The ROYAL MARSDEN NHS Foundation Trust

ICR The Institute of Cancer Research

PROSTATE CANCER UK

TRAP

The TRAP trial: Targeted Radiotherapy in Androgen-suppressed Prostate cancer patients

Protocol version 3.0

Chief Investigator: Dr Alison Tree

Sponsor: The Royal Marsden NHS Foundation Trust, Fulham Road, SW3 6JJ

Funder: Prostate Cancer UK

Coordinating trials unit: The Royal Marsden Clinical Trials Unit

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VERSION / AMENDMENT HISTORY

Version No. / Amendment No.	SUMMARY OF CHANGES
0.36	Protocol synopsis submitted to Royal Marsden CCR In Principle 12 July 2017
0.37 – 0.40	Distribution to co-investigators for review & comment and internal updating of document
0.41	Clean version to MS for inclusion of statistical text and submission to CCR 11/10/17
0.42	Updates to protocol to reflect changes requested by CCR following Full Draft Application to CCR
1.0	Initial Submission to REC / HRA
2.0	1. Change of Trial Statistician / New Signature Page for Statistician 2. Update to List of Abbreviations 3. Update to Section 3.3 to clarify inclusion criteria and PSA values for inclusion criteria 4. Update to Table 1 to clarify meaning of 'visit windows'; permitted time-frame for acquisition of baseline CT scan (42 days); Lung Function Tests and collection of CTCAE / RTOG data 5. Update to section 4.4 to qualify 'unexpected findings' & inclusion of reference to TRAP trial Imaging Manual 6. Update to section 4.2.1 to clarify purpose of Centre-standard blood tests conducted at baseline and updates to 4.2.1, 4.2.4 and 4.2.5 to remove PFT (Pulmonary Function Tests) not required at these time-points. 7. Update to section 4.3 to clarify treatment elapsed times. 8. Update to section 4.4 to clarify scope of unexpected findings of WB DW MRI, procedure for informing PI and reference to the Imaging Manual. 9. Update to cover page and inclusion in section 6. 4 of NCT trial registration details. 10. Updates to section 7.1 to clarify definition of source data. 11. Updates to section 8 to ensure consistency in the reporting period defined for SAEs and clarification of the required expedited reporting procedures. 12. Change of terminology in section 9.4 regarding predictive and non-predictive phenotypes 13. Update to section 10.1 to include reference to Laboratory Manual. 14. Update to section 10.2 to removal of Patient's Date of Birth.

VERSION / AMENDMENT HISTORY

Version No. / Amendment No.	SUMMARY OF CHANGES
	15. Update to section 10.3 to include the correct location for storage of trial blood samples prior to analysis. 16. Addition of text to clarify introduction to Appendix 2
3.0	1. Update to Contacts List: a. Statisticians updated from Ria Kalaitzaki and Henry Nanji to Emily Robinson b. Trial Manager updated from Linda Wedlake to Sijy Pillai 2. Update to Trial Summary: a. Clarified that during follow-up, remote review is conducted until 24 months b. Removal of PSA kinetics at 9 months post SBRT c. Clarified that Quality of Life is assessed until 12 months d. Updated inclusion criteria to include PET as an imaging modality to confirm progression of metastatic lesions e. Clarified that where PET-/CT was used to diagnose oligoprogression, the same imaging modality should be repeated at 6 month follow-up in place of the CT and bone scan f. Clarified that late toxicity will be assessed as per standard of care g. Clarified that PSA will be measured at 6 months (previously omitted in error), and will be measured 6 monthly thereafter instead of 3 monthly 3. Inserted blank CI Signature page – to be signed once approved 4. Inserted blank Statisticians Signature Page – to be signed once approved 5. Update to List of Abbreviations 6. Update to Figure 2 in Section 3.1 to reflect new time points 7. Update to Section 3.2: a. Addition of remote consenting b. Addition of registration instructions 8. Table 1 – Schedule of Treatment and Assessment has been moved from Section 4.1 to 4.2, and has been updated: a. Screening timepoint renamed to Pre-registration, with the window increased from 42 days to 56 days before study enrolment b. Addition of Baseline column to separate assessments from Pre-registration column. Clarified window for baseline is after consent, but prior to SBRT c. Addition of heading 'Post-SBRT Follow-up' d. Addition of note that Haematology and Biochemistry only need to be collected if needed, as per standard of care e. Blinded WBDWMRI, EQ5D questionnaire, and research bloods have been moved from Pre- registration to Baseline timepoint f. Addition of ECOG performance status, PSA, and LFT to Baseline timepoint g. Key has been updated 9. Update to Section 4.2 – Trial Assessments: a. Clarified Section 4.2.1 Pre- registration Assessments to separate from baseline assessments b. Clarified Section 4.2.2 Baseline Assessments

VERSION / AMENDMENT HISTORY

Version No. / Amendment No.	SUMMARY OF CHANGES
	c. Clarified Section 4.2.6 Assessment at 6 months post-SBRT completion to allow the same imaging modality used at baseline to be used at 6 months post-SBRT d. Clarified Section 4.2.7 Additional Assessments thereafter of when survival status, imaging and PSA will be conducted. Survival status and imaging will be captured at 6 months, and 6 monthly thereafter until 24 months or disease progression. Imaging reports will be collected and filed in the ISF until 24 months. The reports will be requested at the end of trial. 10. Update to Section 4.3 – Radiotherapy Treatment & Treatment Delays – added a note that if radiotherapy does not commence within 56 days of consent, this needs to be reported as a protocol deviation 11. Update to Section 5 – Assessment of Disease Progression – clarified that the same imaging modality used at baseline is to be used at 6 month follow-up post SBRT 12. Update to Section 6.1.4 Protocol Amendments – addition of wording that Sponsor Green Light is needed to implement an amendment 13. Update to Section 6.2.3 Monitoring – clarified that the trial monitor will contact sites to conduct on-site monitoring visits 14. Update to Section 7.3 Trial Database & CRF completion – removed wording that data is to be entered by RM-CTU personnel 15. Update to Section 7.5 Record Retention – clarified that records will be archived and retained for a period of 5 years after the conclusion of the trial 16. Update to Section 8 – Safety Reporting – clarified that SAE reports must be sent to RM-CTU/CI within 24 hours/next working day since being notified of the event. 17. Update to Section 8.3 – Reporting Timeframes – all reportable SAEs which indicate an imminent risk of death, serious injury or illness, or requires prompt remedial action will be reported to REC within 7 days, instead of 2 days 18. Update to Section 9.4 – Statistical Analysis Plan – removed previous wording and added wording that an SAP will be written prior to any analysis 19. Update to Section 9.5 – Endpoints – additional wording has been added for clarification 20. Update to Section 10.1 – Tissue Management – Collection – removed the wording Streck tube and added cell free DNA tubes instead 21. Addition of trial ID and timepoint questions to the front of Appendix 1 22. Update to Appendix 2 – Expected Adverse Events – minor clarifications added to the introduction

TABLE OF CONTENTS

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TRIAL SUMMARY

Title	**T**argeted **R**adiotherapy in **A**ndrogen-suppressed **P**rostate cancer patients. (TRAP trial)
Trial Design	A multi-centre phase II trial in patients with oligoprogression treated with **S**tereotactic **B**ody **R**adio**T**herapy (SBRT)
Clinical Indication	Metastatic **C**astrate **R**esistant **P**rostate **C**ancer (mCRPC) patients with oligoprogression after a minimum of 6 months castration in combination with second generation AR targeting therapy
Patient population	Oligoprogressive mCRPC defined as a rising PSA in the presence of two or fewer progressing lesions
Trial Type	Non-randomised, prospective cohort
Type of control	Not Applicable
Treatment Groups	One
Number of trial patients / Sites	84 patients / 4 - 8 UK investigational sites
Estimated duration of trial & completion of Activities	Set up: months 0-6 Recruitment all patients: months 6-30, plus follow-up (24 months) Banking of ctDNA samples: Months 6-36 WBDWMRI: Months 6-36 Late toxicity follow-up: Months 9-42 (thereafter follow up as per standard of care) Analysis: Months 36- 42
Duration of Active Participation	Last research procedure 6 months from start of SBRT, thereafter 12 months follow up on study and 6 monthly remote review thereafter until 24 months.
Study Objectives	*Primary Objective* To assess if SBRT to oligoprogressing sites results in progression-free survival (outside irradiated field) of > 6 months *Secondary Objectives* • To establish the local control rate after SBRT for oligoprogression. • To determine whether circulating tumour DNA (ctDNA) fraction decreases after SBRT to sites of oligoprogression, and whether the kinetics of ctDNA are predictive. • To establish if Whole Body Diffusion Weighted MRI (WBDWMRI) and / or ctDNA and / or patient or tumour demographics at baseline can predict those patients most likely to benefit from SBRT (i.e. predict those who will have progression-free survival for 6 months or more, in comparison to the biomarker negative cohort who are expected to have a progression-free survival of 4 months). • To record PSA response and overall survival after SBRT. • To monitor acute and late toxicity from SBRT in a metastatic cohort. • Capture of EQ-5D Health Questionnaire responses

