Randomised phase II clinical trial of using stereotactic body radiotherapy (SBRT) on first line androgen receptor pathway inhibitor for metastatic prostate cancer

PROTOCOL

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Sponsor:	The Institute of Cancer Research
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Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

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The STAR-TRAP study is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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

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

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
2.0	Amended exclusion criteria (section 5.4) and clarification of protocol assessments (Section 7.3.8 and 8.2.7).

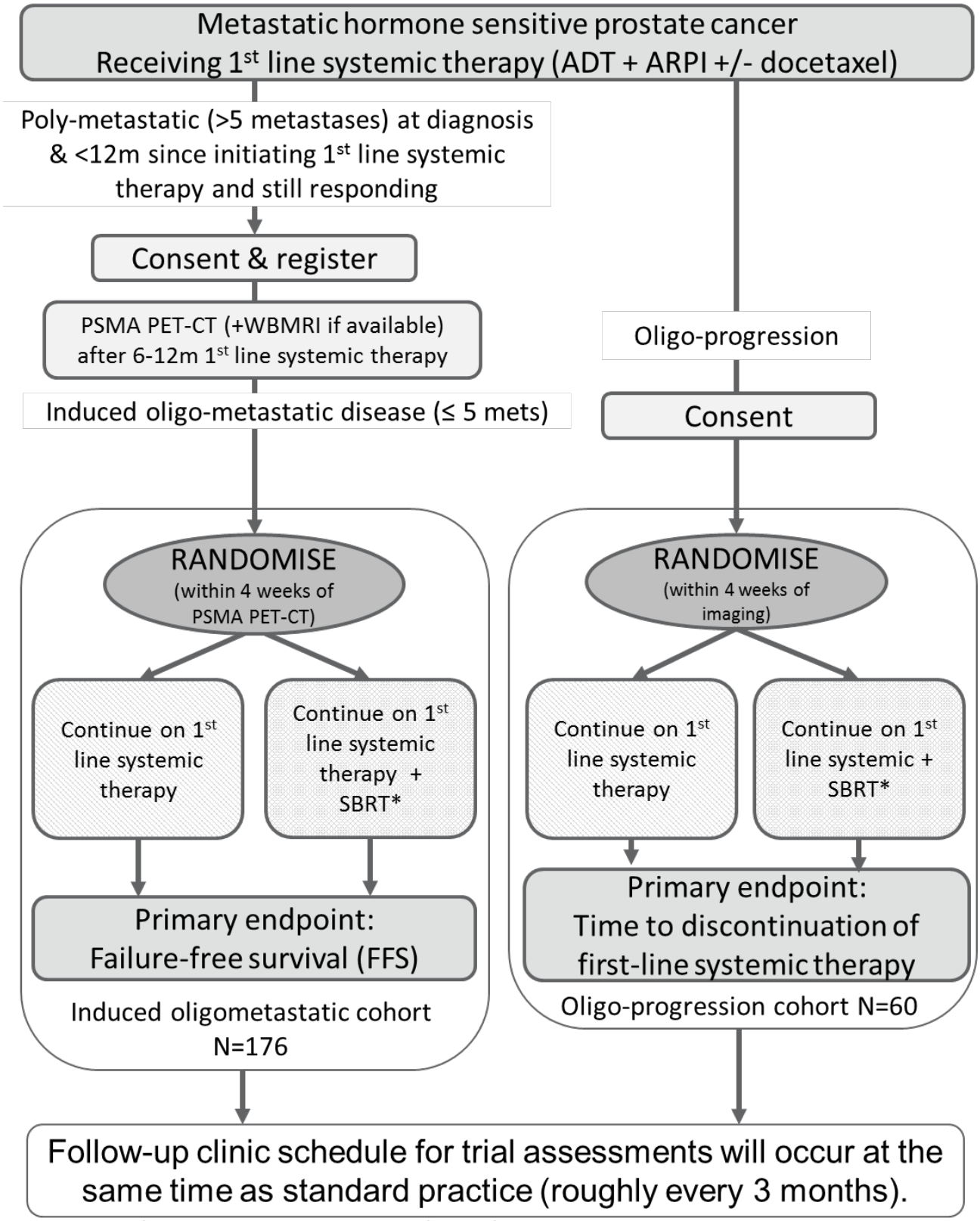
CONTENTS

STAR-TRAP TRIAL SUMMARY

PROTOCOL TITLE	STAR-TRAP: Randomised phase II clinical trial of using stereotactic body radiotherapy (SBRT) on first line androgen receptor pathway inhibitor for metastatic prostate cancer.
TARGET DISEASE	Metastatic hormone sensitive prostate cancer.
TRIAL OBJECTIVES	• iOM Cohort: To assess whether consolidative SBRT added to standard of care (SOC) leads to an improvement in failure free survival in patients with induced oligometastatic HSPC that are receiving first-line systemic therapy. • OP Cohort: To assess whether consolidative SBRT added to SOC delays the time to discontinuation of first-line systemic therapy in patients with mHSPC that have been classified as having disease progression while on first-line systemic therapy. • Assess the effects of SBRT added to SOC on time to discontinuation of first-line systemic therapy (iOM cohort only), time to next systemic treatment, overall survival (OS), radiological progression free survival (PFS), time to second PFS. • Assess if baseline tumour characteristics seen on imaging, biomarkers and/or patient or tumour demographics can identify those patients most likely to benefit from SBRT added to SOC. • Monitor serious adverse events in patients receiving SBRT. • Assess the effects of SBRT added to SOC on symptomatic skeletal events. • Evaluate the impact of consolidative SBRT added to SOC on patient's quality of life. • Feasibility of delivery of consolidative SBRT added to SOC. • Assess the sensitivity to detect metastatic disease for both PSMA PET-CT and WBMRI imaging modalities in patients with mHSPC that are receiving treatment in the first line setting (imaging sub-study). • Assess the ability to detect metastatic disease using PSMA PET CT based on local review compared to central review.
TRIAL DESIGN	Phase II multicentre randomised controlled trial platform.
TRIAL POPULATION	Two cohorts will be studied: Induced oligometastic (iOM) cohort - patients with poly-metastatic disease that has been downstaged by first-line systemic therapy (induced oligometastatic disease). Oligoprogressive (OP) cohort - patients with oligoprogressive disease on first-line systemic treatment.
RECRUITMENT TARGET	176 iOM cohort, 60 OP cohort
TRIAL TREATMENT	First-line systemic therapy (control) or first-line systemic therapy + SBRT.
PRIMARY ENDPOINT	• Induced oligometastatic iOM cohort: failure-free survival (FFS) • Oligoprogressive OP cohort: time to discontinuation of first-line systemic therapy.
SECONDARY ENDPOINTS	• Time to discontinuation of first-line systemic therapy (iOM cohort). • Time to second-line systemic therapy. • Radiological progression-free survival. • Overall survival.

	• Time to second progression-free survival. • Patient reported outcomes (using PRO-CTCAE, EQ5D-5L). • Time to first pain progression and general pain (using Brief Pain Inventory). • Time to symptomatic skeletal event. • SBRT treatment delivered to all eligible metastases.
EXPLORATORY ENDPOINTS	• Burden of disease (number of sites/volume) based on PSMA PET-CT and WBMRI (within imaging sub study). • Burden of disease (number of sites/volume) using PSMA PET-CT based on local review and central review.
SUB-STUDY (SPECIFY)	Imaging sub study – see section 22.
FOLLOW UP	Timings of follow-up are anticipated to be in line with standard of care. See section 7.3 (iOM) and 8.2 (OP).

TRIAL SCHEMA



* Up to 30Gy/3-5 fractions (f) to metastases +/- 33Gy/5f to prostate. SBRT to prostate omitted if prior prostate radiotherapy received

ADT=Androgen deprivation therapy; ARPI=Androgen receptor pathway inhibitor

1. INTRODUCTION

1.1. Background

Over the last decade, the evidence for adding systemic therapy to androgen deprivation therapy has matured and abiraterone (1, 2), enzalutamide (3), apalutamide (4) and docetaxel (5) are available for our patients as first line systemic therapy. Stereotactic body radiotherapy (SBRT) is an advanced type of external beam radiotherapy that delivers an extremely high dose of radiation with great precision and with a favourable toxicity profile. The potential additive benefit of SBRT whilst patients are on first line systemic therapy for metastatic hormone sensitive prostate cancer (mHSPC) has not been explored. In non-small cell lung cancer (NSCLC), there is emerging evidence in the role of consolidative radiotherapy with randomised phase II trials (6, 7) providing evidence of efficacy with a three-fold improvement in progression-free survival. There is a phase III trial (NRG-LU002, ClinicalTrial.gov NCT03137771) recruiting stage IV NSCLC patients to assess the impact of consolidative ablative therapies on overall survival. Here the aim of consolidative radiotherapy is to further diminish the number of cancer cells and enhance the likelihood of achieving a durable effect (as opposed to maintenance therapy which is given to maintain the “remission” and further prevent a relapse). We propose to evaluate this management strategy in patients with poly-mHSPC at diagnosis.

The use of imaging as a biological stratification tool for escalation of therapy is evolving, but not established for metastatic prostate cancer on first line systemic therapy. PSMA PET-CT is emerging as the optimal staging tool for patients with prostate cancer, however, its role in evaluating disease status whilst on treatment is less determined and needs to be assessed, as do other imaging modalities in this setting. Whole body MRI (WBMRI) is used in other tumour settings such as myeloma (8) for response assessment. The majority of patients who have high volume metastatic prostate cancer have bone metastases and therefore the utilisation of WBMRI which forms part of national and international recommendations for imaging patients with metastatic prostate cancer (9) should also be evaluated.

In advanced prostate cancer, metastasis-directed therapy using SBRT has been applied mainly in the recurrent oligometastatic setting (10, 11) and the majority of reports are from retrospective case series, with available data demonstrating high rates of local control (12). The TRAP trial (NCT03644303) is currently evaluating the role of SBRT in patients with castration-resistant prostate cancer who have 1-2 progressing/new lesions on imaging whilst on abiraterone or enzalutamide. There have been no studies evaluating the use of SBRT as a consolidative management option for patients biologically stratified on imaging on first line systemic therapy.

