails will be sent to the participants from the CTRU with a link to the questionnaire for completion. Non-responders will receive a reminder 2 weeks after the initial link to the questionnaire was sent and where records show that it has not been completed. The reminder will be sent electronically by CTRU.

The CTRU will contact sites at intervals throughout the study to remind sites to check that each consenting participant's contact details and status have not changed and that it is still appropriate to send links to the questionnaires.

12.10 Electronic Case Report Forms requiring expedited reporting to CTRU

A number of eCRFs which require expedited reporting to the CTRU, should be entered within the time points specified below:

- A scanned copy of any consent forms must be sent to CTRU via the SFTS and the corresponding eCRF entered as soon as possible following randomisation and confirmation of the participant's 5-digit trial number.
- RT Treatment eCRF must be entered within 7 days of completion of RT to allow the correct administration of electronic QoL questionnaires at 2 weeks post-RT.
- Radiotherapy Related Serious Adverse Event (RRSAE) and Related Unexpected Serious Adverse Event (RUSAE) eCRFs must be entered within 24 hours of the site becoming aware and notifying CTRU by email PointerPC@leeds.ac.uk. Please note: paper RRSAE and RUSAE forms will also be provided as a back-up in the event any urgent reporting is required, and the MACRO database is unavailable.
- Protocol Violation eCRFs must be entered within 24 hours of the site becoming aware and notifying CTRU by email PointerPC@leeds.ac.uk
- Any Notification of Death eCRFs must be entered within 7 days of the site becoming aware and notifying CTRU by email PointerPC@leeds.ac.uk
- Any Withdrawal Request eCRFS must be entered within 7 days of the date of withdrawal and notifying CTRU by email PointerPC@leeds.ac.uk

All other eCRFs must be completed within 28 days of the data collection time points detailed in Tables 2, 3 and 4: Summary of trial assessments.

Only a participant's trial number, date of birth and initials will be added to the eCRFs – site staff are responsible for ensuring any data returned to CTRU does not contain any other personal identifiable data. The exception to this is any copies of the consent form, where the participant/ authorised investigator name and signature must be present.

Following completion of eCRFs, CTRU will contact sites on a regular basis to resolve any missing or discrepant data.

13. Safety reporting

13.1 Non-CTIMP

It has been confirmed by the CI and the MHRA algorithm that POINTER-PC is a non-CTIMP trial.

13.2 General definitions

13.2.1 Radiotherapy Related Adverse Events (RRAEs)

Adverse Events (AEs) are all untoward and unintended responses to a trial treatment related to any dose administered.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to a trial RT treatment qualify as Radiotherapy Related AEs (RRAEs). The expression "reasonable causal relationship" should convey that there are facts (evidence) or arguments to suggest a causal relationship.

Trial treatment in POINTER-PC is defined as RT (ENI or SBRT) with standard of care ADT with or without additional systemic therapy (docetaxel/ second generation androgen receptor antagonist or androgen biosynthesis inhibitor). The trial will only collect RRAEs.

13.2.2 Serious Adverse Events (SAE) and Radiotherapy Related Serious Adverse Events (RRSAE)

An SAE is any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other important medical event

*The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event- it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgement must be exercised in deciding whether an event is *"serious"* in accordance with these criteria.

Where an SAE is deemed to be related to trial RT treatment the event is termed as a RRSAE.

13.2.3 Related Unexpected Serious Adverse Event (RUSAE)

An SAE which is related and unexpected (RUSAE) will require expedited reporting (see Section 12.10 Electronic Case Report Forms requiring expedited reporting to

CTRU) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms related and unexpected as:

- Related: resulted from administration of any research procedures.
- Unexpected: an event that in the opinion of the investigator is not considered expected.

When determining whether an RRSAE is expected or not, please refer to Appendix B for a list of expected RT-related toxicities.

13.3 Reporting requirements for Radiotherapy Related Adverse Events

Information about all RRAEs, whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant eCRF. RRAEs will be collected for all participants from the start of treatment until 3 years post randomisation of the final participant and will be evaluated for duration and intensity according to CTCAE v5.0.