	Exploratory Objectives • To establish if it possible to define a biomarker panel which is present in at least 40% of oligoprogressing patients and which predicts for progression-free survival (median PFS) of more than 6 months. • To ascertain time-to-delay of next line of treatment in the biomarker positive versus the negative groups • To conduct a sub-group analysis of median PFS of local prostate oligoprogression versus metastatic oligoprogression. • To explore whether the kinetics of ctDNA predict time to progression or precede clinical or radiological progression.
Study Endpoints	*Primary Endpoint* • Time to Progression or Death *Secondary Endpoints* • Local control of irradiated metastases on CT and WBDWMRI. • Proportion of patients with oligoprogression who have detectable circulating tumour DNA • ctDNA response to SBRT defined as proportion of patients who convert from detectable to undetectable circulating tumour DNA after SBRT. • Time (in months) to next therapy. • Proportion of patients where WBDWMRI detects further metastases at baseline. • Association between WBDWMRI at baseline (number of metastases, DWI characteristics) and prognosis after SBRT. • PSA kinetics at 3, 6, and 12 months after SBRT, including percentage of patients with a PSA below 75%, 50% and 25% of pre-SBRT baseline. • Overall survival at 12 and 24 months after SBRT • Incidence of acute and late toxicity as determined using CTCAE v4.0 • Quality of Life at end of SBRT, 4 weeks post SBRT, 3 months and 6 months and 12 months post SBRT as determined using the EQ 5D Health Questionnaire instrument. *Exploratory Endpoints* • To establish a biomarker panel which is present in at least 40% of oligoprogressing patients and which predicts for progression-free survival (median PFS) of more than 6 months. • Time-to-delay of next line of treatment in the biomarker positive versus the negative groups • Sub-group analysis of median PFS of local prostate oligoprogression versus metastatic oligoprogression. • To explore whether the kinetics of ctDNA predict time to progression or precede clinical or radiological progression.
Summary of Main Inclusion Criteria	1. Be willing and able to provide written informed consent for the trial and be ≥18 years of age on day of signing informed consent.

	2. Have metastatic CRPC (based on biochemical or pathological diagnosis) and be on Enzalutamide or Abiraterone. 3. Have had a minimum of 6 months on Enzalutamide or Abiraterone with evidence of response (PSA, radiological or symptomatic) 4. Have 1 – 2 metastatic lesions progressing on imaging (CT, bone scan, PET, MRI or other local imaging) or a clinical or imaging diagnosis of progression of a non-irradiated primary site with the remainder of their metastases currently controlled by Enzalutamide or Abiraterone. 5. Have had no previous radical radiation to the index area (defined as unable to deliver SBRT doses in this protocol without taking normal tissues beyond tolerance). 6. Have a Performance Status (PS) assessed using the Eastern Co-operative Oncology Group (ECOG) criteria of 0 – 1. 7. Have an oligoprogressing site, including those that have developed on treatment, in bone, lymph node, prostate or lung but not in liver, brain, adrenal or other sites. 8. Patients may be symptomatic in the oligoprogressing area. However, there is no urgent need to start radiotherapy.
Summary of Main Exclusion Criteria	1. A clinical need exists to switch therapy immediately (e.g. suspicion of rapid clinical progression, urgent need for palliative radiotherapy). 2. Evidence of previous invasive cancer in the last 5 years, with the exception of non-melanoma skin cancer (non-invasive malignancies such as bladder cancer are not excluded). 3. There is a contra-indication to radiotherapy (e.g. inflammatory bowel disease). 4. There is a contra-indication to MRI (e.g. cardiac pacemaker, internal defibrillator, shrapnel injury or claustrophobia). 5. The lesions are not technically suitable for SBRT (e.g. size of > 6 cm)
Treatment / Main Trial Procedures and Follow-up	All patients within the trial will be treated with SBRT to a dose of 30 Gy in 5 fractions on alternate days. For patients with prostate symptoms, 36 Gy in 6 fractions is also allowed. All patients will continue on prescribed Enzalutamide or Abiraterone. Acute toxicity will be assessed at the end of radiotherapy fraction 5/6 (+/- 3 days), at week 4 (+/- 5 days) and at week 12 from the end or radiotherapy. Late toxicity will be assessed as per standard care at 6, 12, 18 and 24 months from the start of radiotherapy. At each assessment, toxicity will be scored according to CTCAE v 4.0 and at every time-point, EQ 5D will be completed by the patient. In between trial visits, patients will be seen for Enzalutamide or Abiraterone prescribing. Opportunistic reporting of significance (Grade 2+) toxicity related to SBRT will be done as appropriate at each scheduled visit. Patients will undergo a CT and bone scan at 3 months and 6 months after SBRT and a research WBDWMRI at 6 months post SBRT. Where PET-CT was used to diagnose oligoprogression, this imaging modality should be repeated

	at the 6 month follow up in place of the CT and bone scans. Thereafter scans will be as per local standard. PSA will be measured at baseline, 4 weeks post SBRT, 3 months and 6 months post SBRT and thereafter 6 monthly. Trial bloods for ctDNA will be taken in duplicate at baseline, on completion of SBRT, at 4 weeks, 3 months and 6 months post SBRT.

CHIEF INVESTIGATOR SIGNATURE PAGE

CHIEF INVESTIGATOR SIGNATURE PAGE

Study Title: TRAP – Targeted Radiotherapy in Androgen-suppressed patients

Sponsor Protocol Number: CCR 4781

As Chief Investigator I agree to conduct this trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in the document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study procedures as planned in the protocol will be explained.

Name of Chief Investigator: Dr Alison Tree

Signed: _____

Date: _____

STATISTICIAN SIGNATURE PAGE

STATISTICIAN SIGNATURE PAGE

Study Title: TRAP – Targeted Radiotherapy in Androgen-suppressed patients

Sponsor Protocol Number: CCR 4781

The signatures below constitute approval of this protocol by the signatories and provides the necessary assurances that this study will be conducted according to EMEA ICH Topic E9 'Statistical Principles for Clinical Trials' and the relevant standard operating procedures and policies used by RMH.