As the treatment paradigm in prostate cancer shifts to bring more treatments earlier in the pathway for patients, the role of radiotherapy needs to be aligned.

Additionally, with the increasing use of more sensitive imaging tools utilised at the time of biochemical progression, the identification of oligoprogression after early systemic treatment in patients diagnosed with metastatic disease will increase and currently there are no trials evaluating SBRT in this setting. Metastasis-directed therapy has been evaluated in phase I/II randomised trials in hormone sensitive oligometastatic prostate cancer patients (STOMP (13), ORIOLE (11), POPSTAR (14)), but in the recurrence setting.

This is first-in-field research investigating a novel therapeutic approach with SBRT in patients with mHSPC.

A single site feasibility study was conducted at Royal Marsden NHS Trust to evaluate the proportion of prostate cancer patients diagnosed with hormone sensitive poly-metastatic disease (more than five metastatic sites) who on imaging are found to have five or fewer active sites of metastatic disease (low volume) after early additional systemic therapy. This study was testing the hypothesis that androgen deprivation therapy (ADT) and a novel hormone therapy (e.g Enzalutamide or Abiraterone) downstages more than 30% of poly-metastatic patients into "low volume" patients as assessed by whole-body MRI. The objectives of the study were to evaluate the distribution of residual tumour burden: intra- versus extra-prostatic disease and to identify how many "poly-metastatic" prostate cancer patients are down-staged to "low volume" metastatic disease after early additional systemic therapy.

Patients who were diagnosed on conventional imaging with poly-metastatic hormone sensitive disease were invited to take part in the imaging study, which included a WBMRI at around 24 weeks after commencing a novel hormone therapy, such as enzalutamide or abiraterone/prednisolone. The choice of novel hormone therapy was at clinician discretion. An induced oligometastatic state was defined as five or less active metastatic sites on WBMRI with or without active disease within the prostate (BUG poster presentation 2023).

22 patients on ADT and either Enzalutamide or Abiraterone and prednisolone were included in the feasibility study. In 16/22 (73%) patients, the WBMRI indicated five or less 'active' metastatic sites. These patients had lower PSA levels at the time of the WBMRI, with median PSA of 0.19ng/ml (IQR: 0.03-0.67) than those whose disease had not down-staged, median PSA of 7.1ng/ml (IQR: 3.2-10.88). Four of the sixteen patients had a complete response on WBMRI.

Over 70% of poly-metastatic hormone sensitive prostate cancer patients in this feasibility study down- staged with five or less 'active' metastases on WBMRI at around 24 weeks after commencement of androgen receptor pathway inhibitor. Therefore, this induced oligometastatic disease state does exist in a substantial proportion of patients.

1.2. Known Risks and Benefits of SBRT

There is no evidence supporting the use of radiotherapy to improve survival in patients presenting with high volume mHSPC (15). The STAR-TRAP platform encompasses two different patient cohorts receiving first-line systemic therapy within this disease setting with randomisation to +/- SBRT in each cohort, therefore enabling efficient trial design, recruitment and conduct. This treatment strategy aligns with the shifting paradigm of intensification of treatment earlier in the patient pathway.

SBRT has been studied in oligorecurrent prostate cancer (a different clinical scenario) and although there is no phase III data in this setting, phase II data suggest promising progression-free survival outcomes. Existing evidence supports safety and minimal toxicity after SBRT to limited metastases, which encourages its use in novel indications, such as is proposed in STAR-TRAP.

The role of SBRT as a consolidative therapy during first-line systemic therapy in prostate cancer has never been investigated. In other tumour types, eg. lung cancer, outstanding early results have been seen (7).

1.3. Description of Population

STAR-TRAP will recruit patients with metastatic hormone sensitive prostate cancer (mHSPC). Two cohorts will be studied: patients with poly-metastatic disease at diagnosis that has been "downstaged" by first-line systemic therapy (induced oligometastatic disease) and patients with oligoprogressive disease on first-line systemic therapy.

Induced oligometastatic disease is defined as:
Patients with poly-mHSPC (>5 metastases) at diagnosis (on any imaging modality), who have PSA<2ng/ml 6-12 months after commencing systemic therapy and on the screening PSMA PET-CT have ≤5 'active' metastases as defined in the PROMISE classification (see appendix 2).

Oligoprogression is defined as:
Patients with ≤5 'active' metastases and/or active disease within the prostate on first-line systemic therapy identified at the point of biochemical failure on any imaging modality (conventional/WBMRI/PET).

This PSA progression can be defined either according to the PCWG3 definition (16) of an increase in PSA greater than 25% and >2 ng/ml above nadir, or a PSA increase of ≥ 25% above the nadir if PSA was < 2 ng/ml at randomisation, or at clinician discretion. Progression needs to be confirmed by a second value ≥ 3 weeks later.

1.4. Study Rationale

For many patients with metastatic prostate cancer at diagnosis, progression of their disease on first line systemic therapy is associated with a reduction in quality of life. It is therefore important to optimise management strategies to delay progression. The potential additive benefit of stereotactic body radiotherapy (SBRT) whilst patients are on first line systemic therapy will be evaluated in this project in two different disease settings (induced oligometastatic (iOM) and oligoprogression (OP) cohorts). SBRT is well tolerated and an established management in other disease states. If the addition of SBRT can consolidate the benefits of first line systemic therapy, prolonging the length of benefit as measured by time to progression or the need for 2nd line therapy, then patients will maintain quality of life for longer.

2. TRIAL OBJECTIVES

2.1. Primary Objective

- iOM Cohort: To assess whether consolidative SBRT added to standard of care (SOC) leads to an improvement in failure free survival in patients with induced oligometastatic HSPC that are receiving first-line systemic therapy.
- OP Cohort: To assess whether consolidative SBRT added to SOC delays the time to discontinuation of first-line systemic therapy in patients with mHSPC that have been classified as having disease progression while on first-line systemic therapy.

2.2. Secondary Objectives

The following apply to both cohorts unless indicated otherwise.

- Assess the effects of SBRT added to SOC on time to discontinuation of first-line systemic therapy (iOM cohort only), time to next systemic treatment, overall survival (OS), radiological progression free survival (PFS), time to second PFS.

- Assess if baseline tumour characteristics seen on imaging, biomarkers and/or patient or tumour demographics can identify those patients most likely to benefit from SBRT added to SOC.
- Monitor serious adverse events in patients receiving SBRT.
- Assess the effects of SBRT added to SOC on symptomatic skeletal events.
- Evaluate the impact of consolidative SBRT added to SOC on patient's quality of life.
- Feasibility of delivery of consolidative SBRT added to SOC.

2.3. Exploratory objectives

- Assess the sensitivity to detect metastatic disease for both PSMA PET-CT and WBMRI imaging modalities in patients with mHSPC that are receiving treatment in the first line setting (imaging sub-study).
- Assess the ability to detect metastatic disease using PSMA PET-CT based on local review compared to central review.

3. TRIAL DESIGN

STAR-TRAP is a phase II multicentre randomised controlled trial platform recruiting patients with metastatic hormone sensitive prostate cancer (mHSPC). Two cohorts will be studied: patients with poly-metastatic disease that has been "downstaged" by first-line systemic therapy (induced oligometastatic disease) and patients with oligoprogressive disease on first-line systemic therapy. These two cohorts are individually powered with distinct primary objectives and endpoints.

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

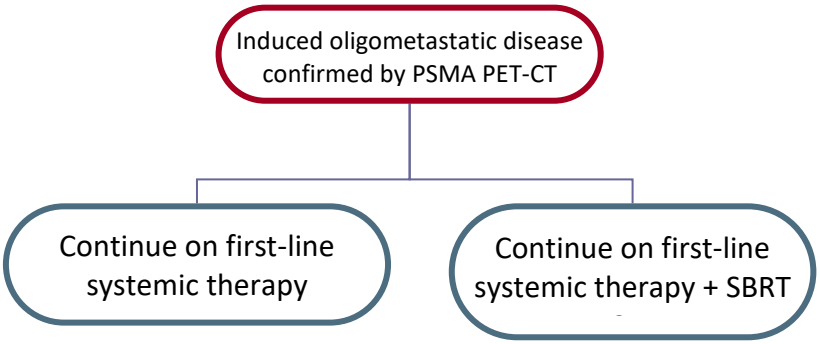
Patients will be allocated between continued first-line systemic therapy (control) or continued first-line systemic therapy + SBRT. Treatment allocation will be by minimisation, with a random element to balance the treatment allocation across the balancing factors and the allocation ratio will be 1:1.

All patients will be assessed as per standard of care, with PSA assessments done at a minimum of 3-monthly. Follow up data will be collected in the clinical trial database via the medical note review form by delegated site personnel every 3 months from randomisation date up to 36 months. Serious adverse events will be assessed in patients with SBRT treatment only, from start of SBRT to 30 days after end of SBRT. Quality of Life questionnaires will be collected at screening, end of SBRT, 12 weeks from the start of SBRT; 6, 9, 12 months and then 4-monthly up to 36 months; or equivalent time points for patients randomised to the control group. NHS numbers will be collected to allow linkage to routine data for efficient collection of late effects, prostate cancer recurrences and deaths as required. ICR-CTSU is currently developing a "long-term follow-up study" to support cross-trial collection of such data.

3.1. Induced oligometastatic disease definition:

Patients with poly-mHSPC (>5 metastases) at diagnosis (on any imaging modality), who have PSA<2ng/ml 6-12 months after commencing ADT + ARPI +/- docetaxel and on "screening" PSMA PET-CT have ≤5 'active' metastases as defined in the PROMISE classification (see appendix 2).

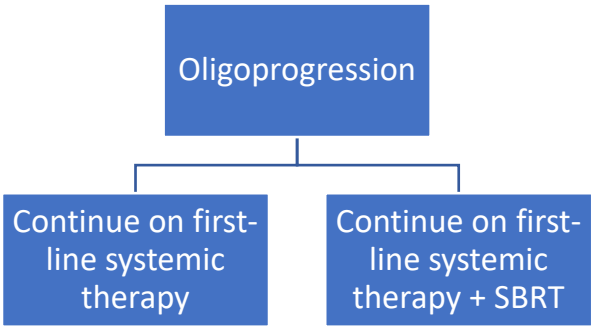
3.1.1. Treatment allocation options for induced oligometastatic disease cohort



3.2. Oligoprogression definition

Patients with ≤5 'active' metastases and/or active disease within the prostate identified on any imaging modality (conventional/WBMRI/PET) at the point of PSA progression while receiving ADT + ARPI +/- docetaxel.

