Study Title: Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone: a randomised controlled feasibility trial

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There are no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. SYNOPSIS

Study Title	Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone: a randomised controlled feasibility trial	
Internal ref. no. / short title	TRoMbone	
Study Design	Randomised controlled feasibility trial	
Study Participants	Men with oligometastatic prostate cancer fit for radical prostatectomy	
Planned Sample Size	50 (randomised 1:1, n=25 each arm)	
Planned Study Period	Set-up: 3 months Recruitment Period: 18 months Follow-up: 3 months Analysis and Report: 3 months	
	Objectives	**Outcome Measures**
Primary	Feasibility of randomisation	Ability to randomise patients to both arms, optimised by a QRI
Secondary	Collect quality of life assessment Collect oncological assessment (routine clinical follow up will yield this data at later time points beyond the study duration)	EQ-5D-5L Time to castrate resistance

2. ABBREVIATIONS

AM	Active Monitoring
ADT	Androgen Deprivation Therapy
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTRG	Clinical Trials & Research Governance, University of Oxford
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NRES	National Research Ethics Service
OPCSG	Oxfordshire Prostate Cancer Support Group
PI	Principal Investigator
PIL	Participant/ Patient Information leaflet
TMG	Trial Management Group
PPI	Patient and Public Involvement
PSA	Prostate-specific antigen
QoL	Quality of Life
QRI	QuinteT Recruitment Investigation
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RP	Radical Prostatectomy
SEER	Surveillance, Epidemiology, and End Results
SWOG	South West Oncology Group
UCLH	University College London Hospitals

3. BACKGROUND AND RATIONALE

3.1. Introduction

Prostate cancer is the commonest cancer and the second most frequent cause of cancer death in Western men[1]. Men presenting with metastatic disease have a median survival of only 42.1 months[2] and current standard-of-care consists of initial androgen deprivation therapy (ADT) followed by chemotherapy and novel agents once the cancer no longer responds to ADT. The burden on the health care setting of treating men with metastatic prostate cancer is vast and a recent study estimated costs of USD20,000 per man[3]. There is emerging data that radical therapy directed at the prostate impacts survival, especially in those with limited metastatic burden, defined as 1-3 skeletal lesions without any visceral metastases (oligo-metastases). Further, many men suffer symptomatic disease progression and eventually require palliative surgical intervention, which is less frequent in those treated with initial radical prostatectomy compared to systemic therapy alone[4,5]. Hence, our ultimate aim is to examine whether radical prostatectomy can impact survival and quality-of-life in men with oligo-metastatic prostate cancer. Currently we have low-level evidence from biological and epidemiological studies and we need to provide a high level of evidence with a clinical trial to properly interrogate the hypothesis that radical prostatectomy improves survival in men with oligo-metastatic prostate cancer. However, randomisation to surgical trials is fraught with difficulty and a number of high-profile prostate cancer trials have failed to recruit. Hence, before commencing a full trial, it is imperative to assess the feasibility of the study. One major success in recruitment terms was the Prostate Testing for Cancer and Treatment (ProtecT) study (http://www.nets.nihr.ac.uk/projects/hta/962099) which employed a QuinteT recruitment investigation (QRI) run by the University of Bristol School of Social and Community Medicine; we will therefore similarly integrate a QRI in this feasibility study.

3.2. Trial Rationale

This trial addresses a critical unmet need in managing the health of men with oligo-metastatic prostate cancer. The impact of the study has the potential to drive a paradigm shift in the management of this condition globally. Newer pharmaceuticals have resulted in a few months extra median survival and have been used in castrate-resistant prostate cancer when the cancer is no longer responsive to ADT. However, radical prostatectomy has the potential to impact survival before the cancer becomes unresponsive to ADT and may do this to a greater extent than novel agents[6]. It may also reduce symptomatic local progression which other therapies cannot offer. With an ageing population there will be a sustained and expanding need for improvements in treatments for metastatic prostate cancer and this research will therefore remain highly relevant and important to the needs of the NHS in the future.