13.4 Reporting requirements for Radiotherapy Related Serious Adverse Events and Related Unexpected Serious Adverse Events

All RRSAEs and RUSAEs for all participants occurring during treatment and until 3 years post randomisation of the final participant must be recorded on the appropriate RRSAE or RUSAE eCRF within 24 hours of the trial site team becoming aware of the event. Site must also notify CTRU by email PointerPC@leeds.ac.uk when done. Please note: a paper RRSAE and RUSAE form will also be provided as a back-up in the event any urgent reporting is required, and the MACRO database is unavailable.

RRSAEs and RUSAEs will be collected until unequivocal disease progression according to the assessment schedule, this is defined as the active trial monitoring period.

For each RRSAE and RUSAE the following information will be collected:

- Full details in medical terms with a diagnosis, if possible
- Case description
- Event duration (start and end dates, if applicable)
- Seriousness criteria
- Outcome
- Action taken
- Assessment of relatedness
- Whether the event is considered expected or unexpected

Assessment of expectedness must be made by an authorised medically qualified person. If such a person is unavailable, initial reports without relatedness and

expectedness assessment should be recorded on the RRSAE or RUSAE eCRF by a healthcare professional within 24 hours but must be followed up by medical assessment as soon as possible thereafter.

Please ensure that each event is reported separately and not combined on one RRSAE or RUSAE form.

Any change of condition or other follow up information should be entered within 24 hours of the research team becoming aware of the information. Events will be followed up until the event has resolved or a final outcome has been reached.

All RRSAEs assigned by the PI or delegate (or following CI review) as unexpected will be classified as a RUSAE and will be subject to expedited reporting to the Sponsor and REC by the CTRU on behalf of the CI in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs) and Sponsor requirements.

As the focus of this study is on the RT and not the medicinal products also being received by trial participants, any suspected, unexpected serious adverse reactions, concerning non-IMPs used in POINTER-PC for research purposes will not be reported by the trial team to the REC. Any serious side effects from already approved medicines, that will be used as standard of care within this trial, will not be reported as a RUSAE in the trial, following local NHS site specific procedures alert the MHRA using the yellow card reporting system at https://yellowcard.mhra.gov.uk/

14. Responsibilities

14.1 Sponsor

The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

14.2 Principal Investigator

- Checking for RRAEs when participants attend for treatment/ during follow up
- Using medical judgement in assigning relatedness and expectedness using Appendix B.
- Ensuring that all RRSAEs (including RUSAEs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that RRSAEs (including RUSAEs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting
- Ensuring that RRAEs are recorded and reported to the CTRU in line with the requirements of the protocol

14.3 Chief Investigator / delegate or independent clinical reviewer

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit
- Using medical judgement in assigning relatedness and expectedness of RRSAEs where it has not been possible to obtain local medical assessment
- Immediate review of all RUSAEs
- Review of specific RRSAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan

14.4 CTRU

- Central data collection and verification of RRAEs, RRSAEs and RUSAEs, according to the trial protocol onto a MACRO database
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan
- Expedited reporting of RUSAEs to the REC and Sponsor within required timelines
- Notifying Investigators of all RUSAEs that occur within the trial which compromise participant safety

14.5 Radiotherapy Trials Quality Assurance

The Radiotherapy Trials Quality Assurance group will work with sites to achieve and approve their radiotherapy quality assurance (RTQA) as well as their PI as part of site setup. Please see the POINTER-PC Radiotherapy Guidelines for further information.

14.6 Trial Management Group

In accordance with the Trial Terms of Reference (ToR), the Trial Management Group (TMG) will provide clinical and practical advice on trial related matters. The TMG is accountable to the TSC and DMEC and are responsible for escalating concerns to these committees.

14.7 Trial Steering Committee

In accordance with the Trial ToR, the TSC will periodically review blinded safety data and liaise with the DMEC regarding safety issues. Ongoing recruitment will be monitored through the TSC and TMG.

14.8 Data Monitoring & Ethics Committee

In accordance with the Trial ToR, the DMEC will periodically review unblinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. A DMEC Charter outlining roles and responsibilities of the DMEC and data for review will be produced prior to recruitment.

Full reports will be presented to the DMEC in confidence at least annually or more frequently as deemed appropriate. The DMEC, in the light of any information reviewed, will report to the TSC and make general recommendations about continuing recruitment to the programme.