3.2.1. Treatment allocation options for oligoprogression cohort



4. STUDY ENDPOINTS

4.1. Primary Endpoint

- Induced oligometastatic (iOM) cohort: failure-free survival (FFS).
- Oligoprogressive (OP) cohort: time to discontinuation of first-line systemic therapy.

4.2. Secondary Endpoints

The following apply to both cohorts unless indicated otherwise.

- Time to discontinuation of first-line systemic therapy (iOM cohort).
- Time to second-line systemic therapy.
- Radiological progression-free survival.
- Overall survival.
- Time to second progression-free survival.
- Patient reported outcomes (using PRO-CTCAE, EQ5D-5L).
- Time to first pain progression and general pain (using Brief Pain Inventory).
- Time to symptomatic skeletal event.
- SBRT treatment delivered to all eligible metastases.

4.3. Exploratory Endpoints

- Burden of disease (number of sites/volume) based on PSMA PET-CT and WBMRI (within imaging substudy).
- Burden of disease (number of sites/volume) using PSMA PET-CT based on local review and central review.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 176 patients to the induced oligometastatic cohort and 60 patients to the oligoprogression cohort.

5.2. Source of Participants

Participants will be recruited from approximately 20 participating sites in the UK. Potential participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

ICR-CTSU encourages investigators to consider equality, diversity and inclusion when recruiting participants into its trials to ensure that everyone eligible is offered the opportunity to consider participation.

Patients recruited to the induced oligometastatic cohort are permitted to subsequently enrol into the oligoprogression cohort provided all eligibility criteria are met at the time of enrolment and providing the primary endpoint for the oligometastatic cohort has been met. i.e. the patient has been classified as having biochemical failure or, new or progressive lesions (local, nodal or distant) on imaging (see section 7.3.5 for definition of biochemical failure in this setting). Sites need to contact the STAR-TRAP trial team prior to a patient's entry into the oligoprogression cohort in this situation to confirm eligibility.

5.3. Inclusion Criteria (applicable at registration and randomisation for the induced oligometastatic cohort and at randomisation for the oligoprogression cohort <u>unless stated otherwise)</u>

1. Histologically confirmed adenocarcinoma of the prostate.
2. Aged ≥ 18 years.
3. On ADT + ARPI (abiraterone, enzalutamide, apalutamide, darolutamide) +/- docetaxel.
4. WHO performance-status 0 to 2.
5. Written informed consent.
6. Additional cohort specific eligibility:

<u>Induced oligometastatic cohort</u>

<u>Registration part:</u>

☐ Metastatic hormone sensitive prostate cancer, poly-metastatic at diagnosis (> 5 metastases) confirmed on any imaging modality.

☐ Receiving ADT + first-line systemic therapy (ARPI +/- docetaxel).

☐ 5-12 months since initiating ADT (including LHRH agonists/antagonists and bicalutamide).

☐ PSA < 2ng/ml (PSA <2ng indicates patient 'eligible' to have PSMA PET-CT to determine oligo metastatic status).

Patients should be registered as close to the date of the PSMA PET-CT scan as possible.

Randomisation part:

☐ ≤ 5 metastases on PSMA PET-CT (performed after 6-12 month of first-line therapy). Patients should be randomised within 4 weeks of their PSMA PET-CT.

Oligoprogression cohort

☐ Metastatic hormone sensitive prostate cancer. Patients may have any number of sites of metastases at diagnosis on any imaging modality.

☐ Receiving ADT + first-line systemic therapy (ARPI +/- docetaxel).

☐ Has biochemical failure*

☐ ≤ 5 metastases and/or active disease within the prostate identified at the point of biochemical failure on any imaging modality (e.g. conventional/WBMRI/PET).

*biochemical failure is defined either using the PCGW3 definition (16) (a PSA increase that is ≥ 25% and ≥ 2ng/ml above the nadir) OR a PSA increase of ≥ 25% above the nadir if PSA was < 2 ng/ml at randomisation OR at clinician discretion. Progression needs to be confirmed by a second value ≥ 3 weeks later.

5.4. Exclusion Criteria (applicable at registration and randomisation for the induced oligometastatic cohort and at randomisation for the Oligoprogression cohort unless stated otherwise)

1. Prior radiotherapy at or near a metastatic site to be treated in STAR-TRAP that precludes the safe delivery of SBRT. Patients that have received prior SBRT to the prostate for localised prostate cancer treatment are permitted, but the patients will not be suitable to receive SBRT to the prostate in STAR-TRAP.
2. Co-morbidities precluding staging or follow up imaging, or precluding procedures required to facilitate SBRT.
3. Any single metastasis >6cm (>5cm for lung metastases).
4. Spinal cord compression (SCC), or impingement of the cord or any other situation whereby the clinician feels urgent radiotherapy (within 24 hours) to the spine is required. Patients are allowed to enter STAR-TRAP if they have a previous history of SCC, providing other eligibility criteria are met.
5. Any condition or significant clinical co-morbidities which would precludes the safe delivery of SBRT to any sites of metastatic disease and prostate (if applicable). A non-exhaustive list is provided below and research teams at site should consult this when assessing patient suitability for SBRT prior to randomisation:
    - A history of clinically significant diffuse interstitial lung disease or radiological evidence of idiopathic pulmonary fibrosis if SBRT to lung metastases or lesions adjacent to lungs are considered
    - Clinically significant colitis i.e. ulcerative colitis /Crohn's disease if SBRT to the pelvis or abdomen is considered

    If the treating clinician is concerned about any co-morbid condition, they should contact the STAR-TRAP Trial CI (startrap-icrctsu@icr.ac.uk) prior to randomisation.
6. Any active malignancies (i.e., progressing or requiring any treatment in the previous 36 months) other than prostate cancer (except non-muscle invasive bladder cancer; non-melanomatous skin cancer, small renal masses or a malignancy that is considered cured with minimal risk of recurrence).

5.5. Life Style Guidelines

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

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

6. SCREENING

6.1. Screening Log

All participating sites will be required to keep a log of all patients who are potentially eligible for this study (i.e. patients with metastatic hormone sensitive prostate cancer). The information collected on the log will include:

- Date patient identified
- Screening outcome (patient ineligible/patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable).

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

6.2. Procedure for Obtaining Informed Consent

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

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

Patients should be made aware that participation in the Quality of Life (QoL) study is mandatory since adverse events will be captured using PRO-CTCAE.

Patients being entered by participating sites able to perform WBMRI scans will be asked to consent to participate in the imaging sub-study. Patients should be made aware that participating in the imaging sub-study is entirely voluntary. A decision not to participate in the imaging sub-study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

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

6.3. Participation in other Clinical Trials

Participation in other interventional/non-interventional clinical trials will be considered on a case-by-case basis by the Trial Management Group. Participating sites should contact the STAR-TRAP trial team to discuss each case.

7. INDUCED OLIGOMETASTIC DISEASE COHORT

7.1. Registration – iOM cohort

In order for iOM patients to receive a PSMA PET-CT +/- WBMRI scan they must be consented and sites should register the patients centrally with ICR-CTSU before protocol required screening assessments at registration commence.

Patients should be registered by emailing **randomisation-icrctsu@icr.ac.uk** to request a call back
09.00-17.00 (UK time) Monday to Friday (excluding bank holidays)

All patients should be registered after consent and scans should be arranged as soon as possible. The PSMA PET-CT +/- WBMRI scan should be undertaken after 6-12 month of first-line systemic therapy. The interval between PSMA PET-CT and WBMRI should be within 4 weeks, if WBMRI scan is to be performed.

A registration and eligibility checklist must be completed prior to registration.

The following information will be required at registration:

- Name of hospital, consultant and person registering patient.
- Confirmation that patient has given written informed consent for trial registration and for any sub-studies.
- Confirmation that patient is eligible for trial registration by completion of the eligibility checklist.
- Patient's full name, hospital number, and date of birth.

The caller will be given the patient's unique registration number (Registration ID).

ICR-CTSU will email the data management contact at the recruiting site to confirm a patients' registration into the trial.

7.2. Treatment allocation– iOM cohort

To be eligible for the study, please refer to section 5.3 and 5.4.

Patients must have their treatment allocated centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should have their treatment allocated by emailing **randomisation-icrctsu@icr.ac.uk** to request a call back
09.00-17.00 (UK time) Monday to Friday (excluding bank holidays)

Treatment allocation should take place within 4 weeks of PSMA PET-CT and as close to the **planned** start date of SBRT as possible (ideally within 8 weeks). An eligibility checklist and randomisation form must be completed prior to treatment allocation.

The following information will be required at treatment allocation:

- Name of hospital, consultant and person randomising patient.

- Confirmation that patient has given written informed consent for trial participation and for any sub-studies
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist.
- Patient's postcode and NHS/CHI number.
- Type and Start date of first-line systemic therapy.
- PSA result at screening.
- Site of metastases at diagnosis.

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation.

ICR-CTSU will email the data management contact at the recruiting site to confirm a patients' entry into the trial.

7.3. Trial Assessments – iOM cohort

7.3.1. Registration Part – iOM cohort

The main inclusion criteria, inclusion criteria for iOM cohort registration part and exclusion criteria in section 5.3 and 5.4 should be confirmed before the trial is discussed with the participant and obtaining informed consent. The relevant registration form and eligibility checklist should be completed and patients registered with ICR-CTSU as outlined in section 7.1.

The following assessments should be done after consent for registration is obtained.
- PSMA PET-CT.
- WBMRI (if patient is taking part in the imaging sub-study and WBMRI is available at site).