Lead Statistician: **Emily Robinson**

Title: _____

Signed: _____

Date: _____

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title: TRAP – Targeted Radiotherapy in Androgen-suppressed Patients

Sponsor protocol number: CCR 4781

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations, the guidelines of Good Clinical Practice (GCP) the Declaration of Helsinki and the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Site Address: _____

_____

_____

Name of Investigator: _____

Title: _____

Signed: _____

Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
Abi	Abiraterone
ADC	Apparent Diffusion Coefficient
AE	Adverse Event
AR	Androgen Receptor
BED	Biologically Effective Dose
bPFS	Biochemical Progression Free survival
CCR	Joint RM / ICR Committee for Clinical Research
cfDNA	Circulating cell-free DNA
CRF	Case report Form
CRPC	Castration Resistant Prostate Cancer
ctDNA	Circulating tumour DNA
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DNA	Deoxyribonucleic acid
DWI	Diffusion-weighted Imaging
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Enza	Enzalutamide
FEV1	Forced expiratory volume (1st exhale)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
IDMC	Independent Data Monitoring Committee
LFT	Lung Function Test
LHRH	Luteinizing hormone-releasing hormone
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NIHR	National Institute of Health Research
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PS	Performance Status
PSA	Prostate Specific Antigen
PSMA PET	Prostate-Specific Membrane Antigen Positron Emission Tomography
PTV	Planning Target Volume
PFTs	Pulmonary Function Tests
QA	Quality Assurance
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

LIST OF ABBREVIATIONS

Abbreviation	Definition
RM-CTU	Royal Marsden Clinical Trials Unit
RTOG	Radiotherapy Oncology Group
RTTQA	Radiotherapy Trials Quality Assurance Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBRT	Stereotactic Body Radiotherapy
SmPC	Summary of Product Marketing Characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
TLCO	Transfer factor of the lung for carbon monoxide
TMG	Trial Management Group
UCL	University College Hospital, London
WBDWMRI	Whole Body Diffusion Weighted MRI

1. BACKGROUND

Patients with prostate cancer have many more options now, compared with 10 years ago. Most are treated sequentially with LHRH analogues, Bicalutamide (with LHRH analogues continuing), Abiraterone (1) or Enzalutamide (2) Docetaxel (3) Cabazitaxel (4) and (for bone-predominant disease) Radium (5). For many men with metastatic disease, the cancer develops resistance to successive systemic therapies, and eventually all treatment options are exhausted, and the patient succumbs to their disease. It is therefore vital to find ways of evading prostate cancer resistance. SBRT has the advantage that it ablates tissue irrespective of the underlying genetic deficit within the progressing metastasis. If the resistant clones are localized to 1-2 metastases and can be ablated, the patient can continue to receive the benefit of their systemic therapy which may continue to control the remainder of their disease for many months, possibly even years.

We now know that in CRPC, each metastasis has a distinct genotype and hence can respond, progress and develop resistance to systemic agents at differing rates (6,7). Intra-patient inter-metastatic heterogeneity can manifest clinically as progression at a limited number of metastases or at the primary site (possibly due to emergence of treatment-resistant clones at these sites) with ongoing disease control at the majority of metastatic sites, referred to as oligoprogression. Treatment of oligo-progressing metastases could also reduce the risk of polyclonal seeding of resistant clones to other sites, delaying polymetastatic progression (8).

For these patients, current treatment guidelines suggest treatment discontinuation or change after a confirmatory scan or PSA rise, with use of radiotherapy solely for symptom control. In the interim, some centres add Dexamethasone to Abiraterone (9).

SBRT is a recognised technique for the elimination of isolated metastases in lung and brain tumours. Stereotactic body radiotherapy (SBRT) achieves local control of a metastasis in 80-90% of cases with almost no significant toxicity (10,11). This is achieved with very few side effects, but we don't know if it can also be useful in patients with polymetastatic disease. In the oligometastatic, rather than oligoprogressing setting, we now have significant experience with SBRT. Data from 73 patients treated at the Royal Marsden shows that, across a range of tumour sites, 2 year local control of the metastasis after SBRT was 88% (10). In a combined oligometastatic prostate cancer cohort from 7 centres across Europe, local control of the metastasis was 99% in patients who received a biologically effective dose of >100 Gy (12). There is, therefore, significant evidence supporting the assertion that SBRT can control the metastatic site. The question is, in the oligoprogressing state, whether it is worthwhile to

only target 1 or 2 sites, or whether patients quickly develop polymetastatic progression.

SBRT is available in most UK radiotherapy centres via the NHS England Commissioning through Evaluation scheme and within the CORE trial. Many UK centres, therefore, already have experience and expertise with SBRT techniques. The TRAP trial uses a modest fractionation of 30 Gy in 5 fractions which, with an a/b ratio of 1.5 Gy gives a BED of 150 Gy. In the series by Ost et al (12) a BED of >100 Gy was associated with a 99% 2-3 year local control of metastatic disease. This dose is also safe when delivered to the prostate – 36.25 Gy in 5 fractions given daily or alternate daily is the standard SBRT dose delivered in the PACE trial (NCT01584258). A dose of 36 Gy in 6 fractions weekly is standardly given at the Royal Marsden hospital to men too frail to attend the hospital for daily radiotherapy to the prostate.

Circulating cell-free tumour DNA (ctDNA) can be detected in progressing metastatic CRPC patients and gives an indication of the clonal heterogeneity and dynamics of progressing metastases (6,7). This allows genomic characterisation of metastases and evaluation of indices of clonal diversity, circulating tumour load and circulating tumour DNA dynamics after treatment. We will use a well-established and validated panel of common mutations in prostate cancer (see references above) which will be used in this project.

WBDWMRI is a novel technique, showing better sensitivity than standard imaging (13), but one which is able to be implemented in any radiology department with an MRI scanner. New guidelines, co-authored by two co-investigators, have set standards for widespread implementation (14). Single centre reproducibility of measurements is excellent, and this trial will facilitate dissemination of this technique to multiple UK sites. DWI is a functional MRI technique that studies the motion of water molecules within a tissue. Its quantitative parameter, Apparent Diffusion Coefficient (ADC) is an objective measurement of this water diffusion, which has been demonstrated to inversely correlate with cellularity in different tumour types including bone marrow malignancies (15). We have shown that changes in ADC values after treatment do correlate with tumour response in advanced prostate cancer patients (16).

As this is a multicentre trial running across the UK, imaging for eligibility needed to be pragmatic and commonly used. For this reason, standard metastatic prostate cancer imaging (CT and bone scan) has been used for eligibility. It may be that, through this trial and others like it, we will advise a change in standard practice for radiological assessment, but at present these remain the standard scans to assess men with metastatic disease.

The analysis of cancer DNA in blood is an exciting new technique which is receiving much attention as a robust and easily obtained marker of cancer's activity. Plasma DNA studies have identified tumour aberrations in all progressing metastatic CRPC patients (6,7) and the dynamics of circulating tumour DNA associate with outcome in multiple tumour types (17,18). TRAP 1 will use these two state-of-the-art techniques, ctDNA and WBDWMRI, combined. We believe this will be first time this has been done not only in prostate cancer but in any cancer. This, combined with ctDNA and patient demographics, may provide a predictive biomarker panel which will improve stratification of oligo-progressors to determine who benefits most. This is first-in-field trial investigating a novel approach in metastatic prostate cancer with informative translational research to increase mechanistic knowledge.

We hypothesise that irradiation of progressing metastases in patients with oligo-progression, whilst receiving potent AR targeting treatment, will associate with durable ongoing disease control at responding sites, prolonged time to next treatment and consequently, improved patient outcomes. We hypothesise that there will not be overlap between resistance to systemic AR targeting and radiation, thus allowing effective personalised treatment of resistant metastases. However, we hypothesise that patients with oligo-progression are a heterogeneous population including patients with progressing but as yet undetectable metastases by imaging. Therefore, in summary we aim to evaluate whether PFS after SBRT is significantly longer than expected PFS without SBRT. As an explanatory endpoint, we aim to potentially identify a biomarker panel including ctDNA and WBDWMRI which allows more accurate selection of patients in whom the sole sites of progressing disease can be treated with SBRT.

2. TRIAL OBJECTIVES

2.1 Primary Objectives

To determine the median progression-free survival following SBRT to oligoprogressing sites.

2.2 Secondary Objectives

- To establish the local control rate after SBRT for oligoprogression.
- To record PSA response and overall survival after SBRT.
- To monitor acute and late toxicity from SBRT in a metastatic cohort.

2.3 Exploratory Objectives

- To establish a biomarker panel which is present in at least 40% of oligoprogressing patients and which predicts for progression-free survival (median PFS) of more than 6 months.
- To determine time to delay of next line of treatment in the biomarker positive versus the negative groups
- To explore median PFS in the subgroups of local prostate oligoprogression versus metastatic oligoprogression.
- To determine if ctDNA mutational load is reduced after SBRT to sites of oligoprogression, and whether the kinetics of ctDNA predict time to progression.

3. TRIAL DESIGN

A multicentre phase II trial where all eligible patients will receive SBRT to oligoprogressing lesions.