15. Endpoints

15.1 Primary endpoints

- SBRT versus ENI: Metastasis-free survival (defined as time from randomisation to progression of the treated node(s), new nodal, bone or visceral metastatic disease, or death due to PCa)
- ENI-5 versus ENI-20: PROM-assessed late bowel toxicity at 3 years, measured using the Expanded Prostate Cancer Index Composite 26-item questionnaire (EPIC-26) bowel domain summary score.

15.2 Secondary endpoints

- Overall survival (defined as time from randomisation to death from any cause)
- Biochemical progression free survival (defined as ≥2 ng/ml increase in PSA above the nadir value achieved after completion of RT)
- Failure free survival (defined as time from randomisation to biochemical failure, commencement of further anticancer therapy for PCa, progression of the treated node(s), new nodal, bone or visceral metastases or death from PCa
- Patterns of first failure: Local, treated-node(s), other regional/ pelvic lymph node(s), para-aortic lymph node(s), other extra-pelvic lymph node(s), bone metastasis, visceral metastasis (liver, lung), other metastasis
- Treatment compliance: treatment duration, number of fractions, total dose received and whether treatment was delivered as planned
- Urinary, bowel, hormonal and sexual toxicities, measured using the relevant EPIC-26 function and other sub-domains at baseline and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT
- HRQoL, measured using European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline and at 2 weeks, 3 months, 6 months, 12 months, 24 months and 36 months post-RT
- Clinician-reported toxicity at baseline, end of treatment, 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months post-RT and annually thereafter until 3 years post **randomisation** of the final participant and maximum acute (≤3 months) and late (>3 months) bowel and urinary toxicity measured using Common Toxicity Criteria for Adverse Events (CTCAE) v5.0
- Safety and toxicity overall and at end of treatment and each follow up timepoint on the basis of Radiotherapy Related Adverse Events (RRAEs), Radiotherapy Related Serious Adverse Events (RRSAEs) and Related and Unexpected Serious Adverse Events (RUSAEs) and measured using CTCAE.

16. Data Management – Data Collection, Recording and Handling

16.1 Source Data

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. To allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained. Source data is kept as part of the participants' medical notes generated and maintained at site.

Source data should be clearly identified with awareness of the variation in practice at sites.

Below is an example of the way in which source data can be identified.

Table 5: Example source data

Data	Source
Participant Reported Outcomes	This is stored electronically for those forms completed via REDCap. However, for those participants who complete a paper CRF, the original participant-completed CRF is the source and will be sent to and kept at the CTRU.
Clinical Event Data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on CTRU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.

16.2 Source Documents

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, PET-CT or CT images, RT dose data, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

16.3 Electronic Case Report Form (CRF) Completion

Only CRFs specified in this protocol must be used (See **Tables 2, 3 and 4: Summary of trial assessments**). The delegated staff completing the eCRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by data entry being completed in the Electronic Data Capture (EDC) system's audit trail.

An eCRF (and/or a pCRF) is required, and relevant forms should be completed for each individual participant.

It is the responsibility of the PI to ensure the accuracy of all data entered in the eCRFs (and/or pCRFs) and confirm accordingly. The APL will identify all personnel with responsibilities for data collection.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried by CTRU Data Management. Staff delegated to complete eCRFs will be trained to adhere to GCP requirements and trial-specific guidelines as appropriate.

16.4 Electronic Case Report Form Data Collection and Completion Guidance

Participating sites will record trial participant data submitted via RDE onto eCRFs, using the MACRO database system, which will be managed by the CTRU. CTRU will provide access to the RDE system once a site is authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided. RDE/ eCRFs must only be completed by personnel authorised to do so by the PI at site, as recorded on the APL. Login details will be provided for these personnel only and should not be shared with others.

The EPIC-26 and EORTC QLQ-C30 questionnaires will be completed by trial participants either electronically via the electronic patient reported outcome software REDCap or on paper. Questionnaire data entered on REDCap will be directly accessible by the trial data management staff at CTRU. Paper questionnaires will be completed in clinic wherever possible or, if taken home to complete, returned at the next clinic visit for appointment up to 6 months and the research

team will then send on to the CTRU. Once the participant commences 6-monthly follow-up appointments, they should post questionnaires completed at home directly to the CTRU using an envelope provided by the research team. If there is a telephone appointment instead of a clinic visit, and the participant has selected paper questionnaires, the participant will post the completed questionnaires back to the CTRU using an envelope provided by the research team, as detailed in section 12.9.3.