7.3.2. Randomisation Part: Screening Assessments and treatment allocation – iOM cohort

Written informed consent should be obtained prior to treatment allocation. Medical history should be reviewed to check against the main inclusion criteria, inclusion criteria for iOM cohort randomisation part and exclusion criteria in section 5.3 and 5.4. The following assessments should be conducted prior to treatment allocation:

- Assessment of performance status, using WHO (see Appendix 1).
- Testosterone level.
- PSA level (pre-registration).
- Quality of Life questionnaire (One booklet containing: PRO-CTCAE, EQ5D, skeletal events & brief pain inventory short form (BPI-SF)).

7.3.3. Follow-up – iOM cohort

For patients in both groups the following assessments should be conducted following a standard of care schedule up to approximately 36 months following treatment allocation.
- PSA – to be performed at intervals per standard of care but should be at least once 3-monthly.
- Radiological assessments for disease status.
- SAE assessment – up to 30 days after end of SBRT (only for patients allocated to and received SBRT).
- Occurrence of skeletal events (symptomatic pathologic fracture, spinal cord compression, radiation to bone or surgery to bone).
- Disease status.
- Survival.
- Subsequent prostate cancer therapy.

These assessments should be reviewed by delegated site staff every 3 months following treatment allocation up to approximately 36 months and recorded in the medical note review form and all relevant CRFs. Where necessary, detailed information not normally recorded on medical notes should be recorded using the proforma provided by ICR-CTSU.

7.3.4. Quality of Life study – iOM cohort

Quality of Life questionnaires (PRO-CTCAE, EQ5D, skeletal events & BPI-SF) should be conducted according to the following schedule.

- Screening
- End of SBRT for patient allocated to SBRT / approximately 10 weeks after treatment allocation for patients allocated to SOC
- Week 12 from first SBRT fraction for patients allocated to SBRT / approximately 20 weeks after treatment allocation for patients allocated to SOC
- At 6, 9, 12 and approximately 4-monthly after treatment allocation. These will be sent to the patient's home address directly from ICR-CTSU, once sites have confirmed the patient is still suitable to receive the QoL booklet.

7.3.5. Procedure at suspected biochemical/radiographic progression – iOM cohort

Biochemical progression is based on PCWG3 which is defined as a PSA increase of ≥ 25% and ≥ 2 ng/mL above the nadir (since diagnosis of induced oligometastatic disease). The progression needs to be confirmed by a subsequent PSA at least 3 weeks apart.

If patients are found to have biochemical progression and progression of their local or metastatic disease is suspected, imaging is recommended to determine radiographic progression and identify sites of progression.

Radiographic progression: is based on clinical assessment after appropriate imaging with new or progressive lesions (local, nodal or distant) observed.

If patients are found to have radiographic progression or symptoms of progression, it is recommended that a PSA level is recorded to assess whether the patient has biochemical failure if the patients PSA was not measured prior to imaging or symptoms.

Details of management after progression should be documented (section 7.3.6 and 7.3.7)

Patients should continue to be followed up with the study assessments regardless of the patient's progression status.

7.3.6. Decision to switch to second line therapy (end of first line therapy) – iOM cohort

The following should be collected when the patient switches to second line treatment:

- Date the decision to switch management was made and the first line treatment was stopped.
- Medical indicators that triggered the switching to second line treatment. It is recommended that PSA is measured at the point first line therapy is stopped.
- Details related to any second line therapy received.

If the first line therapy is stopped but no second line therapy started this should be documented in the CRFs.

7.3.7. Subsequent progressions after end of first line therapy – iOM cohort

Patients may progress after commencing 2nd line therapy. Details on progression in this setting should be captured. Second progression-free survival will be defined as the time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient is receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first. If patients do not commence a subsequent therapy (i.e. 2nd line therapy) details related to subsequent progressions should be captured where possible. Progression in this setting is defined as for the first progression (see section 7.3.5).

7.3.8. Schedule of Assessments - iOM cohort

Timepoint / Assessments	Trial Entry		Follow up (up to 36 months from randomisation)		Quality of Life administration (post randomisation)[d]	
	Registration	Screening (Randomisation Part)	Standard of care assessments	3-monthly medical notes review	SOC arm: Wks 10 & 20 from randomisation SBRT: End of SBRT & 12 wks from start SBRT	Months from randomisation: 6, 9, 12,16, 20, 24,28, 32, 36
Informed Consent	x	x				
Histologically confirmed adenocarcinoma of the prostate	x					
PSA	x[a]		x[b]			
Medical history and concomitant medication check at trial entry	x					
WHO performance status	x					
Testosterone		x				
Radiological assessment (PSMA-PET-CT)		x				
Radiological assessment (WBMRI)		(x)[c]				
Quality of Life[d]		x			x	x
Radiological assessments for disease status (e.g. conventional/WBMRI/PET/bone scan)			x[e]			
SAE Assessment			x[f]			
Skeletal events (Clinician reported)			x[g]			
Disease status			x[g]			
Survival			x[g]			
Subsequent prostate therapy			x[g]			
Concomitant medication – bone and pain medications				x		
CRF completion of medical note review form				x[h]		

[a] PSA <2 ng/ml pre-registration indicates patient is 'eligible' to have PSMA PET-CT to determine oligo metastatic status.

[b] PSA should be performed at regular intervals as per centre defined standard of care with details recorded on the relevant CRFs. It is recommended that PSA should be performed at least once every 3 months. All tests performed should be recorded. If biochemical progression is suspected, imaging is recommended to determine radiographic progression and identify sites of progression.

[c] WBMRI can be performed if available or routine at centre, provided patient consented to imaging sub-study.

[d] Quality of Life questionnaire includes PRO-CTCAE, EQ5D, Brief Pain Inventory-Short Form and skeletal events. Month 6 to 36 months will be sent to the patient's home address directly from ICR-CTSU, once patient status is ascertained. All other booklets will be handled by sites.

[e] Radiological assessments to be performed as standard of care with details recorded on the relevant CRFs. All radiological assessments performed should be recorded. If radiological progression is suspected, it is recommended that a PSA level is recorded to assess whether the patient has biochemical failure if the patient's PSA was not measured prior to imaging or symptoms.

[f] SAE is reported only for participants randomised to first line systemic therapy + SBRT. SAEs should be reported from first SBRT fraction to 30 days after the end of SBRT.

[g] Clinician reported skeletal events, disease status, survival and subsequent prostate therapy are to be collected through medical notes. Participants are not required to attend hospital visit. Sites should arrange follow up visits as standard of care.

[h] These assessments (g) should be reviewed by delegated site staff every 3 months following treatment allocation up to approximately 36 months and recorded in the medical note review form and all relevant CRFs. Where necessary, detailed information not normally recorded on medical notes should be recorded using the proforma provided by ICR-CTSU.

8. OLIGOPROGRESSION COHORT

8.1. Treatment allocation – OP cohort

To be eligible for the study, please refer to section 5.3 and 5.4.

Participants must have their treatment allocated centrally by ICR-CTSU before trial treatment can commence.

Patients should have their treatment allocated by emailing **randomisation-icrctsu@icr.ac.uk** to request a call back
09.00-17.00 (UK time) Monday to Friday (excluding bank holidays)

Treatment allocation should take place as close to the **planned** start date of SBRT as possible (ideally within 8 weeks). An eligibility checklist and randomisation form must be completed prior to treatment allocation.

The following information will be required at treatment allocation:

- Name of hospital, consultant and person registering patient.
- Confirmation that patient has given written informed consent for trial participation.
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist.
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants).
- Type of first line systemic treatment
- Type of imaging modality that was used to confirm OP cohort eligibility (see section 5.3).
- Site of metastases at diagnosis

If the patient has previously been recruited into and treated in the iOM cohort, the following information will be required in addition to the above:

- *iOM cohort randomisation ID*
- *Confirmation that the iOM primary endpoint has been confirmed as met by the ICR-CTSU STAR-TRAP trial team*

The caller will be given the patient's unique randomisation number (Trial ID).

ICR-CTSU will email the data management contact at the recruiting site to confirm a patients' entry into the trial.

8.2. TRIAL ASSESSMENTS

8.2.1. Screening Assessments - OP cohort

Written informed consent should be obtained prior to treatment allocation. Medical history should be reviewed to check against the main inclusion criteria, inclusion criteria for OP cohort and exclusion criteria in section 5.3 and 5.4. The following assessments should be conducted prior to treatment allocation:

- Assessment of performance status, using WHO (see Appendix 1).
- Radiological assessment (e.g. conventional/WBMRI/PET/bone scan) confirming 5 or less 'active' sites +/- active prostate disease.
- Testosterone level.
- PSA level.
- Quality of Life questionnaire (One booklet containing: PRO-CTCAE, EQ5D skeletal events & BPI-SF).

8.2.2. Follow-up - OP cohort

For patients in both groups the following assessments should be conducted following a standard of care schedule up to approximately 36 months following treatment allocation.

- SAE assessment – up to 30 days after end of SBRT (only for patients allocated to and received SBRT).
- PSA – to be performed at intervals per standard of care but should be at least once every 3 months.
- Radiological assessments for disease status
- Occurrence of skeletal events (symptomatic pathologic fracture, spinal cord compression, radiation to bone or surgery to bone).
- Disease status.
- Survival.
- Subsequent prostate cancer therapy

These assessments should be reviewed every 3 months following treatment randomisation up to approximately 36 months and recorded in the medical note review form and all relevant CRFs. Where necessary, detailed information not normally recorded on medical notes should be recorded using the proforma provided by ICR-CTSU.

8.2.3. Quality of Life study – iOM cohort

Quality of Life questionnaires (PRO-CTCAE, EQ5D, skeletal events & BPI-SF) should be conducted according to the following schedule.

- Screening
- End of SBRT for patient allocated to SBRT / approximately 10 weeks after treatment allocation for patients allocated to SOC
- Week 12 from first SBRT fraction for patients allocated to SBRT / approximately 20 weeks after treatment allocation for patients allocated to SOC
- At 6, 9, 12 and approximately 4-monthly after treatment allocation. These will be sent to the patient's home address directly from ICR-CTSU, once sites have confirmed the patient is still suitable to receive the QoL booklet.