3.1 Trial Overview

Figures 1 and 2 depict the identification of potential participants to the TRAP trial (Figure 1) and trial treatment and measurements (Figure 2). If TRAP I is successful, a further randomised controlled trial (TRAP II) will be designed (Figure 2) to evaluate the efficacy of SBRT versus continued Abiraterone/Enzalutamide, with or without a dexamethasone regardless of biomarkers. However, if the primary objective of TRAP I fails, but successfully returns a panel of predictive biomarkers (exploratory analysis) which shows biomarker positive group of patients have significantly longer PFS than biomarker negative group (assuming median survival of 6 and 4 months, respectively), a further randomised controlled trial (TRAP II) will be considered accordingly.

Figure 1: Flowchart – Identification of potential participants to the TRAP trial

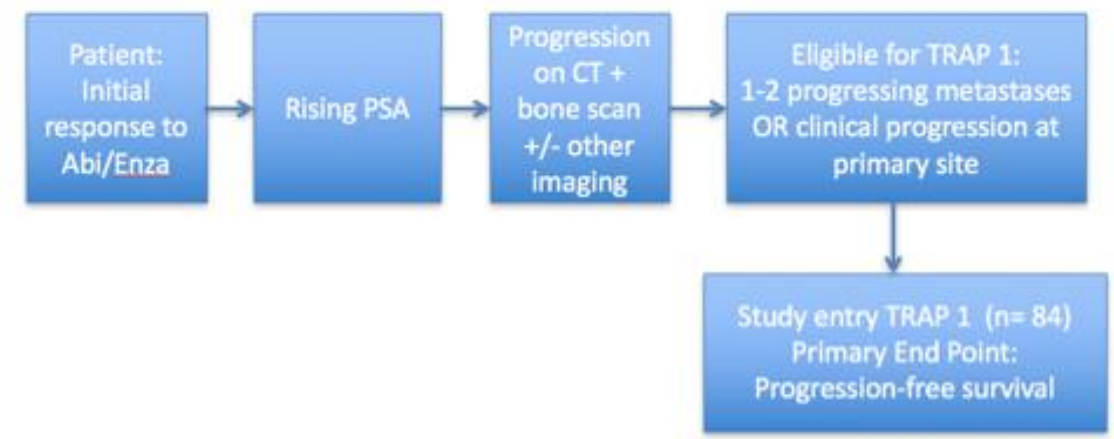
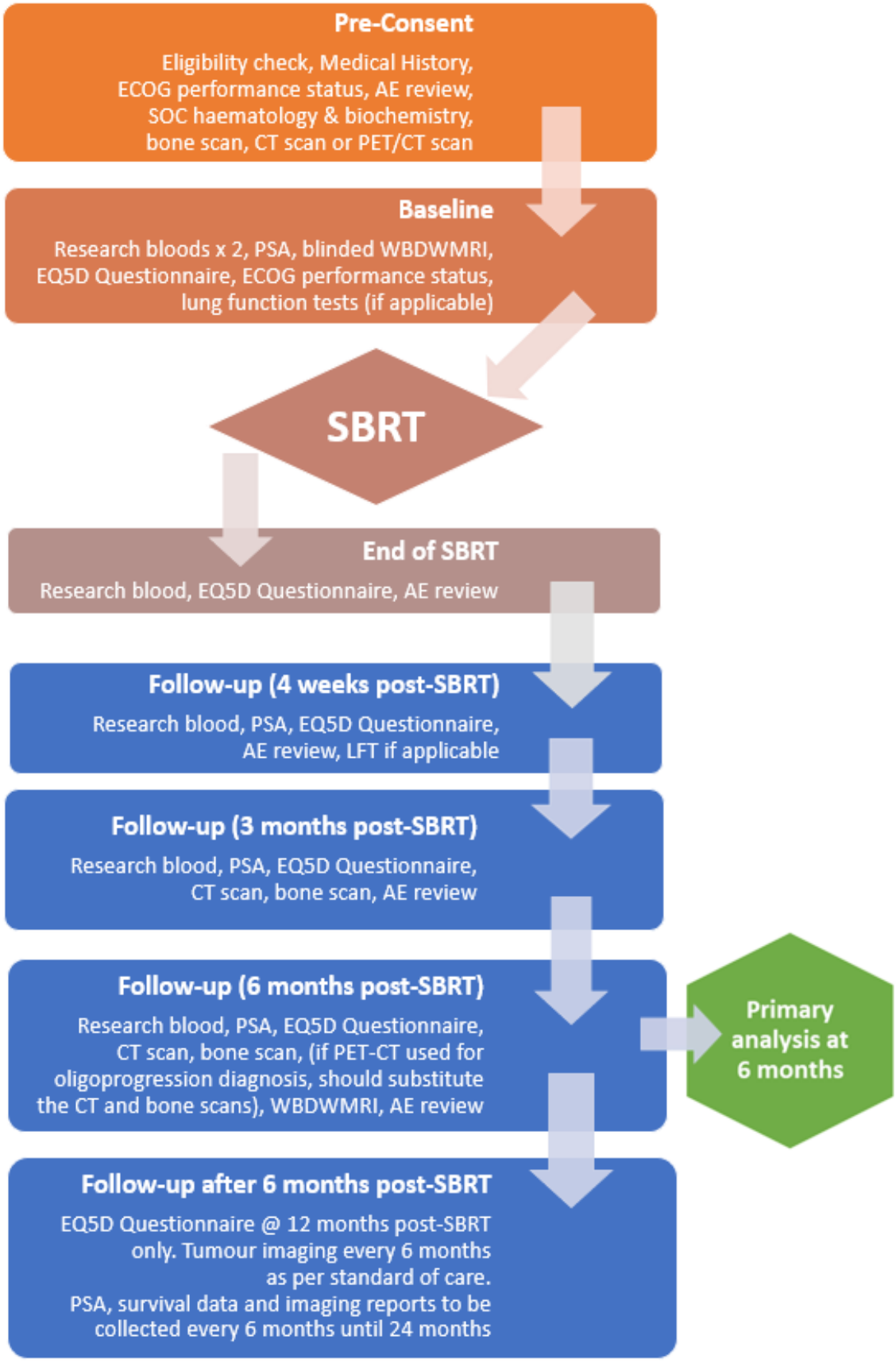


Figure 2: Flowchart – Trial treatment procedures showing 'gateway' to TRAP II, for key to acronyms see List of Abbreviations.



3.2 Participant Recruitment

Patients will be recruited from outpatient clinics at participating centres. Potential participants will be those patients with a rising PSA and demonstrable disease progression on CT / Bone Scan or other criteria, and with 1 -2 progressing metastases or clinical progression at the primary site (Figure 1). On determination of eligibility, patients may be consented 'remotely' (i.e. not through a face-to-face consultation) using the following procedure:

- A TRAP Patient information sheet and Consent form should be sent to the patient with reply-paid envelope
- A follow-up telephone call should be made to discuss the Patient information sheet with the patient
- Providing the patient has already had 24 hours to read the patient information sheet and is in agreement with participating in the trial, the patient may complete the Consent form by initialling all the boxes and appending their full signature and date of signature
- The patient should return the completed Consent form in the reply-paid envelope to TRAP (site) team
- The recruiting clinician at the site to countersign and date the Consent form when received
- An annotation should be made in the Clinical Notes to:

  a) Explain the delay in obtaining date of patient signature versus clinician signature

  b) Confirmation of the date the follow-up telephone call was made with the patient (confirming identity first) to discuss the Consent form

The Principal Investigator should ensure that each patient, prior to inclusion in the trial, is given full and adequate verbal and written information regarding the objectives and procedures of the trial and the possible risks involved. Sufficient time (a minimum of 24 hours) should be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment.

Following obtaining informed consent and completion of screening assessments, the treating investigator may deem the patient as eligible for trial entry and registration. The TRAP Patient Registration Form will need to be completed by site staff, and the form should be emailed to RM-CTU via the trial email address: Trap.Trial@rmh.nhs.uk in order to be assigned a Trial ID number which will be used to identify the patient. The original registration documents should be retained by the site in the Investigator Site File. Baseline assessments, such as the collection of research blood samples, should only be performed after receiving the Trial ID number from RM-CTU.