Participating sites will be expected to maintain a file of essential trial documentation in the skeleton ISF, which will be provided by the CTRU, and keep copies of all completed paper CRFs for the trial.

It is the responsibility of the site staff to ensure the electronic and skeleton ISF is properly maintained during the duration of the trial.

16.5 Data Validation

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data, as applicable. Data entry is the responsibility of the trial site staff whilst data queries and self-evident corrections are the responsibility of the trial team.

16.6 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

16.7 Data Security

- The University of Leeds has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data.
- CTRU has arrangements in place for the secure storage and processing of the trial data which comply with UoL policies. The Trial Database System incorporates the following security counter measures:
    - Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
    - Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.
    - Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

- System Management: The MACRO and REDCap systems will be developed by the Database Team and will be implemented and maintained by the Database Team.
- EDC System Design: The EDC System will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.
- Operational Processes: The data will be processed and stored within CTRU unless specifically noted.
- System Audit: The System will benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment
- Data Protection Registration: The UoL's Data Protection Registration number is Z553814X
- NHS Digital Security and Protection Toolkit (DSPT) Organization code: ECC0010

17. Statistical considerations

17.1 Sample size

480 participants will be recruited from 35-40 UK RT centres over 4 years and allocated 2:1:1 as follows: SBRT (240 participants), ENI-20 (120 participants) and ENI-5 (120 participants).

17.1.1 ENI versus SBRT:

Based on the best available evidence, 3-year MFS is anticipated to be approximately 68% with SBRT. This estimate is based on the 3-year MFS observed by De Bleser et al from a large multicentre retrospective observational study[9]. A hazard ratio of 0.65 is deemed to represent a minimal clinically relevant treatment effect for the use of ENI, corresponding to an improvement in 3-year MFS of 9.8% for ENI compared with SBRT. To demonstrate an increase in 3-year MFS to 77.8% with 80% power and a 2-sided 5% significance level, a total of 169 MFS events are required. With recruitment over 4 years, a minimum follow-up of 3 years and a maximum follow up of 7 years post randomisation, this corresponds to a total sample size of 432 patients (216 participants treated using SBRT and 216 participants treated using ENI). Accounting for a 10% drop out rate, a total of 480 patients are required.

17.1.2 ENI-5 versus ENI-20:

In order to exclude a minimum clinically important difference (MCID) of 5.0 points at 3 years for PROM-assessed bowel toxicity with ENI-5 compared to ENI-20 with 80% power and 1-sided 5% significance level, a total of 160 participants are required. These calculations use a non-inferiority margin for ENI-5 vs ENI-20 of 5.0 points using the EPIC-26 questionnaire. Assuming a standard deviation (SD) of 12.6 (1/3 SD=4.2), this corresponds to an effect size of 0.4 based on data presented by Skolarus et al, for which a MCID of between 4 and 6 points is recommended[36]. With a total of 120 patients per arm based on the SBRT versus ENI sample size requirements, this allows for up to 33% dropout at 3 years.

17.2 Statistical analysis

17.2.1 General Considerations

Statistical analysis is the responsibility of the CTRU Statisticians. The analysis plan detailed below provides an overview of the analyses to be performed. A full statistical analysis plan will be written and approved by the TMG before any analyses are undertaken.

Data will be analysed and reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [29]. All analyses on the SBRT versus ENI endpoint will be conducted on an intention to treat (ITT) basis, analyses on the ENI-5 versus ENI-20 endpoint will be conducted on a per protocol basis and safety and clinically assessed toxicity data will be analysed using the safety population (participants analysed according to the treatment they received). Final analysis of the ENI-5 vs. ENI-20 comparison will take place once all participants have reached at

least 3 years post-randomisation. Final analysis of the SBRT vs. ENI comparison will take place once at least 169 events have occurred for the MFS endpoint.

Participant demographics, primary disease and prior treatment characteristics and current disease and treatment characteristics will be summarised by treatment arm in the ITT population. For categorical variables, frequency tables, with proportions expressed as percentages, will be presented. Continuous variables will be reported using mean, median and range.

17.2.2 Interim analysis

No formal interim analyses are planned, and no formal stopping rules are defined. However, the independent DMEC will monitor safety and toxicity data. An initial safety report will be presented to the DMEC after 40 patients (approximately 20 participants treated using SBRT, 10 participants treated using ENI-20 and 10 participants treated using ENI-5) have been recruited and have at least 3 months follow-up data to monitor acute toxicity.