In fact, the study idea bore out from a patient encounter in which a 53-year old patient with a young family who was diagnosed with skeletal-metastatic prostate cancer of low volume asked the Chief Investigator (CI) why surgery was not an option and instead the only initial management was hormonal therapy. Over the past 2-3 years the CI has thus worked up this research question and has involved the Oxfordshire Prostate Cancer Support Group (OPCSG) at every stage. They helped develop the research question as many were involved in a national trial with radiotherapy (STAMPEDE) and were curious as to whether surgery could have been an option. They identified that it was important to assess quality-of-life issues as well as oncological outcomes. They stated that filling in multiple questionnaires was laborious and suggested that the Application limited the number used. Many said that if they had been given the option

of a surgical trial as well as a radiotherapy trial (STAMPEDE) they would have chosen the surgical one, but suggested we initially ensure the surgery was technically feasible and safe. Hence, the CI spent 2 years collecting this data as discussed in the section below. The patient and public involvement (PPI) also suggested that the trial should start with a feasibility component as they were unclear as to whether patients would accept randomisation. Hence, this study protocol is for an initial feasibility trial with a view to a full RCT to be applied for later via other funding mechanisms if feasibility is demonstrated. An OPCSG member and the original patient will provide PPI input throughout the study by serving on the Trial Steering Committee.

3.3. Supporting Data

Data supporting the use of radical surgery in other cancers:

A meta-analysis of 6,885 advanced ovarian carcinoma patients and a recent Cochrane review have concluded that there is a clear survival benefit with debulking of the primary tumour[7,8]. EORTC and SWOG studies demonstrated that nephrectomy before systemic therapy improves 1-year survival by 13-26% compared to systemic therapy alone and this has transformed the management of metastatic renal cell carcinoma[9,10]. Observational data also supports radical therapy for glioblastoma[11], peritoneal carcinomatosis from gastrointestinal cancer[12], and metastatic colon cancer[13].

Data supporting the use of radical prostatectomy in metastatic prostate cancer:

The 'seed and soil' hypothesis postulates that a receptive microenvironment ('soil') allows disseminating malignant cells ('seed') to engraft into and form metastases with soil development now thought to be driven by factors secreted by the primary tumour[14]. There is evidence that the primary tumour can seed to distant sites and cancer cells at those end-sites can further seed the primary lesion, leading to a vicious circle of metastasis[15]; this 'self-seeding' phenomenon is dependent on the presence of an intact primary focus[16]. Furthermore, disseminated tumour cells in men with clinically localized prostate cancer before prostatectomy confer a 5-fold increased risk of future metastases but these same cells detected after surgery do not increase such risk[17-19]. Collectively, these biological data suggest that an intact primary lesion drives metastatic progression.

There are no published prospective studies that directly evaluate the role of cytoreductive surgery in advanced prostate cancer. A subgroup analysis of SWOG 8894 on 1286 men with metastatic prostate cancer showed a reduced risk of death in those who had previously undergone radical prostatectomy compared to those that had not[20]. Another study of 161 men who all received ADT for failure post-radical therapy showed that time to subsequent failure after ADT was longer in the surgical cohort than the radiotherapy one[21]. A report of 916 men with metastatic prostate cancer that originally received either radical prostatectomy or radiotherapy for clinically localized disease also showed a substantial reduction in prostate cancer mortality rates for the surgically-treated group[22]. It may therefore be that surgical cytoreduction is the optimal radical treatment option in metastatic disease.

Recent observational cohort studies from the US SEER database and the Munich Cancer Registry found that men with metastatic prostate cancer treated with radical therapy had higher 5-yr survival than those

treated with systemic therapy alone[23,24]. We recently showed that at least 1206 men in Sweden have been treated with initial radical therapy (surgery or radiotherapy) for likely metastatic or micro-metastatic prostate cancer from 1996-2010[25], and on further interrogation of 18,352 cases found that men who underwent initial ADT without radical therapy were approximately 3-times more likely to die of prostate cancer than those that had radical therapy. These data are in preparation for submission to *European Urology*.