3.3 Inclusion Criteria

The inclusion criteria are as follows:

- Metastatic CRPC patients (biochemical or pathological diagnosis) on Enzalutamide or Abiraterone
- 1-2 metastatic lesions progressing on imaging (CT, bone scan, MRI, or other local imaging) or clinically or a clinical/ imaging diagnosis of progression of a non-irradiated primary site with the remainder of their metastases currently controlled by Abiraterone or Enzalutamide. Patients with one oligoprogressing metastasis and a progressing primary site are also eligible.
- No previous radical radiation to the index area (defined as unable to deliver the SBRT doses in this protocol without taking normal tissues beyond tolerance)
- PS 0-1 as determined using the ECOG criteria
- Oligoprogressing site in bone, lymph node, prostate or lung (liver, brain, adrenal or other sites are excluded) This includes sites that have developed on treatment.
- Minimum of 6 months on Enzalutamide/Abiraterone with evidence of response: response is defined as PSA <90% of its baseline value for >6 months (i.e. a reduction in PSA of at least 10%), radiological response or symptomatic response. The use of nadir scans is encouraged (i.e. CT scan +/- bone scan at nadir PSA response). If nadir scan is done, then patient must have had a minimum of 6 months on treatment with response. If a nadir scan is not done, then the patient must have a minimum of 12 months on Abi/Enza and a new/growing/active lesion(s) compared to baseline imaging.
- Patients can be symptomatic in the oligoprogressing area as long as there is no urgent need to start radiotherapy.

3.4 Exclusion Criteria

The exclusion criteria are as follows:

- Clinical need to switch therapy immediately (e.g. no suspicion of rapid clinical progression)
- Previous invasive cancer in the past 5 years, with the exception of non-melanoma skin cancer and small renal masses under surveillance (non-invasive malignancies such as non-muscle invasive bladder cancer are not excluded)
- Contra-indication to radiotherapy (e.g. inflammatory bowel disease, where relevant)
- Contra-indication to MRI (e.g. Cardiac pacemaker, Internal defibrillator, shrapnel injury, claustrophobia)
- The lesions are not suitable for SBRT (e.g. size of > 6 cm)

4. TRIAL TREATMENT AND ASSESSMENT PROCEDURES

An overview of study treatment procedures is given in Table 1.

4.1 Hormone Treatment

Patients will be on Abiraterone (plus prednisolone or dexamethasone) or Enzalutamide. This treatment should proceed as per normal with all usual checks as per standard of care. Most patients will be seen more frequently than outlined in this protocol for Abiraterone or Enzalutamide prescription. It is acknowledged that neither drug is licenced in conjunction with radiotherapy, although both are regularly used in this context. Patients will be made aware of this as part of the patient information sheet and consenting process.

The schedule of trial assessments is given in Table 1 together with radiotherapy and hormone treatment schedules.

4.2 Trial Assessments

Table 1 - Schedule of Treatment and Assessment

Assessment/event	Pre-registration	Baseline	Post-SBRT Follow-Up					
			End of SBRT	4 weeks post SBRT	3 months post RT	6 months post RT	Every 6 months thereafter until progression	6 monthly survival review (notes only)
Permitted Visit Window (weeks)	Up to 56 days before study enrolment	After consent, prior to SBRT	Up to +1 week	± 1 week	± 2 weeks	± 2 weeks	± 4 weeks	
Informed Consent	**X**							
Inclusion/Exclusion Criteria	**X**							
Demographic, Medical & Treatment History	**X**							
Survival Status, Local imaging reports								**X**
ECOG Performance Status	**X**	**X**						
Adverse Events Review – CTCAE and RTOG	**X**		**X[4]**	**X[4]**	**X[4]**	**X[4]**		
Haematology & Biochemistry *(if needed as SoC)*	**X**		**If clinically indicated**					
Tumour Imaging (SoC 6 monthly) and RECIST/PCWG criteria measurements	**X[1]**				**X**	**X[3]**	**SOC (6 monthly)**	
PSA		**X**		**X**	**X**	**X**	**X**	
WBDWMRI (research)[6]		**X (blinded)**				**X**		
EQ5D Health Questionnaire		**X**	**X**	**X**	**X**	**X**	**X (at 12 months only)**	
Lung function tests (only if lung mets– estimate 10% patients only)		**X**		**X[7]**				
SBRT			**X**					
Research Blood Samples for ctDNA (max 6 per patient)		**X[5]**	**X[2]**	**X**	**X**	**X**		
Hormone treatment	**Continue as clinically indicated**							

Key:

Permitted Visit Window: Permitted period of time either side of scheduled measurement
LFTs: Lung Function Tests (FEV1, TLCO (diffusion), FVC)

1. Initial CT and bone scans can be obtained up to 56 days prior to study enrolment
2. Aim to take immediately after final fraction
3. If PET/CT or other imaging modality was used to diagnose oligoprogression at trial entry, this should be repeated at 6-month follow-up, where PET/CT can be completed instead of a CT and bone scan.
4. Where possible, face-to-face consultations should be encouraged up to and including the 6-month follow-up time-point (remote consultations are permitted where this is not possible); further consultations may be done remotely after 6 months as deemed appropriate
5. Two samples of research blood for baseline ctDNA, ideally done on separate visits, separated by >24 hours apart if possible.
6. If WBMRI has been conducted as standard of care, and as per the TRAP protocol, within 56 days of trial consent, then this does not need to be repeated for the TRAP trial, even if not blinded.
7. Lung function tests can be done between 4 weeks and 3 months after SBRT.

4.2.1 Pre-registration Assessments

These are the following assessments, which should be performed prior to trial registration in order to confirm eligibility.

- Assessment of eligibility, medical and treatment history, performance status, and current adverse events/symptoms (using CTCAE v4.0)
- CT and bone scan (must be done within 56 days prior to consent). Where PSMA PET CT has been used to diagnose oligoprogression, a separate CT is not required.
- Centre-standard biochemistry and haematology tests with clinician review to ensure patient is suitable for radiotherapy, where needed.

4.2.2 Baseline Assessments

These are:

- Baseline PSA
- Baseline EQ5D Health Questionnaire
- WBDWMRI (blinded)
- Lung function test (if having a lung metastasis or mediastinal node treated) and baseline oxygen saturations
- Where considered appropriate e.g. for tracking delivery or to aid pre-treatment verification 3-5 fiducials markers may be placed around the lesion, into stable structures where possible, under CT guidance. A single fiducial centrally located within a lesion may suffice for small,

circular lesions. This will be considered for lung metastases but can be considered for other sites. Clotting screen and ECG should be performed pre-insertion of lung fiducials.

- For prostate, fiducial markers are optional. If used, rectal swabs are advocated to detect Ciprofloxacin resistant coliforms. Targeted antibiotic prophylaxis is recommended (19).
- For patients who have had fiducial markers inserted, the localisation scan is ideally done no earlier than 7 days after insertion to account for potential fiducial marker migration.
- Two samples for baseline ctDNA, ideally done on separate visits >24 hours apart.

4.2.3 Assessments at the end of SBRT Treatment

- CTCAE and RTOG toxicity completed
- Capture of EQ5D Health Questionnaire responses
- ctDNA sample taken

4.2.4 Assessment at 4 weeks post-SBRT completion

- CTCAE and RTOG toxicity completed
- Capture of EQ5D Health Questionnaire responses
- ctDNA sample taken
- PSA blood test
- Lung Function Tests (lung/mediastinal metastases only)

4.2.5 Assessment at 3 months post-SBRT completion

- CTCAE and RTOG toxicity completed
- Capture of EQ5D Health Questionnaire responses
- ctDNA sample taken
- PSA blood test
- CT scan and bone scan

4.2.6 Assessment at 6 months post-SBRT completion

- CTCAE and RTOG toxicity completed
- Capture of EQ5D Health Questionnaire responses
- ctDNA sample taken

- PSA blood test
- CT scan and bone scan or PET/CT if that was used to diagnose oligoprogression at study entry
- WBDWMRI

4.2.7 Additional Assessments thereafter

- Capture of EQ5D Health Questionnaire responses at 12 months only
- PSA will be collected 6-monthly up until 24 months or disease progression.
- Survival data and systemic therapy details will be collected remotely 6-monthly up to 24 months.
- Scans will be conducted as per standard of care. Imaging reports will be collected until 24 months and will be kept in the ISF. These reports will be requested at the end of the trial.