With the permission of the independent DMEC and TSC, we plan to publish descriptive summaries of the acute toxicity (clinician assessed and PROM assessed) by arm up to 3 months after approximately 120 participants have been recruited and have been followed up at least 3 months, if this is not deemed to be contraindicated or affect the scientific integrity of the trial or future recruitment. This is to demonstrate safety and acceptability.

17.2.3 Primary endpoint analysis

17.2.3.1 ENI versus SBRT:

MFS timed from the date of randomisation will be compared between the two treatment groups (SBRT versus ENI-5 + ENI-20) using a Cox proportional hazards model, adjusted for the minimisation factors, if appropriate. The hazard ratio (HR) for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% confidence intervals (CIs) and associated p-value testing for the difference between the arms. The assumptions of the Cox model will be tested. This will be the analysis of primacy.

Participants who are metastasis-free at the time of analysis, or who have come off trial prior to observing their primary endpoint (e.g. withdrawals with no further follow up, losses to follow-up or death not due to PCa), will be censored at the last date they were known to be alive and metastasis -free. The number of deaths due to causes other than PCa will be summarised, and a competing risks analysis may be performed.

MFS will be presented for each arm via Kaplan-Meier (KM) curves. The median MFS, MFS at pre-specified timepoints (12, 24, 36 months), and corresponding 95% CIs will be presented along with the log-rank test statistic (and associated p-value) which tests for a difference in the median time to MFS.

17.2.3.2 ENI-5 versus ENI-20:

The difference in mean adjusted-for-baseline bowel toxicity score between ENI-5 and ENI-20 at 3 years post-RT will be presented with corresponding 2-sided 90% confidence intervals. Treatment groups will be compared using a linear regression model, adjusted for the minimisation factors and baseline bowel toxicity score. The lower bound of the 90% confidence interval for the difference in mean adjusted scores will be compared with the non-inferiority margin of -5.0 (the data will be assumed to be normally distributed). This will be the analysis of primacy.

The primary analyses for each comparison are not hierarchical and are independent research questions therefore adjustment for multiple testing is not required.

17.2.4 Secondary endpoint analysis

Endpoints relate to each comparison (ENI vs SBRT and ENI-5 vs ENI-20) unless otherwise specified.

Time to event endpoints (including OS, FFS and bPFS) will be presented using KM curves. A Cox proportional hazards model will be used to compare treatment groups, adjusting for the minimisation factors, if appropriate. The parameter estimates, hazard ratios and corresponding 95% and 90% (for ENI-5 vs ENI-20 only) confidence intervals will be presented. Test statistics will be presented as per the primary analysis for ENI vs SBRT only. For ENI-5 vs ENI-20 the treatment groups will be compared on a non-inferiority basis. The proportion of participants experiencing each event will be presented by treatment group and overall. (ENI vs SBRT, and ENI-5 vs ENI-20)

Participants who are event-free at the time of analysis, or who come off trial prior to observing an event (e.g. withdrawals, losses to follow-up, or death), will be censored at the last date they were known to be alive and event-free. The number of deaths due to causes other than PCa will be summarised, and a competing risks analysis may be performed.

The proportion of participants experiencing each CTCAE grade of bowel and urinary and other toxicities will be summarised for each treatment arm, for the overall treatment period and at each follow-up assessment. The maximum CTCAE grade of toxicities experienced for bowel and urinary toxicity and overall will be summarised for acute (≤ 3 months) and late (> 3 months) toxicities.

Safety and toxicity will be summarised on the basis of Radiotherapy Related Serious Adverse Events (RRSAEs) and Related and Unexpected Serious Adverse Events (RUSAEs) and measured using CTCAE at the end of treatment and at each follow up time point and overall.

Descriptive summaries will be presented by treatment arm for the pattern of failure. Data will be presented for the type and site of recurrence e.g. nodal, bone, visceral and, if nodal, which lymph nodes showed evidence of relapse.

Summary statistics will be presented for the number of fractions and total dose of radiotherapy received in each treatment arm and duration of treatment. Whether

treatment was delivered as per protocol will be summarised, with reasons if not per protocol.