8.2.4. Procedure at Disease Progression/recurrence following trial randomisation - OP cohort

Patients may have already met the definition of biochemical progression at randomisation, however patients may progress further while still on first line treatment. Details relating to the indication for stopping first line therapy should be documented. This will include details on PSA levels, radiographic progression and symptomatic progression.

If progression is suspected, imaging is recommended to determine sites of recurrence.

Radiographic progression: is based on local clinical assessment after appropriate imaging with new or progressive lesions (local, nodal or distant) observed.

Details of management after progression should be documented (section 8.2.5 and 8.2.6).

Patients should continue to be followed with the study assessments regardless of the patient's progression status.

8.2.5. Decision to discontinue first line therapy (and switch to second line therapy) - OP cohort

The following should be collected when the patient discontinues first line therapy/switches to second line treatment:

- Date the decision to switch management was made and the first line treatment was stopped.
- Medical indicators or other decisions (e.g., patient choice) that triggered the discontinuing of first-line therapy and switching to second line treatment. It is recommended PSA is measured at the point first line therapy is stopped.
- If the first line therapy is stopped but no second line therapy started this should be documented.
- Details related to any second line therapy received (date started and type).

8.2.6. Subsequent progressions after end of first line therapy – OP cohort

Patients may progress after commencing 2nd line therapy. Details on progression in this setting should be captured. Second progression-free survival will be defined as the time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient is receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first. If patients don't commence a subsequent therapy (i.e. 2nd line therapy) details related to subsequent progressions should be captured where possible. Progression in this setting is define as for the first progression (see section 8.2.4).

8.2.7. Schedule of Assessments - OP cohort

Timepoint / Assessments	Trial Entry	Follow up (up to 36 months from randomisation)		Quality of Life administration (post randomisation)[c]	
	Screening (Pre-randomisation)	Standard of care assessments	12 weekly medical notes review	SOC arm: Wks 10 & 20 from randomisation SBRT: End of SBRT & 12 wks from start SBRT	Months from randomisation: 6, 9, 12,16, 20, 24,28, 32, 36
Informed Consent	x				
Histologically confirmed adenocarcinoma of the prostate	x				
PSA	x[a]	x[b]			
Medical history and concomitant medication check at trial entry	x				
WHO performance status	x				
Testosterone	x				
Quality of Life[c]	x			x	x
Radiological assessments for disease status (e.g. conventional/WBMRI/PET/bone scan)		x[d]			
SAE Assessment		x[e]			
Skeletal events (Clinician reported)		x[f]			
Disease status		x[f]			
Survival		x[f]			
Subsequent prostate therapy		x[f]			
Concomitant medication – bone and pain medications			x		
CRF completion of medical note review form[g]			x		

[a] PSA <2 ng/ml pre-registration indicates patient is 'eligible' to have PSMA PET-CT to determine oligo metastatic status.

[b] PSA should be performed at regular intervals as per centre defined standard of care with details recorded on the relevant CRFs. It is recommended that PSA should be performed at least once every 3 months. All tests performed should be recorded. If biochemical progression is suspected, imaging is recommended to determine radiographic progression and identify sites of progression.

[c] Quality of Life questionnaire includes PRO-CTCAE, EQ5D, Brief Pain Inventory-Short Form and skeletal events. Quality of Life questionnaire includes PRO-CTCAE, EQ5D, Brief Pain Inventory-Short Form and skeletal events. Month 6 to 36 months will be sent to the patient's home address directly from ICR-CTSU, once patient status is ascertained. All other booklets will be handled by sites.

[d] Radiological assessments to be performed as standard of care with details recorded on the relevant CRFs. All radiological assessments performed should be recorded. If radiological progression is confirmed, it is recommended that a PSA level is recorded to assess whether the patient has biochemical failure if the patient's PSA was not measured prior to imaging or symptoms.

[e] SAE is reported only for participants randomised to first line systemic therapy + SBRT. SAEs should be reported from first SBRT fraction to 30 days after the end of SBRT.

[f] Clinician reported skeletal events, disease status, survival and subsequent prostate therapy are to be collected through medical notes. Participants are not required to attend hospital visit. Sites should arrange follow up visits as standard of care.

[g] These assessments (f) should be reviewed by delegated site staff every 3 months following treatment allocation up to approximately 36 months and recorded in the medical note review form and all relevant CRFs. Where necessary, detailed information not normally recorded on medical notes should be recorded using the proforma provided by ICR-CTSU.

8.3. TRIAL TREATMENT – BOTH COHORTS

Participants allocated SBRT will be planned to receive 33Gy in 5 fractions to the prostate and seminal vesicles and up to 30Gy in 3-5 fractions to 'active' metastases on alternate days. If there are no 'active' metastases, prostate SBRT only will be delivered.

For participants who received prior prostate radiotherapy, prostate SBRT will be omitted.

For participants in the iOM cohort, 'active' metastases (is defined on PSMA PET-CT which determined eligibility.

8.3.1. Treatment Timelines - Both cohorts

Radiotherapy should commence as soon as possible and ideally within 8 weeks following treatment allocation (the expectation being that this allows sufficient time for planning). Radiotherapy treatment can start on any day of the week with fractions given on alternate days. Treatment should be given in a single phase and should ideally be planned to be delivered within 14 days of starting.

8.3.2. Systemic treatment - Both cohort

Prior to randomisation into STAR-TRAP, patients will be receiving systemic treatment for mHSPCa in accordance with local hospital policy and local funding arrangements. This will include ADT and include androgen receptor pathway inhibitor (abiraterone, apalutamide, enzalutamide, darolutamide) +/- docetaxel chemotherapy. This treatment should continue as per standard of care and is not affected by registration/treatment allocation into the study.

9. RADIOTHERAPY QUALITY ASSURANCE

Radiation will be delivered according to UK SABR consortium guidelines and dose volume constraints and in line with existing RTQA procedures for other SBRT trials. A quality assurance program will be instigated to ensure the safety and consistency of radiotherapy delivery at participating sites.

9.1. Pre-trial quality assurance programme

Will be streamlined (where appropriate) and based on participation in previous radiotherapy trials and SABR commissioning through NHS England.

9.2. On-trial quality assurance programme

- On trial case reviews.
- Dosimetry site visit (subject to prior RTQA dosimetry accreditation).
- DICOM data collection for all patients.

Further details included in the STAR-TRAP Radiotherapy Guidance document.

9.3. Radiotherapy Planning and outlining

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

9.4. Radiotherapy delivery

SBRT will be delivered with either image-guided VMAT, MR Linac or Cyberknife to ensure precision of delivery.

10. CENTRAL REVIEW OF PSMA PET-CT scans

iOM patients who are registered and randomised into the STAR-TRAP study will have their PSMA PET-CT scans assessed via prospective or retrospective central review.

Prospective "real-time" review will take place for the first patient from each participating site. Requirements for further prospective reviews will be discussed by clinical members of the STAR-TRAP TMG.

Retrospective review will take place for all further patients recruited from each participating site. The aim is for timely retrospective review within 1-2 months of receipt of the PSMA PET-CT scan. For further information please refer to the STAR-TRAP trial guidance notes.

11. SUPPORTIVE CARE GUIDELINES

If the participant is receiving abiraterone, it is recommended that prednisolone is taken with abiraterone. In the event of patient catheterisation during the course of SBRT it is expected that the participant will continue and complete radiotherapy in accordance with their allocated treatment group. As the bladder requires filling prior to SBRT delivery, the catheter must be clamped or a flip-valve used.
Participants' symptoms should be managed according to local practice, although the following are suggestions for patient care:

- Slow flow and frequency – tamsulosin or alfuzosin are often helpful.
- Dysuria/frequency – check for evidence of infection and treat if present with appropriate antibiotics, anticholinergics (e.g. oxybutynin, tolterodine, solifenacin), NSAIDs, analgesics.
- Diarrhoea – loperamide or opioid.
- Proctitis – suppository +/- local anaesthetics (e.g. sheriproct, proctosedyl).
- Bone pain analgesia.
- Bone health - alendronic acid 70mg or risedronate 35mg weekly if no contraindication, plus Vitamin D (800 IU/day of cholecalciferol). Calcium supplements are recommended if dietary calcium uptake is inadequate.

11.1. Concomitant Therapy

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. The use of bone protecting agents (bisphosphonates, denosumab) calcium supplements, vitamin D supplements and, regular pain medications for prostate cancer, must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

11.2. Non-permissible Medications/Therapies

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

- Radiosensitisers such as methotrexate.

12. DISCONTINUATION FROM TREATMENT

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

- Disease progression
- Unacceptable toxicity

Participants who discontinue treatment should continue to be followed up.

13. CHANGE IN PARTICIPATION STATUS

Participants may choose to change, reduce or stop their participation after joining the trial.

Within STAR-TRAP the following changes in participation are possible:

- Stopping trial specific follow up – data will continue to be requested from routine visits.
- Stopping routine clinical follow up – data will continue to be requested from details in the patients' medical record (e.g. date of progression/death).
- Stopping participation in -sub studies.
- Stopping future sharing of data.
- Withdrawal of consent for any further data to be submitted – data up to the point of withdrawal will be retained as described in the patient information sheet.

Changes in participation should be led by the participant and no assumptions should be made on their behalf. If this occurs, a change in participation status form should be submitted to ICR-CTSU to report the details of the reduction in participation. For further guidance on the types of change in participation status and guidance on loss of contact, please refer to trial guidance notes.

14. SAFETY REPORTING

14.1. Definitions

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

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the first fraction of SBRT and within 30 days of the last fraction of SBRT and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

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

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

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

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

Definitions of causality

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

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

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see Appendix A3)

14.2. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs after the first fraction of SBRT and up to 30 days following the last fraction of radiotherapy must be reported by the study team at the participant's site. SAE reporting is not required for patients allocated to SOC or for patients allocated to but did not receive SBRT.

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

The ICR-CTSU safety desk
Email: sae-icr@icr.ac.uk for the attention of the STAR-TRAP Trial team

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

All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative for the SAE form to be valid. However, this should not delay reporting if it is not available immediately.

14.3. Reporting Adverse Events to ICR-CTSU

For the purposes of STAR-TRAP, adverse events are being collected directly from patients completing PRO-CTCAE booklets.