4.3 Radiotherapy Treatment & Treatment Delays

Radiotherapy should be planned as per current TRAP radiotherapy instructions (see separate radiotherapy QA protocol). Radiotherapy trial QA is outlined in Section 6 below. Any deviations from the radiotherapy protocol need to be notified to the Chief investigator in writing/email. If radiotherapy does not commence within 56 days of consent, this constitutes a protocol deviation and should be reported as such.

Radiotherapy in this setting is not known to be time-critical. Treatment should aim to be completed in 10 days, with the exception of weekly prostate radiotherapy which may be up to 6 weeks. Apart from this, treatment courses which occur over more than 19 days should be reported as a protocol deviation.

4.4 Whole Body Diffusion Weighted MRI technique and protocol

WBDWMRI will be obtained at baseline and at 6 months after SBRT. Whole Body Diffusion Weighted MRI (WBDWMRI) will be acquired from skull base (C2-vertebra) to femora (greater trochanters) using a standardised protocol according to a detailed imaging manual that will be provided to all centres. The WBDWMRI images will be reported according to a dedicated proforma that will include overall assessment of the disease burden and quantitative assessments of the SBRT treated lesions. Scans will be reviewed for the following unexpected findings

- malignant spinal cord compression
- new hydronephrosis
- new fractures

Lead PI at the site (or delegate) will be informed of any of these urgent clinical findings on the MRI to determine if action is required.

Clinicians will be blinded to the baseline WBDWMRI which will not be read until 6 months when both will be reported together. Patients will be informed and consented for this at trial entry. Acquisition and transfer of anonymised MRI images to the Lead Site (Royal Marsden NHS Foundation Trust) should be carried out as described in the Trial's Imaging Manual.

5. ASSESSMENT OF DISEASE PROGRESSION

Disease progression is defined in 4 ways which may co-exist. These are outlined below:

- **PSA progression**: PSA must rise by at least 25% over post-SBRT baseline (set at 4 weeks), confirmed by a second reading at least 4 weeks later.
- **Radiological progression:** Defined as at least 2 new lesions on bone scan or unequivocal RECIST progression of soft tissue on CT, or evidence on other local imaging of disease progression (e.g. PET progression).
- **Symptomatic progression:** new or progressing symptoms at the site of a metastasis.
- **Date at which the clinician decides to stop Abiraterone/Enzalutamide for progression**

It is recognised that in clinical practice the judgement of disease progression is a clinical one and repeat imaging may not be required in all cases, but TRAP investigators will be encouraged to adhere to the progression criteria above. After 6 months the WBDWMRIs from baseline and 6 months will be analysed. These may show MRI progression which is not seen on other imaging. The treating clinician should change therapy only where they believe this is in the patient's best interests. Where imaging diagnosis of oligoprogression was performed using PET-CT modality, this modality should be repeated at the 6-month follow-up.

6. TRIAL APPROVALS & MANAGEMENT

This trial will be conducted in accordance with the conditions and principles of GCP as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations and GCP guidelines. It will also adhere to the Sponsor's SOPs and local centres' SOPs as appropriate and other regulatory requirements as amended.

6.1 Trial Approvals

6.1.1 Radiotherapy Quality Assurance (RTTQA)

Radiotherapy Quality Assurance (QA) provision for the trial has been discussed with the National Radiotherapy Trials (RTTQA) Group. The service support costs associated with protocol adherence for radiotherapy planning and treatment delivery will be covered by the central QA group funding along with support for QA of clinical outlining. Appropriate QA approval for previous UK radiotherapy studies will be taken into consideration to reduce QA workload.

Centres wishing to recruit to this study will be asked to provide evidence of quality assurance of SBRT prior to patient recruitment commencing. Centres who have already been accredited as part of the commissioning through evaluation (CtE) scheme, or who are accredited as part of the CORE trial will not need to submit any further benchmark or prospective review cases. Centres that have not completed this QA will be expected to complete benchmark cases for all anatomical sites eligible for TRAP, and to submit their first case in each anatomical site (spine, node, lung) for prospective review. Clinicians who have completed the QA may train others at their site but remain in overall responsibility for all the contours and plans used within the trial.

6.1.2 Sponsor and Regulatory Approvals

Before starting the trial, the protocol, patient information sheet, consent form, and any other written information that will be provided to the patients must be approved by the Royal Marsden/Institute of Cancer Research joint Committee for Clinical Research (CCR). Once approved, the study will then be submitted to the local REC and HRA for review and approval. The trial will not begin until favourable opinion from REC and HRA is received.

6.1.3 Local Centre (Site) Approval and Management

The Principle Investigator at each site is responsible for any site-specific assessments and for obtaining applicable local approvals (e.g. capacity review) for the study. All participating sites will be required to sign a non-commercial agreement to be signed by the participating site and the Sponsor's representative. This agreement includes the requirement for the Site to adhere to the trial protocol and subsequent amendments.

6.1.4 Protocol Amendments

Any protocol amendment should be agreed with the TMG (see below) and be approved by the sponsor prior to submission and review by REC and HRA. Once a favourable opinion from all of these institutions have been received, the amendment can be distributed to sites for each to complete their local capacity review. Prior to implementation at the site, a local approval from the site's R&D should be obtained, as well as Sponsor Green Light to implement the amendment

It is the responsibility of the RM-CTU to submit amendments to the Sponsor for approval and to distribute them to all participating centres for capacity review and implementation. Amendments requiring REC approval may be implemented only after a copy of the REC/HRA's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC/HRA approval. However, in this case, approval must be obtained as soon as possible after implementation.

6.1.5 Insurance Arrangements

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence.

6.1.6 Provision of Information to the Participant's GP

It is the Investigator's responsibility to inform the patient's GP by letter that the patient is taking part in the study provided the patient agrees to this, and information to this effect is included in the PIS and ICF. A copy of the letter should be filed in the ISF. A template letter approved by the REC/HRA will be provided by the Sponsor to all participating sites.

6.2 Trial Management

6.2.1 RM-CTU Trial Management Responsibilities

RM-CTU is responsible for ensuring appropriate Sponsor oversight for the trial and for obtaining the required Sponsor and regulatory approvals, including co-ordinating the production and incorporation of protocol amendments. RM-CTU is also responsible for conducting a Site Initiation Presentation and confirming when each recruiting site (Centre) is ready to open to recruitment. In addition, RM-CTU is responsible for the processing of trial safety data including expedited reporting to the relevant authorities.

6.2.2 Trial Management Group

A Trial Management Group (TMG) will be set up with membership and remit as defined in the TMG Charter. Membership will include Chief Investigator, Trial Statistician, Co-Investigators and the RM-CTU Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG has operational responsibility for the conduct of the trial and for overseeing its timely completion including achievement of recruitment targets. The TMG will meet with a frequency as determined by the Chief Investigator in discussion with the Trial Manager. The frequency of meetings and / or the need for ad-hoc meetings will reflect emerging needs.

6.2.3 Monitoring

During the trial, monitors appointed by the RM QA Manager, will be responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be discussed with the site for resolution. Any systematic inconsistencies may trigger an on-site monitoring visit.

If an on-site monitoring visit is required, the trial monitor will contact the site to agree a convenient date. The site must ensure that relevant site files and patient notes are available for review. RM-CTU staff conducting on-site monitoring will review the investigator site file and carry out source data verification to confirm compliance with the protocol and trial agreement.

6.2.4 Independent Data Monitoring Committee (IDMC)

An IDMC will be set up with membership and remit as defined in an IDMC Charter. The purpose of the Committee will be to ensure the ongoing safety of trial participants through regular scrutiny of trial

safety related data. The IDMC membership will include the trial statistician who will periodically examine data for anomalies and outliers, such as too few or too many events.