Mean scores with corresponding 95% CIs will be calculated for all domains of the EORTC QLQ-C30 and urinary, bowel, hormonal and sexual toxicities using the relevant EPIC -26 function and other sub domains for each treatment group and overall, at each follow-up time point. Data will also be summarised descriptively using plots of mean QoL over time, using scales and summary tables by treatment arm and overall. Change in mean score from baseline with 95% CIs will be reported at each follow-up time point.

A repeated measures analysis will also be undertaken for PROM data taking into account scores at each follow up timepoint. Treatment groups will be compared using a mixed effects linear regression model, adjusted for the minimisation factors and baseline QoL scores.

18. Trial monitoring

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/ documents as required. Participants are informed of this in the participant information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

18.1 Trial Steering Committee and Data Monitoring & Ethics Committee

The trial will be overseen by an independent TSC and DMEC.

The DMEC will monitor the trial data, safety including RRSAEs and RUSAEs, treatment-related mortalities and the associated ethics of the trial. Listings of RRSAEs and RUSAEs will be provided to the DMEC on a regular basis. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan, by the CTRU, at least annually. Frequency may change depending on safety concerns and recruitment numbers.

After each review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

18.2 Data monitoring

A Trial Monitoring Plan (TMP) will be developed and agreed by the TMG and TSC based on the trial risk assessment.

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants. The CTRU/ Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/ Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

18.3 Clinical governance issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC, Sponsor and, where applicable, to individual NHS Trusts.

19. Quality assurance processes

19.1 Quality assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006, and through adherence to CTRU SOPs.

19.2 Serious breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

20. Ethical considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

20.1 Ethical approval

Ethical approval will be sought through the HRA. The trial will be submitted to and approved by a REC, the HRA and the appropriate Site-Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, PISs, consent forms and all other relevant trial documentation.

21. Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and GDPR and operationally this will include:

- Consent form from participants to take part in the trial.
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is randomised into the trial. All other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and / or further collection of data, their data will remain on file and will be included in the final trial analysis.

22. Archiving

22.1 Trial data and documents held by CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures and Funder's requirements for a minimum of 5 years.

22.2 Trial data and documents held by research sites

Site data and documents will be archived at the participating research sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

22.3 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

23. Statement of indemnity

The University of Leeds has cover for liabilities/prospective liabilities arising from negligent harm and in some circumstances, non-negligent harm. Clinical negligence indemnification will rest with the participating Trusts.

24. Publication policy

The trial has been registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment. The trial is registered with the ISRCTN registry and has been allocated the ISRCTN number 11089334.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions (www.icmje.org). These state that authorship credit should be based only on the following conditions being met:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published

In light of this, the CI, trial leads and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting, and reporting the trial. A publication plan will be developed for use throughout the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the DMEC and TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

With the permission of the independent DMEC and TSC, we plan to publish descriptive summaries of the acute toxicity by arm up to 3 months after approximately 120 participants have been recruited and have been followed up at least 3 months, if this is not deemed to be contraindicated or affect the scientific integrity of the trial or future recruitment.

An electronic copy of peer-reviewed, published papers arising from this research will be deposited in the Europe PubMed Central database.

25. References

1. National Cancer Registration and Analysis Service (NCRAS). CancerData: Prostate Cancer. 2018 Available from: https://www.cancerdata.nhs.uk/getdataout/prostate. [Accessed 24/06/2021]

2. European Association of Urology. Prostate cancer. 2021 Available from: https://uroweb.org/guideline/prostate-cancer/. [Accessed 10th May 2021]

3. Freedland, S.J., E.B. Humphreys, L.A. Mangold, et al., Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. J Clin Oncol, 2007. **25**(13): p. 1765-71.

4. National Comprehensive Cancer Network. Prostate cancer (version 2.2021). 2021 Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459. [Accessed 10th May 2021]

5. Bernstein, A.N., J.E. Shoag, R. Golan, et al., Contemporary Incidence and Outcomes of Prostate Cancer Lymph Node Metastases. The Journal of Urology, 2018. **199**(6): p. 1510-1517.

6. De Visschere, P.J.L., C. Standaert, J.J. Fütterer, et al., A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer. European Urology Oncology, 2019. **2**(1): p. 47-76.

7. Chalkidou, A., T. Macmillan, M.T. Grzeda, et al., Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. The Lancet Oncology, 2021. **22**(1): p. 98-106.