14.4. Review of Serious Adverse Events

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

SAEs assessed as having a causal relationship to study treatment (i.e. SBRT) and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 14.5).

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

14.5. Expedited Reporting of Related Unexpected SAEs

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

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

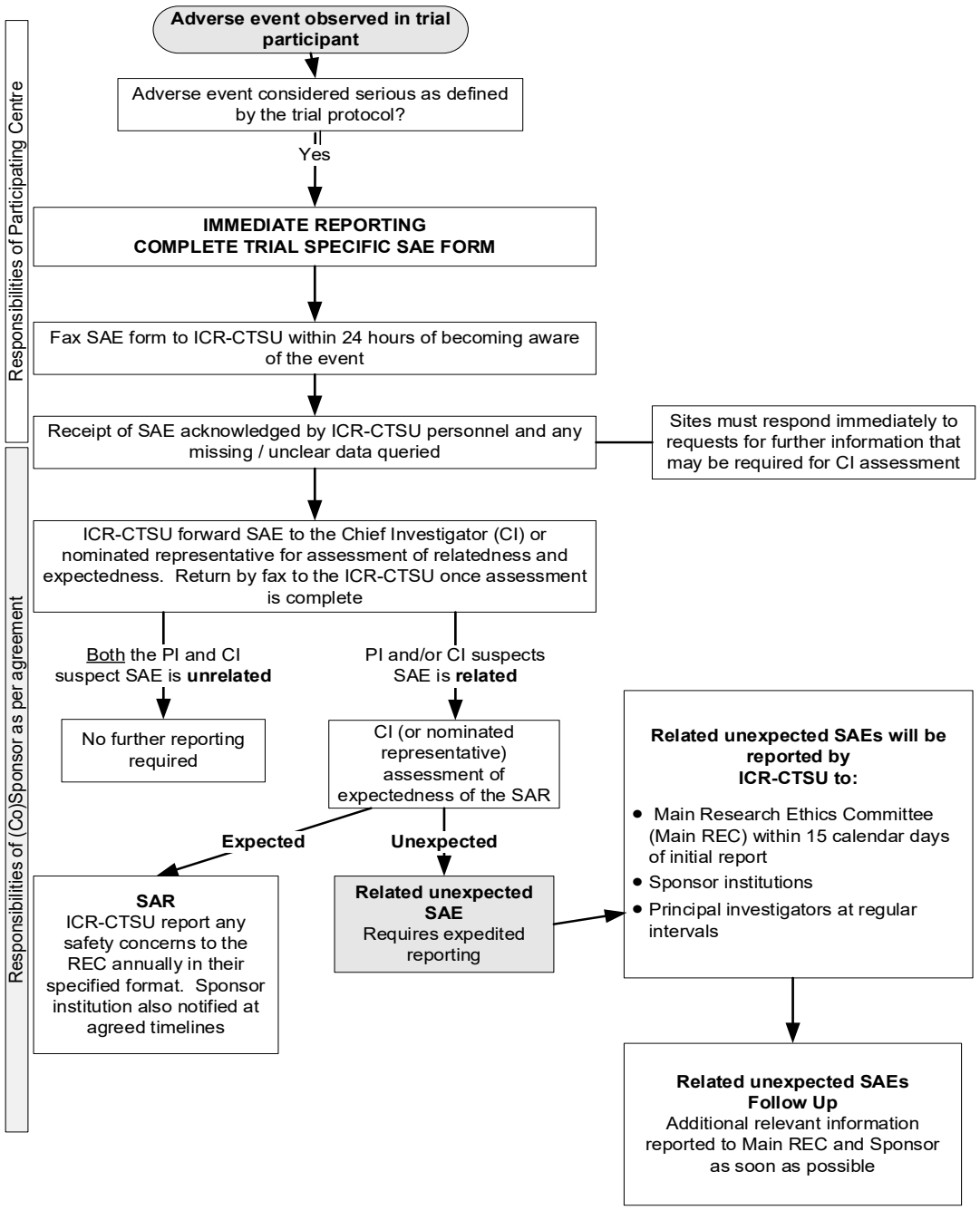
14.6. Follow up of Serious Adverse Events

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

14.7. Reporting Pregnancies

If any trial participants' partner becomes pregnant while receiving SBRT or up to 90 days after receiving SBRT this should be reported to ICR-CTSU using the pregnancy reporting form. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above. Pregnancy reporting is not required for patients allocated to SOC or patients allocated to but did not receive SBRT.

Figure 3: Flow diagram for SAE reporting, and action following report



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

15. STATISTICAL CONSIDERATIONS

15.1. Statistical Design and Sample Size Justification

Each cohort is powered independently using a phase II screening design (relaxed 15% one-sided alpha).

Induced oligometastatic cohort

The sample size is calculated using the log-rank test assuming a one year FFS estimate of 80% in the SOC group. Data from the LATITUDE trial (2) (18) showed patients receiving abiraterone had approximately 60% radiographic PFS rate at 2 years from the start of first-line treatment. As patients in STAR-TRAP are required to have had 6-12 months first-line treatment prior to their PSMA-PET CT to determine eligibility for the trial, we estimate a FFS of 80% at one year from randomisation. In addition, we expect radiological PFS (rPFS) and FFS to be similar (4). Patients eligible for trial entry will be a good prognosis group as they have not progressed within the first six months of therapy and will have been down-staged so we believe this to be an appropriate FFS estimate for the trial population. The target treatment effect is HR=0.57, this was used by Gomez et al (7) in the lung trial of local consolidative therapy using SBRT. This lung trial was stopped early by the Data Safety & Monitoring Board because of significant progression-free survival (PFS) benefit seen (HR=0.35, 90%CI 0.18-0.66).

The sample size was calculated using STATA artsurv software based on the following design parameters and assumptions:

- 1:1 allocation ratio
- 2 years of staggered recruitment (15%, 25%, 30% and 30% in each six-month period)
- 1-year minimum follow-up
- 80% power (chosen as it represents adequate power and an achievable target sample size)
- A 15% one-sided “relaxed” alpha was chosen as it provided an acceptable alpha for a randomised phase II design (17) and an achievable sample size
- Expected 4% loss to follow-up at 1 year
- Hazard ratio of 0.57 (approximately equivalent to an absolute difference of 9% in FFS)

In order to achieve 80% power, a total of 46 events are needed (26 control arm events) and we anticipate that this will be achieved through recruitment of **176 patients** (88 per group), followed up for a minimum of 1 year.

Oligoprogression cohort:

The sample size is calculated using the log-rank test, the primary endpoint is time to second line treatment. Patients in this cohort will be randomised at the time of biochemical failure whilst on their first line treatment. We estimate the median time from biochemical failure to starting second line treatment will be 6 months in the SOC group (1). We expect the addition of SBRT to extend the time to second line therapy starting after biochemical failure to 12 months. This difference of 6 months equates to a HR=0.5.

The sample size was calculated using STATA artsurv software based on the following design parameters and assumptions:

- 1:1 allocation ratio
- 2 years of staggered recruitment (15%, 25%, 30% and 30% in each six-month period)
- 1-year minimum follow-up

- 90% power
- A 15% one-sided “relaxed” alpha was chosen as it provided an acceptable alpha for a randomised phase II design (17) and an achievable sample size Expected 4% loss to follow-up at 1 year
- Hazard ratio of 0.5 (approximately equivalent to an absolute difference of 50% in time to discontinuing first lines treatment)

In order to achieve 90% power, a total of 46 events are needed (30 control arm events) and we anticipate that this will be achieved through recruitment of **60 patients** (30 per group), followed up for a minimum of 1 year.

For the exploratory imaging sub-study, a sample size of 80 patients has been set. This is based on funds available to pay for the additional WBMRIs and is felt to be a large enough sample to provide useful comparisons.

15.2. Treatment Allocation

Participants will be randomised between first-line therapy and first-line therapy + SBRT on a 1:1 basis.

Patients will be centrally randomised via ICR-CTSU in a 1:1 allocation ratio using minimisation with a random element. The two cohorts will have separate minimisation algorithms.

Balancing factors for the induced oligometastatic cohort will be radiotherapy centre, the inclusion of chemotherapy to first-line systemic treatment (ADT + ARPI vs ADT + ARPI + docetaxel), PSA at randomisation (≤0.2ng/ml vs 0.21 to ≤2.0ng/ml) and site of metastases at diagnosis (visceral vs. non-visceral).

Balancing factors for the oligoprogression cohort will be radiotherapy centre, the inclusion of chemotherapy to first-line systemic treatment (ADT + ARPI vs ADT + ARPI + docetaxel), imaging modality to determine eligibility (conventional imaging vs PSMA PET-CT) and site of metastases at diagnosis (visceral vs non-visceral).

Patients with both visceral and non-visceral sites of disease will be classed as having visceral disease.

15.3. Endpoint Definitions

15.3.1. Definition of events are used in composite endpoints

Biochemical failure events: defined as a PSA increase of ≥ 25% and ≥ 2 ng/mL above the PSA nadir since diagnosis of induced oligometastatic disease. The progression needs to be confirmed by a subsequent PSA at least 3 weeks apart (as per section 7.3.5).

Radiographic progression: is based on local clinical assessment after appropriate imaging with new or progressive lesions (local, nodal or distant) observed (as per section 7.3.5).

Death from prostate cancer: Patients will be classified as having a prostate cancer death if the primary cause of death reported on the CRF is prostate cancer or if the death is deemed prostate related or prostate cancer is a contributing cause. Deaths classified as not from prostate cancer will be centrally clinically reviewed.

15.3.2. Primary endpoint

Induced oligometastatic cohort: Failure free survival (FFS) - defined as time from randomisation to first biochemical failure; new, radiological progression; or prostate cancer death.

Oligoprogressive cohort: Time to discontinuation of first-line systemic therapy - defined as time from randomisation to time the patient discontinues their first line systemic therapy where the reason for stopping is related to progression and if a patient were to commence a new treatment for their prostate cancer it would need to be a second line therapy or related to palliative care.