All interim analyses will be supplied in confidence by the trial statistician to the IDMC together with any other analyses the IDMC request. The IDMC will advise on the frequency of reviews of the data on the basis of accrual and event rates, for example when 25% of the anticipated recruitment target (i.e. n=21) has been achieved, following which, meetings will be held at 6-monthly intervals. Following each meeting the IDMC will report their findings and recommendations to the chair of the Trial Management Group

6.3 Licenses and Agreements

The EQ 5D questionnaire will be used on the trial is reproduced in Appendix 1. Confirmation that the questionnaire will be used for academic research purposes only in connection with the TRAP trial has been provided to the questionnaire's licensor (Euro QoL Group) allowing use of the questionnaire free of charge. No data from completed questionnaires will be transferred to a third party (e.g. Euro QoL Group)

6.4 Trial Registration & NIHR Portfolio Listing

The TRAP trial has been registered on ClinicalTrials.Gov database (NCT03644303) and has been granted NIHR support, which ensures its adoption onto the national (NIHR) trial portfolio.

7. DATA MANAGEMENT

7.1 Trial Source Data and Patient Confidentiality

The Chief Investigator is responsible for ensuring that the patient's confidentiality is maintained in compliance with the UK Data Protection Act of 1998. The patient's medical notes will be regarded as source data and may be supplemented when required by Source Data Worksheets as determined by the CI or PI. Medical notes will, in all circumstances, constitute the master record and will contain full patient details, including date of birth. The CRFs will identify the participant only by their trial ID and initials. The PIS should state that in the event that trial personnel require access to the participant's trial-related records, confidentiality will be preserved. Requests from patients for access to data about them held at RM-CTU should be directed to the Trial Manager, who in the first instance will refer the request to the Trust's Data Protection Officer.

7.2 Trial Data Management

The PI at each participating centre is responsible for ensuring that appropriate trial data management procedures are adhered to at their site including:

- Ensuring that sufficient data is recorded for all participating patients to enable accurate linkage between source data and CRFs
- Ensuring that source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- Ensuring that original consent forms are dated and signed by both patient and investigator and are kept together in the ISF, with a copy of the specific patient information sheet(s) given at the time of consent
- Ensuring that all essential documents are retained after the trial ends to comply with current legislation

No trial document should be destroyed without prior written agreement between the Sponsor and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

7.3 Trial Database & CRF Completion

RM-CTU will responsible for providing a trial database to accommodate and securely hold all trial data. The database specification will be approved by the trial statistician who will also perform database testing prior to the database going 'live'. Case Report Forms (CRFs) will be used for the collection of trial data. RM-CTU will be responsible for informing sites on the correct completion of CRFs and providing adequate guidance and access to the database for CRF data entry.

Only those personnel listed on the Delegation Log as having CRF completion responsibilities should enter or change data in the CRFs. If a patient withdraws from the study, the reason must be noted on the CRF. All data will be entered in a clinical trials database.

Queries regarding correct completion of CRFs will be raised centrally by the Trial Manager / Trial Monitor and discussed with the participating site for resolution. The Trial Management Group reserves the right to amend or add to the CRF 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 RM-CTU.

7.4 End of Trial Report

Clinical data will be presented at the end of the trial based on final data listings. The CI/delegate together with the trial statistician will prepare a brief clinical study report / publication based on the final data listings. A summary of the report must be provided to the Research Ethics Committee within 1 year from the submission of the end of trial notification.

7.5 Record Retention

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified in accordance with current legislation.

RM-CTU will maintain essential documents to facilitate the management of the trial, audit and inspection in accordance with local SOPs and in compliance with the clinical trial regulatory requirements. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period permitted by the hospital, institution, or practice. Records will be archived and retained for a period of at least 5 years after the conclusion of the trial, in accordance with the required regulations.

8. SAFETY (ADVERSE EVENT) REPORTING

8.1 Reporting period for Serious Adverse Events (SAEs)

In the TRAP trial, SAEs will be collected from the **start date of the patient's radiotherapy (or the date of insertion of fiducials, where used) until 30 days from the end of radiotherapy treatment**. All events will be recorded in the medical notes and the appropriate section of the CRF and/or AE log. Sites will be expected to complete a study specific SAE Reporting Form, and must send to RM-CTU/the Chief Investigator within 24 hours/next working day since being notified of the event.

8.2 Definitions

8.2.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the protocol treatment.

8.2.2 Serious Adverse Event (SAE)

Adverse event that

a) Led to a death,

b) Led to a serious deterioration in health that either:

- Resulted in a life-threatening illness or injury, or
- Resulted in a permanent impairment of a body structure or a body function, or
- Required in-patient hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

A planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

SAEs are defined as those occurring from placement of fiducials (where used) or start of radiotherapy up to 30 days from the end of radiotherapy treatment or to start of next line of therapy, whichever is sooner, with the exception of Grade 3+ toxicities deemed probably or definitely related to radiotherapy (also called Severe Adverse Reactions, or SARs) which are reportable until the patient develops progressive disease. Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

8.2.3 Causality

The analysis of causality will be determined with reference to Table 2 plus the list of expected SBRT toxicities listed in Appendix 2. The toxicities of Abiraterone or Enzalutamide do not need to be reported as SAEs unless these could also be possibly related to SBRT.

Table 2 – Analysis 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.

8.3 Expedited Reporting of Adverse Events

SAEs are reportable to REC as detailed below:

8.3.1 Reportable Events

The following events are considered reportable to REC by expedited reporting within 15 days of becoming aware of the event:

- Any unexpected SAE (excluding those resulting in hospitalisation listed in Appendix 2 of CTCAE ≤ grade 2) occurring from placement of fiducials (where used) or start of radiotherapy up to 30 days after completion of radiotherapy AND thought possibly, probably or definitely related to SBRT.
- Any SAE of CTCAE ≥ Grade 3 occurring from placement of fiducials (where used) or start of radiotherapy up to 30 days after completion of radiotherapy OR until start of next line of therapy, whichever is sooner, AND thought possibly, probably or definitely related to SBRT.

All other adverse events should be recorded on the CRF at the time-points as specified in Table 1

8.3.2 Data to be Reported

For each event, the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)

- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial procedures) in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

8.3.3 Reporting Timeframes

All reportable events must be sent to RM-CTU **within 24 hours** of the site staff becoming aware of the event. RM-CTU will notify the Chief Investigator. The responsibility of notifying reportable events to REC has been delegated by the Sponsor to the Chief Investigator. Notification to REC should occur within 15 days of the CI first becoming aware of the event. Follow-up information should be sent to RM-CTU as soon as it becomes available but no later than **5 working days**. Events will be followed up until the event has resolved or a final outcome has been reached.

All reportable SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients / subjects, users or other persons or a new finding to it must be reported to the REC immediately, but not later than **2 calendar days** after awareness by Chief Investigator of a new reportable event or of new information in relation with an already reported event.

9. STATISTICAL CONSIDERATIONS

9.1 Rationale

It is recognised that many patients with oligoprogressing prostate cancer will progress to polymetastatic progression within 4 months, and will at that point require chemotherapy. In the long term, for commissioning purposes, it will be critically important to identify those patients likely to remain oligoprogressive long enough to benefit from SBRT. At this stage, however, it is recognised that this is a novel group of patients, previously treated in the same way as polymetastatic patients, and hence pilot data is needed before a larger randomised trial is proposed and future treatment options are identified.

9.2 Sample Size (Study Powering)

Assuming median progression-free survival of the existing (i.e., null median PFS) and the novel treatments (i.e., alternative median PFS) are 4 and 6 months, respectively, with 24 months accrual time, 30 months maximum follow up time and 2-sided type 1 error of 5%, a sample size of 84 provides 96% power for one-sample Log-Rank test . Note: the power calculated using an in-house R script (20). The R script output is identical to the output of one arm survival analysis – CRAB: Cancer Research And Biostatistics – https://stattools.crab.org/Calculators/oneArmSurvivalColored.html (21). The study has been overpowered to improve the chance of biomarker exploration (exploratory outcome) which is likely to affect the survival. Progression-free survival is defined as the time between the final day of SBRT and the first confirmed progression (as defined above) or start of next line of therapy, whichever occurs sooner.