8. NHS England. Clinical Commissioning Policy: Stereotactic ablative radiotherapy (SABR) for patients with previously irradiated, locally recurrent primary pelvic tumours (All ages) [201002P] (URN: 1909). 2021 Available from: https://www.england.nhs.uk/publication/clinical-commissioning-policy-stereotactic-ablative-radiotherapy-sabr-for-patients-with-previously-irradiated-locally-recurrent-primary-pelvic-tumours-all-ages/. [Accessed 24/06/2021]

9. De Bleser, E., B.A. Jereczek-Fossa, D. Pasquier, et al., Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. Eur Urol, 2019. **76**(6): p. 732-739.

10. Ost, P., D. Reynders, K. Decaestecker, et al., Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol, 2018. **36**(5): p. 446-453.

11. Phillips, R., W.Y. Shi, M. Deek, et al., Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA oncology, 2020. **6**(5): p. 650-659.

12. Ost, P., B.A. Jereczek-Fossa, N. Van As, et al., Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences. Clin Oncol (R Coll Radiol), 2016. **28**(9): p. e115-20.

13. Decaestecker, K., G. De Meerleer, B. Lambert, et al., Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol, 2014. **9**: p. 135.

14. Murray, L.J., J. Lilley, M.A. Hawkins, et al., Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review. Radiother Oncol, 2017. **125**(2): p. 213-222.

15. Fodor, A., G. Berardi, C. Fiorino, et al., Toxicity and efficacy of salvage carbon 11-choline positron emission tomography/computed tomography-guided radiation therapy in patients with lymph node recurrence of prostate cancer. BJU International, 2017. **119**(3): p. 406-413.

16. Lépinoy, A., Y.E. Silva, E. Martin, et al., Salvage extended field or involved field nodal irradiation in 18F-fluorocholine PET/CT oligorecurrent nodal failures from prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging, 2019. **46**(1): p. 40-48.

17. Vaugier, L., C. Palpacuer, E. Rio, et al., Early Toxicity of a Phase 2 Trial of Combined Salvage Radiation Therapy and Hormone Therapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGOPELVIS GETUG P07). International Journal of Radiation Oncology*Biology*Physics, 2019. **103**(5): p. 1061-1067.

18. De Bruycker, A., A. Spiessens, P. Dirix, et al., PEACE V – Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. BMC Cancer, 2020. **20**(1): p. 406.

19. Bravi, C.A., N. Fossati, G. Gandaglia, et al., Long-term Outcomes of Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer After Radical Prostatectomy: Not as Good as Previously Thought. European Urology, 2020. **78**(5): p. 661-669.

20. Brand, D.H. and J.R. Yarnold, The Linear-Quadratic Model and Implications for Fractionation. Clin Oncol (R Coll Radiol), 2019. **31**(10): p. 673-677.

21. Dearnaley, D., I. Syndikus, H. Mossop, et al., Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. The Lancet Oncology, 2016. **17**(8): p. 1047-1060.

22. Widmark, A., A. Gunnlaugsson, L. Beckman, et al., Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet, 2019. **394**(10196): p. 385-395.

23. Palma, D.A., R. Olson, S. Harrow, et al., Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers

(SABR-COMET): a randomised, phase 2, open-label trial. The Lancet, 2019. **393**(10185): p. 2051-2058.

24. Reis Ferreira, M., A. Khan, K. Thomas, et al., Phase 1/2 Dose-Escalation Study of the Use of Intensity Modulated Radiation Therapy to Treat the Prostate and Pelvic Nodes in Patients With Prostate Cancer. Int J Radiat Oncol Biol Phys, 2017. **99**(5): p. 1234-1242.

25. Fairmichael, C., K.M. Redmond, S.O. Osman, et al., The stereotactic prostate radiotherapy (SPORT) trial: A randomized feasibility study comparing prostate SABR to prostate and pelvic nodal SABR. Journal of Clinical Oncology, 2021. **39**(6_suppl): p. 248-248.

26. Murthy, V., M. Gupta, G. Mulye, et al., Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Clin Oncol (R Coll Radiol), 2018. **30**(7): p. 442-447.