15.3.3. Secondary endpoints

- Time to discontinuation of first-line systemic therapy (induced oligometastatic cohort): time from randomisation to time the patient discontinues their first line systemic therapy where the reason for stopping is related to progression and if a patient were to commence a new treatment for their prostate cancer it would need to be a second line therapy or related to palliative care.
- Time to second-line systemic therapy: time from randomisation to time the patient starts second-line systemic therapy. If a patient doesn't start a second-line therapy but stops first-line the date the patient stops their first-line therapy will be used instead.
- Radiological PFS: time from randomisation to radiographic progression or death from any cause.
- Overall survival: time from randomisation to death from any cause.
- Time to second PFS: time from randomisation to first clinician determined disease progression (PSA progression, radiographic progression, clinical progression or death from any cause) after patients stop their first line therapy.
- Patient reported outcomes (using PRO-CTCAE, EQ5D -5L). Frequency of each PRO-CTCAE will be reported. Specific details of items to be analysed will be included in the SAP.
- Time to pain progression. Pain progression is defined as a 2-point increase from baseline (i.e. randomisation) Brief Pain Index (BPI-SF) based on 'worst pain' question.
- General pain (using Brief Pain Inventory): Details of specific items and composite scores to be analysed will be included in the SAP.
- Time to symptomatic skeletal event: time from randomisation to first skeletal related event (symptomatic pathologic fracture, spinal cord compression, radiation to bone or surgery to bone). In addition, date of death from prostate cancer where the patient doesn't have a prior skeletal related event will be included as an event. Where patients' death is not prostate related, and they have no prior skeletal event the patients will be censored at the date of death.
- SBRT delivered to all eligible metastases: This will be measured as the proportion of patients that received the target dose.

15.3.4. Exploratory endpoint

- Burden of disease based on PSMA PET-CT imaging compared with WBMRI: The number/volume and site of active metastases on screening PSMA PET-CT and WBMRI will be compared. This will be presented at the disease site level with the number and percentage of sites matching overall and by site.
- Burden of disease (number of sites/volume) based on local review and central review: This will be based on PSMA PET-CT measures. This will be presented at the disease site level with the number and percentage of sites matching overall and by site.

15.4. Statistical Analysis Plan

All statistical analysis will be conducted by the ICR-CTSU at The Institute of Cancer Research (or for exploratory endpoints in collaboration with the statistical team at ICR-CTSU). Analysis methods are outlined

here, in brief. Full details will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

The two cohorts will be analysed independently. The primary analysis is planned to take place once all patients have 12 months follow up. The Independent Data Monitoring Committee (IDMC) will monitor the accumulation of follow-up data and primary endpoint events in the trial and will advise on when the dataset is sufficiently mature for analysis. Secondary time to event data and quality of life data will be reported at the time of the primary analysis. In addition, a long term follow up analysis will take place when all patients have reached 36 months follow up to assess the long-term robustness of the efficacy analysis and to assess the long-term impacts of SBRT on the patient's quality of life.

Baseline characteristics will be reported by allocated treatment. Details of SBRT planning and treatment delivered will be summarised.

Efficacy analyses, including the primary endpoint comparison, will include all randomised participants according to allocated treatment arm (intention-to-treat). Quality of life analyses will be performed on the treatment received analysis set, consideration will be given to also performing the analysis by allocated treatment, to be defined within the Statistical Analysis Plan.

The primary endpoint, as well as other time-to-event endpoints, will be presented by treatment arm using Kaplan-Meier curves; estimated 1-year event rates will be given along with confidence intervals. Hazard ratios (presented with confidence intervals and p-values) will be estimated from Cox proportional hazards model with adjustment for minimisation factors if numbers allow. In addition, models that include baseline factors will be considered to assess whether baseline characteristics can identify patients most likely to benefit from SBRT. Baseline characteristics will include (but not be limited to) staging, Gleason score/Grade Group, PSA, site of metastatic disease and number of sites. Proportional hazards assumptions will be checked and, if violated, appropriate alternative methods will be applied. Significance level for the primary endpoint will be 0.15 using one-sided test reflecting the alpha used in the sample size.

Time to event endpoints are:

- Failure free survival
- Time to second-line systemic therapy
- Radiological PFS
- Overall survival
- Time to second PFS
- Time to pain progression
- Time to symptomatic skeletal event

Sensitivity analyses of the primary endpoints will be carried out with time measured from initiation of novel hormone therapy or docetaxel instead of from randomisation.

Firstline treatment details will be reported. Reasons for stopping first line therapy will be summarised and compared between treatment groups. This data may be included in adjusted analysis as appropriate.

SAE are to be collected only for the patients receiving SBRT. Note the definition of SAEs means the patient needs to have received the study intervention. Therefore, the SAE's are include for completeness as the only other adverse events included are skeletal events. No formal comparisons will be made for the SAE data and this data will be tabulated and line listing presented.

PRO scores will be generated using standard algorithms for the questionnaires. Key PRO measures of interest will be listed in the SAP. Time to worsening of symptoms is of key interest and time to event analysis methods as described above while be used. In addition, the data will be presented at each time point. Consideration will be given to providing formal comparison at 12 and 36 months. As well as performing analyses to account for the longitudinal nature of the data (for example generalised estimating equations/mixed effects models) will be consider to provide an overall quality of life and potential account for missing data.

Handling of missing data, in particular for time dependent QoL assessments will be described in the SAP as with this patient group it may not be appropriate to consider the data as missing at random.

Results will be analysed and published in peer reviewed journals once primary endpoint data are mature. A dissemination plan will be developed with input from our PPI collaborators.

15.5. Interim Analyses and Stopping Rules

There are no formal stopping rules. Feasibility of recruitment will be formally assessed 1 year after trial opening and will consider acceptance and accrual rates and the proportion of patients "down-staged" on imaging in the induced oligometastatic cohort. Feasibility of treatment delivery will be assessed by monitoring the number of active metastatic sites and number of sites successfully treated with SBRT.

16. TRIAL MANAGEMENT

16.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Clinical Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include at least one lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2. Trial Steering Committee (TSC)

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

16.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chairperson and at least two further members with clinical or statistical expertise (at least

one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

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

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.
The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

17. RESEARCH GOVERNANCE

17.1. Sponsor Responsibilities

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

17.2. Participating Site Responsibilities

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

18. TRIAL ADMINISTRATION & LOGISTICS

18.1. Site Activation

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

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2. Data Acquisition

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

18.3. Central Data Monitoring

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

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

18.4. On-Site Monitoring

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

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

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

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

18.6. Archiving

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

19. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

19.1. Risk Assessment and Approval

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

19.2. Public and Patient Involvement

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

19.3. Ethics Approvals

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

19.4. Trial Conduct

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

19.5. Informed Consent

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

Patients should be asked to sign the current ethics approved STAR-TRAP consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the

circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved STAR-TRAP patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

19.6. Patient Confidentiality

Patients will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data.

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

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

19.7. Data Protection

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

19.8. Liability

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

20. FINANCIAL MATTERS

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

21. PUBLICATION POLICY

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

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

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

It is an expectation that all publications relating to the trial are published as "open-access".

22. ASSOCIATED STUDIES

22.1. Imaging sub-study

The use of imaging as a biological stratification tool for escalation of therapy is evolving, but not established for patients on first line systemic therapy. PSMA PET-CT is emerging as the optimal staging tool for patients with prostate cancer, however, its role in evaluating disease status whilst on treatment is less determined and needs to be assessed, as do other imaging modalities in this setting. WBMRI is used in other tumour settings such as myeloma (8) for response assessment. The majority of patients who have high volume metastatic prostate cancer have bone metastases and therefore the utilisation of WBMRI which forms part of national and international recommendations for imaging patients with metastatic prostate cancer (9) should also be evaluated.

In centres with access to WBMRI - iOM patients will be asked to receive a WBMRI scan in addition to their PSMA PET-CT. These patients must registered centrally with ICR-CTSU before protocol required screening assessments commence. The numbers of patients taking part in this sub-study is estimated to be no more than 80 patients.

Endpoints related to this study are described in the exploratory endpoint section of the protocol.

22.2. Quality of Life Study

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

The NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement system (18) was developed to evaluate symptomatic toxicities by self-report in adults, adolescents and children participating in cancer clinical trials. It was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE).

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

The Brief Pain Inventory – Short Form (BPI-SF) is used to evaluate the severity of pain and its impact on the participant's daily functioning.

The QoL study will not be optional for trial participants. Clinician reported adverse events (with the exception of skeletal related events) are not being collected therefore patient reported outcomes will provide important summary measures relating to any quality-of-life benefits of SBRT. We aim to include as many participants as possible to allow full determination of QoL by treatment arm and to support exploratory analyses. Given the size of the study and the use of focused questionnaires, the introduction of web-based data capture directly from participants will be explored. This may provide opportunities for related trial methodology research, e.g. comparison of response rates to paper based and web based completion.

Participants will complete the questionnaires at screening, at the end of SBRT*, week 12 from the start of SBRT*, 6, 9, 12 months and every 4 months thereafter up to 36 months from randomisation.

**For participants randomised to first-line therapy only, the end of SBRT visit would be approximately 10 weeks after randomisation (participants in the SBRT arm would be receiving SBRT within 8 weeks after randomisation). The week 12 from start of SBRT visit would be approximately 20 weeks after randomisation.*

23. REFERENCES

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A1. WHO performance status

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

A2. PROMISE classification

Within STAR-TRAP, induced oligometastatic disease is defined as:

Patients with polymetastatic hormone sensitive prostate cancer (>5 metastases) at diagnosis, who have PSA<2ng/ml 6-12 months after commencing systemic therapy and on the “screening” PSMA PET-CT have ≤5 ‘active’ metastases as defined in the PROMISE classification (see below).