9.3. Verification of Efficacy (Future)

If the primary outcome is successful (i.e., the null hypothesis of one-sample survival test is rejected, which means the alternative median PFS is significantly longer than null median PFS) we plan for an adequately powered RCT (TRAP II) to test SBRT + drugs versus drugs alone. However, if the null hypothesis of one-sample survival test is accepted, depending on the findings of exploratory analysis we consider a trial stratified by biomarker (+) vs. biomarker(-) to confirm the effect on median PFS independently.

9.4 Statistical Analysis Plan

A full statistical analysis plan (SAP) will be written by the trial statisticians and agreed by the trial team before any analysis is undertaken.

9.5 Endpoints

9.5.1 Primary Endpoint

Time from end of SBRT to Progression or Death from any cause (Progression Free Survival – PFS). Patients who remain alive at the time of the analysis will be censored at the date of last follow up. A one-sample Log-Rank test (22) will be used to compare the observed PFS of the patients (alternative PFS) with their expected (null) PFS (based on 4 months median PFS using the existing treatment) with 2-sided type I error of 5%. Kaplan–Meier estimator of survival function, and median survival with 95% Confidence interval will also be reported.

9.5.2 Secondary Endpoints

The secondary endpoints and statistical methods employed will include:

- ctDNA response to SBRT including proportion of patients in whom at least one mutation becomes undetectable after SBRT.

  Descriptive statistics (will be defined as frequency)

- Overall local control (defined as stable disease or partial response of irradiated metastases 6 months post SBRT) on CT and WBDWMRI

  Descriptive statistics (frequency)

- Acute (</= 30 days from end of SBRT) and Late Toxicity (>30 days) as per CTCAE v4.0

  Descriptive statistics (frequency) with Grade 3+ toxicity being the event of primary interest.

- QoL assessed using the EQ 5D Questionnaire

  Change from the baseline to each time-point will be plotted

- Time to next therapy (months)

  Defined as time from end of SBRT to start of new systemic therapy or death

  Survival function and median survival with 95% confidence intervals will be estimated using Kaplan Meier curve.

- Proportion of patients where WBDWMRI detects further metastases at baseline

  Descriptive statistics will be employed including 95% CIs.

- Association between WBDWMRI at baseline (number of metastases, DWI characteristics) and prognosis after SBRT

  Correlation, and/or regression and/or survival (for prognosis) models will be used whenever appropriate.

- Overall survival at 12 & 24 months after SBRT, the end of SBRT until the date of Death from any cause. Patients who remain alive at the time of the analysis will be censored at the date of last follow up.

  OS will be analyzed similarly to primary endpoint PFS.

- PSA kinetics at 3, 6, & 12 months after SBRT, including percentage of patients with PSA below 75%, 50% & 25% of pre SBRT baseline

9.5.3 Exploratory Endpoints

It is envisaged that an 'oligoprogression predictive' and 'oligoprogression non-predictive' binary ctDNA phenotype be defined and will be used in combination with WBDWMRI components to distinguish between biomarker +ve (i.e. patients most likely to benefit from SBRT) *versus* biomarker –

ve patients. WBDWMRI components may comprise number of lesions and/or DWI characteristics in dominant metastasis. Candidate biomarkers have been defined as above and also include number of measurable metastases, presence of superscan on bone scan, PSA level at trial entry and time between presentation with localised disease and development of metastatic disease (months).

- To establish a biomarker panel which predicts for a prolonged progression-free survival

  Survival function and median survival with 95% confidence intervals for Biomarker +ve and Biomarker -ve patients will be estimated using Kaplan-Meier curve. Log-Rank test will be used to estimate the significance of the difference between PFS of Biomarker +ve *versus* Biomarker –ve groups.
- To explore whether the kinetics of ctDNA predict time to progression or precede clinical or radiological progression

9.5.4 Sub-group Analysis

We will include a planned subgroup analysis of the median PFS in patients with local prostate oligoprogression *versus* metastatic oligoprogression. Methods employed will include Kaplan-Meier analysis or the Cox-Proportional Hazard Regression model or other appropriate survival model to estimate the hazard ratio.

10. TISSUE MANAGEMENT

Tissue samples (peripheral blood for ctDNA analysis) will be managed in compliance with the code of practice and standards as defined in the Human Tissues Act 2004 and in compliance with local (Trust) policies.

10.1 Collection

Collection of samples will adhere to the timetable of assessments (see Table 1). Samples will be collected in cell free DNA tubes which will be provided to all sites and will be handled in accordance with the manufacturer's recommendations to ensure stability of sample. The TRAP Laboratory manual describes the procedures required for initial processing and transfer of blood samples to University College, London (UCL) where analysis will take place.

10.2 Identification

Sample tubes will be pre- labelled with:

- Patient's Trial Identification Number
- Date of collection
- Trial Time-point

No details which allow the patient's identity to be revealed will be recorded. Sample request forms (i.e. pouches containing tubes) which may be labelled with the patient's name must be destroyed in line with procedures for the destruction of confidential waste.

10.3 Storage

Blood samples will be transferred from their site of collection to UCL. Full contact and address details are given in the TRAP Laboratory Manual. On arrival, they will be logged in a TRAP Tissue Receipt Register and stored at -80^{o}C. Transfer of samples from their site of collection to site of analysis (UCL) will be recorded on the TRAP CRF as detailed in the TRAP Laboratory Manual.

10.4 Analysis

Blood samples will be analysed for ctDNA in the laboratories of Dr Attard, UCL using documented Standard Operating Procedures under the guidance of TRAP Co-Investigator Dr G Attard.

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APPENDIX 1 – EQ 5D HEALTH QUESTIONNAIRE

Trial ID: _____ Patient Initials: _____

Visit / Time-point: _____ Date completed: _____

Health Questionnaire – EQ 5D™

Self-Complete

English version for the UK

EQ 5D™ by permission: EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

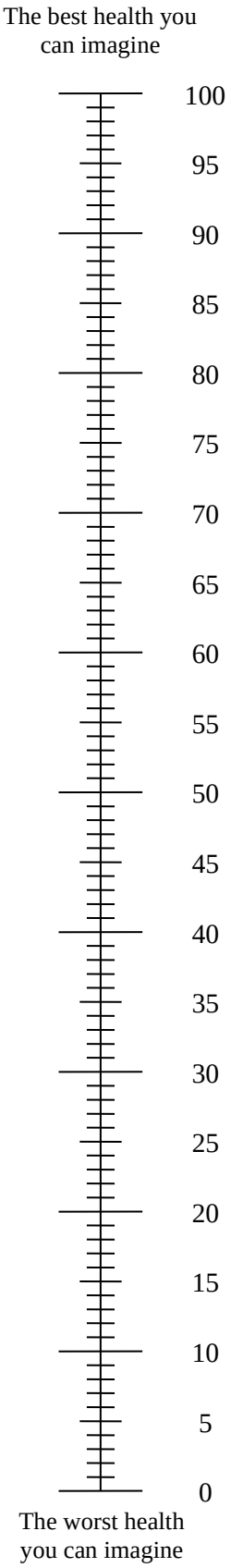
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 2 - EXPECTED ADVERSE EVENTS AFTER SBRT

Hospitalisation for any of the following adverse events does not need to follow SAE reporting procedures detailed in the protocol if the event is grade ≤2 (CTCAE v4.0). All grade 3 events resulting in an SAE thought possibly, probably, or definitely related to SBRT should be reported.

SBRT site:

Thoracic and mediastinum

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

Abdomen

- Nausea
- Vomiting
- Spinal/other bone fracture
- Upper GI ulcer
- Duodenal/Gastric ulcer
- Upper GI bleeding
- Liver enzymes: ALT/AST/Bilirubin derangement thought to be related to SBRT

Pelvic

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

General

- Fatigue
- Pain flare

Dermatology/Skin

- Dermatitis
- Hair loss (to treatment area)

Related to fiducial marker insertion

- Bleeding
- Sepsis (urinary and systemic)
- Discomfort
- Pneumothorax not requiring admission