27. Musunuru, H.B., L. D'Alimonte, M. Davidson, et al., Phase 1-2 Study of Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation in Patients With High-Risk Prostate Cancer (SATURN): Early Toxicity and Quality of Life. Int J Radiat Oncol Biol Phys, 2018. **102**(5): p. 1438-1447.

28. Pinitpatcharalert, A., L. Happersett, M. Kollmeier, et al., Early Tolerance Outcomes of Stereotactic Hypofractionated Accelerated Radiation Therapy Concomitant with Pelvic Node Irradiation in High-risk Prostate Cancer. Advances in radiation oncology, 2019. **4**(2): p. 337-344.

29. Schulz, K., D. Altman, and D. Moher, CONSORT 2010 statement: updated Guidelines for Reporting Parallel Group Randomised Trials. BMC medicine, 2010. **8**: p. 18.

30. Miralbell, R., S.A. Roberts, E. Zubizarreta, et al., Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9-2.2) Gy. Int J Radiat Oncol Biol Phys, 2012. **82**(1): p. e17-24.

31. Murray, J., C. Cruickshank, T. Bird, et al., PEARLS: A multicenter phase II/III trial of extended field radiotherapy for androgen-sensitive prostate cancer patients with PSMA-avid pelvic and para-aortic lymph nodes at presentation. Journal of Clinical Oncology, 2022. **40**(6_suppl): p. TPS199-TPS199.

32. Prostate Cancer UK. PACE-NODES: A clinical trial to test a rapid form of radiotherapy. 2022 Available from: https://prostatecanceruk.org/research/research-we-fund/ma-ct20-005. [Accessed 19th May 2022]

33. Syndikus, I., C. Cruickshank, J. Staffurth, et al., PIVOTALboost: A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost (CRUK/16/018). Clin Transl Radiat Oncol, 2020. **25**: p. 22-28.

34. Abeshouse, A., J. Ahn, R. Akbani, et al., The Molecular Taxonomy of Primary Prostate Cancer. Cell, 2015. **163**(4): p. 1011-1025.

35. Burnet, N.G., G.C. Barnett, H.R. Summersgill, et al., RAPPER — A Success Story for Collaborative Translational Radiotherapy Research. Clinical Oncology, 2019. **31**(7): p. 416-419.

36. Skolarus, T.A., R.L. Dunn, M.G. Sanda, et al., Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. Urology, 2015. **85**(1): p. 101-105.

26. Appendix

Appendix A – NCI CTCAE

Toxicities will be assessed based on the latest NCI-CTCAE version 5.0 which can be found here https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix B - Treatment toxicities

Table 6 Expected RRAEs or RRSAEs following radiotherapy

	SBRT/ ENI	***ADT***
Gastrointestinal	✓	
Abdominal pain	✓	
Anorexia	✓	✓
Bowel haemorrhage	✓	
Bowel obstruction	✓	
Bowel perforation	✓	
Bowel stenosis	✓	
Colitis	✓	
Constipation	✓	
Diarrhoea	✓	✓
Enteritis	✓	
Faecal incontinence	✓	
Fistula	✓	
Malabsorption	✓	
Nausea	✓	✓
Proctalgia	✓	
Proctitis	✓	
Rectal bleeding	✓	
Rectal stenosis	✓	
Rectal urgency	✓	
Vomiting	✓	✓
General symptoms		
Fatigue	✓	✓
Hot flushes		✓
Secondary malignancy	✓	
Metabolic disorders		
Dyslipidaemia		✓
Impaired glucose tolerance		✓
Insulin resistance		✓
Weight gain		✓
Musculoskeletal		
Arthralgia		✓
Bone pain		✓
Bone fracture	✓	✓
Muscle weakness		✓
Myalgia		✓
Neuropathy	✓	
Osteoporosis		✓

Psychiatric		
Anxiety		✓
Depression		✓
Insomnia		✓
Mood alteration		✓
Reproductive system and breast disorders		
Breast pain		✓
Erectile dysfunction	✓	✓
Gynaecomastia		✓
Loss of libido		✓
Sexual dysfunction	✓	✓
Testicular atrophy		✓
Urinary		
Bladder perforation	✓	
Bladder stenosis	✓	
Cystitis	✓	
Dysuria	✓	
Fistula	✓	
Haematuria	✓	
Urinary frequency	✓	
Urinary incontinence	✓	
Urinary obstruction	✓	
Urinary pain	✓	
Urinary urgency	✓	