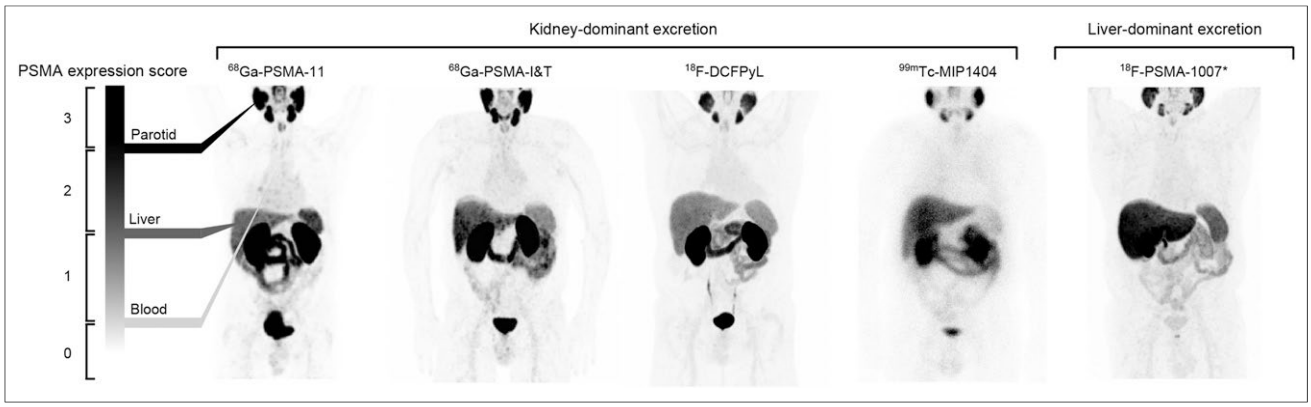
A combination of the level of uptake (Table 1) linked with morphological imaging appearances from CT or MRI can be used to determine lesion positivity using the schema below (Figure 2). For lesions that give an "equivocal" score then they can count as positive if there is additional evidence available (imaging / biopsy) and a prospective central review and discussion for those equivocal lesions with no additional imaging or histology.

miPSMA expression score (Table 1)

Score	Reported PSMA expression	Uptake (PROMISE V2)
0	No	Equal to or lower than blood pool
1	Low	Equal to or lower than liver and higher than blood pool
2	Intermediate	Equal to or lower than parotid gland and higher than liver
3	High	Higher than parotid gland

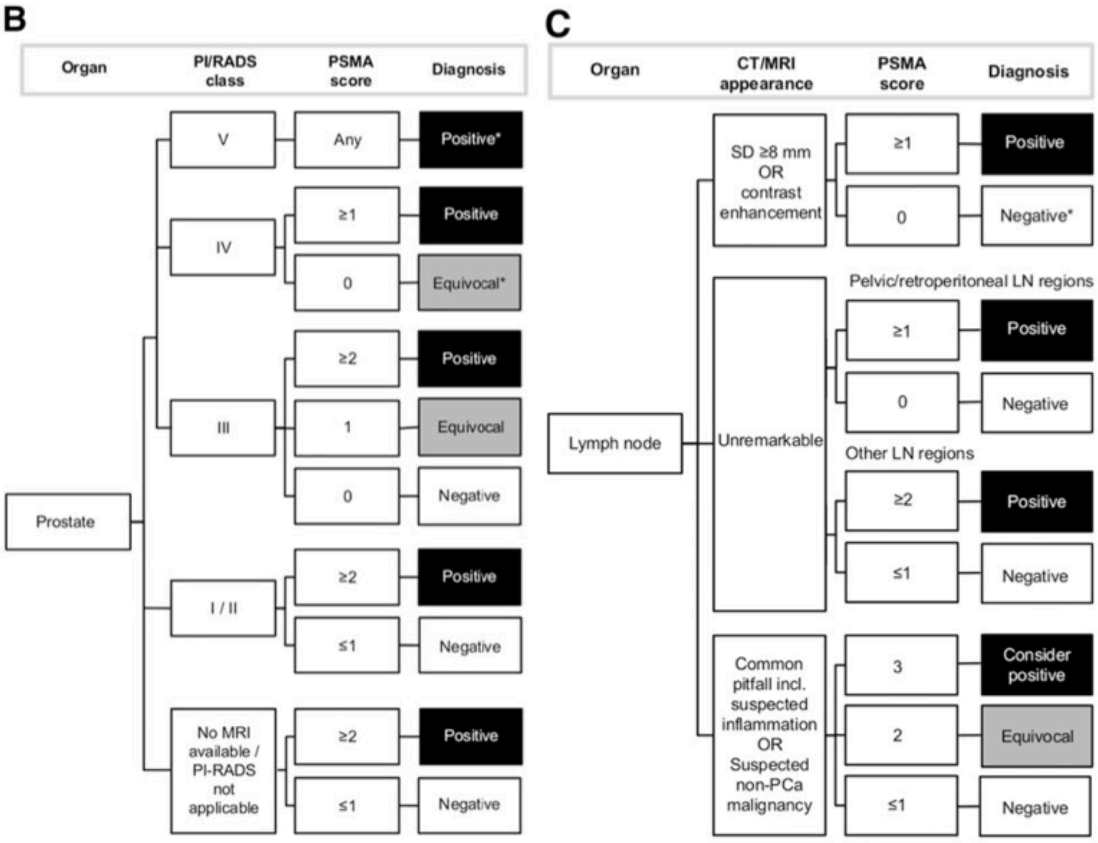
*For PSMA ligands with liver-dominant excretion (e.g. 18F-PSMA1007) spleen is recommended as reference organ instead of liver.

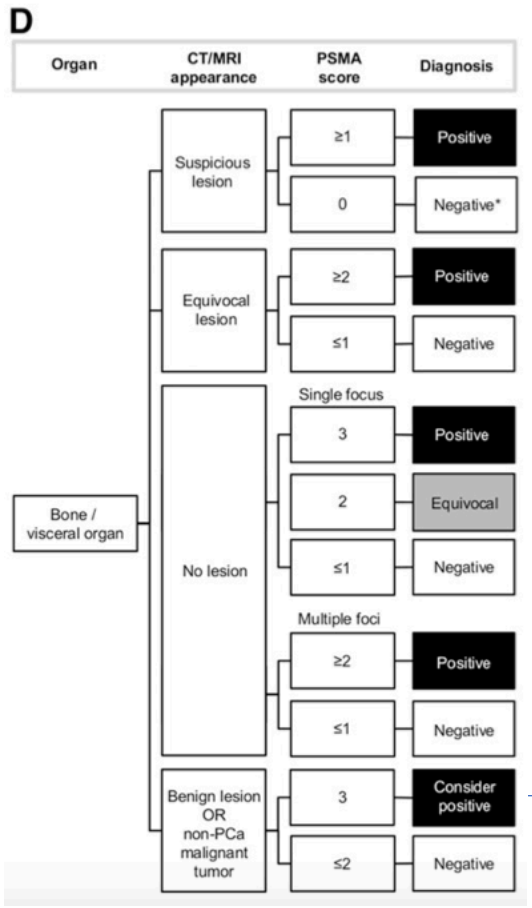
miPSMA expression score (Figure 1)



Thresholds are demonstrated on ^{68}Ga-PSMA11 PET maximum-intensity projection (left). For comparison, images are shown for 68Ga-PSMA-I&T scan, 18F-DCFPyL maximum-intensity projection at 1 h, 99mTc-MIP1404 planar scan at 3 h, and 18F-PSMA-1007 scan.

Figure 2 - PROMISE guide for interpretation of PSMA PET lesions. Criteria are given separately for imaging, imaging of prostate for tumour detection (B), imaging of lymph nodes (C), and imaging of bone or visceral organs (D). LN = lymph node; PCa = prostate cancer; SD = short-axis diameter





Within STAR-TRAP, a benign lesion OR non-PCa malignant tumour" should be considered NEGATIVE even if PSMA score 3

Images and tables taken from the following publication(s):

1. Eiber M, Herrmann K, Calais J, Hadaschik B, Giesel FL, Hartenbach M, Hope T, Reiter R, Maurer T, Weber WA, Fendler WP. Prostate Cancer Molecular Imaging Standardized Evaluation **(PROMISE):** Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. J Nucl Med. 2018 Mar;59(3):469-478. doi: 10.2967/jnumed.117.198119.

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A3 Expected toxicities of SBRT

The following are expected toxicities of SBRT:

Thoracic and mediastinum

- Pericarditis
- Dysphagia
- GI haemorrhage
- Gastritis
- Cough
- Pneumonitis
- Dyspnoea

L1-3, Liver, Adrenal, Kidney, Para-aortic

- Nausea
- Vomiting
- Spinal fracture
- Upper GI ulcer
- Duodenal/Gastric ulcer
- Upper GI bleeding
- Liver enzymes: ALT
- Bilirubin

L4-5, Sacrum, pelvic bones, pelvic nodes/side wall

- Diarrhoea
- Proctitis
- Lower GI ulcer
- Lower GI bleeding
- Rectal Haemorrhage
- Haematuria
- Urinary frequency
- Urinary incontinence
- Urinary retention
- Urinary urgency

General

- Fever
- Fatigue
- Myelitis

Dermatology/Skin

- Dermatitis
- Hair loss (to treatment area)

Related to fiducial marker insertion

- Bleeding
- Sepsis (urinary and systemic)
- Pneumothorax

*Clinical judgement may be exercised when considering the expectedness of events relating to SBRT.

A4 GLOSSARY

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ARPI	Androgen Receptor Pathway Inhibitor
BPI-SF	BriefPain Inventory - Short Form
CI	Chief Investigator
CRF	Case Report Form
DFS	Disease Free Survival
f	Fraction
FFS	Failure-Free Survival
GCP	Good Clinical Practice
Gy	Gy
ICR	The Institute Of Cancer Research
IDMC	Independent Data Monitoring Committee
iOM	Induced Oligometastatic
LHRHa	Luteinising Hormone-Releasing Hormone analogue
MDT	Multi-disciplinary team
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
NCI PRO-CTCAE	National Cancer Institute Patient Reported Outcomes version of Common Terminology Criteria for Adverse Events
OP	Oligoprogression
OS	Overall Survival
PCWG3	The Prostate Cancer Working Group 3
PFS	Progression Free Survival
PRO	Patient Reported Outcome
PSA	Prostate-specific Antigen
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RTQA	Radiation Therapy Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Body Radiotherapy
SCC	Spinal Cord Compression
SOC	Standard of Care
TMG	Trial Management Group
TSC	Trial Steering Committee
VMAT	Volumetric Modulated Arc Therapy
WBMRI	Whole body MRI
WHO	World Health Organisation