Data supporting the safety of radical prostatectomy in metastatic disease:

Despite the above evidence supporting the use of surgery, 2 ongoing randomised trials (1 UK: STAMPEDE-NCT00268476; 1 Dutch: HORRAD-NTR271) are using radiotherapy instead due to concerns regarding the safety of radical prostatectomy in this setting. There is 1 ongoing feasibility trial in metastatic prostate cancer using radical prostatectomy (US: NCT01751438) but this trial offers men a choice of surgery or radiotherapy and is thus not truly randomised. We therefore compiled a cohort of 106 men from the United States, Germany, Italy, and Sweden who underwent radical prostatectomy for known newly diagnosed metastatic disease and found similar rates of re-operations, re-admissions, transfusions, and 21 specific complications as in our previous meta-analysis on 286,876 men after radical prostatectomy for standard indication[26]. These data have been recently published in *European Urology*[27].

Data supporting limiting the study to oligo-metastatic prostate cancer:

The recent landmark CHAARTED study has shown that men presenting with oligo-metastatic prostate cancer (≤3 skeletal lesions) have improved overall survival to those with poly-metastatic disease (>3 skeletal deposits)[28], and thus oligo-metastatic disease might represent a transitory disease phenotype with its own distinct molecular signature[29].

All of the above observational data in support of radical prostatectomy for metastatic disease are heavily confounded by selection bias with those undergoing radical treatment likely having fewer skeletal metastases than those undergoing ADT alone; hence, any actual survival benefit may be confined to cases with lower metastatic burden. Study proposals for oligo-metastatic prostate cancer specifically are in development by other investigators, but all involve treating the metastatic sites rather than giving radical therapy as in the current proposal[30-33]. The impact of treating the oligo-metastatic sites with stereotactic body radiotherapy (SBRT) evaluates a different research question and the feasibility of this approach will be investigated in the UK CORE trial which will open to recruitment in early 2016.

The current AJCC TNM staging system of prostate cancer groups all skeletal-metastatic patients together as M1b[34] and there are no official statistics as to numbers presenting with newly diagnosed oligo-metastatic prostate cancer. Therefore, we have conducted a prospective audit of 12 geographically diverse UK cancer centres over a 3-month period and found that 15-20% of newly diagnosed skeletal-metastatic patients present with oligo-metastases. None of the current randomised trials are recording number of skeletal metastases and thus our proposal represents a novel opportunity to evaluate response specifically in the oligo-metastatic population.

The chief investigator on this proposal has co-authored a recent systematic review on the topic that can be accessed for further details of the study rationale[35].

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s)of evaluation of this outcome measure (if applicable)
Primary Objective To test the feasibility to randomise men in the UK to a trial investigating radical prostatectomy (RP) in oligo-metastatic prostate cancer	Feasibility to randomise as determined by 50 patients recruited over 18 months after an initial 3-month set up period; this will be optimised by a QRI	Recruitment will be monitored at 3 months after the start of accrual by the TMG and TRoMbone statistician
Secondary Objectives To collect the quality of life in men who have received treatment for oligo-metastatic prostate cancer To collect oncological outcome in men who have received treatment for oligo-metastatic prostate cancer QuinteT Recruitment Investigation (QRI) to understand recruitment challenges for this trial and inform optimal recruitment strategies	EQ-5D-5L questionnaire and safety of treatment arms at follow-up visits Time to castrate resistance Findings of the QuinteT Recruitment Investigation (QRI)	3 months post randomisation Routine clinical follow up time points at 3-6 monthly intervals post-treatment allocation will provide these routine data which are not collected as part of the trial

5. STUDY DESIGN

In this study we will evaluate feasibility; i.e. investigate whether patients can be recruited and randomised, prove equipoise, confirm patient 'flow' through the study, and assess safety of the intervention.

PICO

***Population*:** Men aged less than 75 years presenting with newly diagnosed oligo-metastatic, locally-resectable prostate cancer; ECOG performance status 0-1.

***Intervention*:** Radical prostatectomy plus Standard Care.

***Comparator*:** Standard Care, currently ADT +/- other systemic therapies.

***Outcome*:** Feasibility: 50 patients recruited over 18 months after an initial 3-month set up period.

Men diagnosed with prostate cancer are discussed at the multi-disciplinary team (MDT) meeting as part of routine clinical care; those identified as having a high risk of metastatic disease undergo bone specific imaging as routine care. Those found to have oligo-metastatic prostate cancer will be screened for trial eligibility. The type of bone specific imaging will be determined by what standard practise is at the local site. Sites will require access to these images to determine eligibility for TRoMbone.

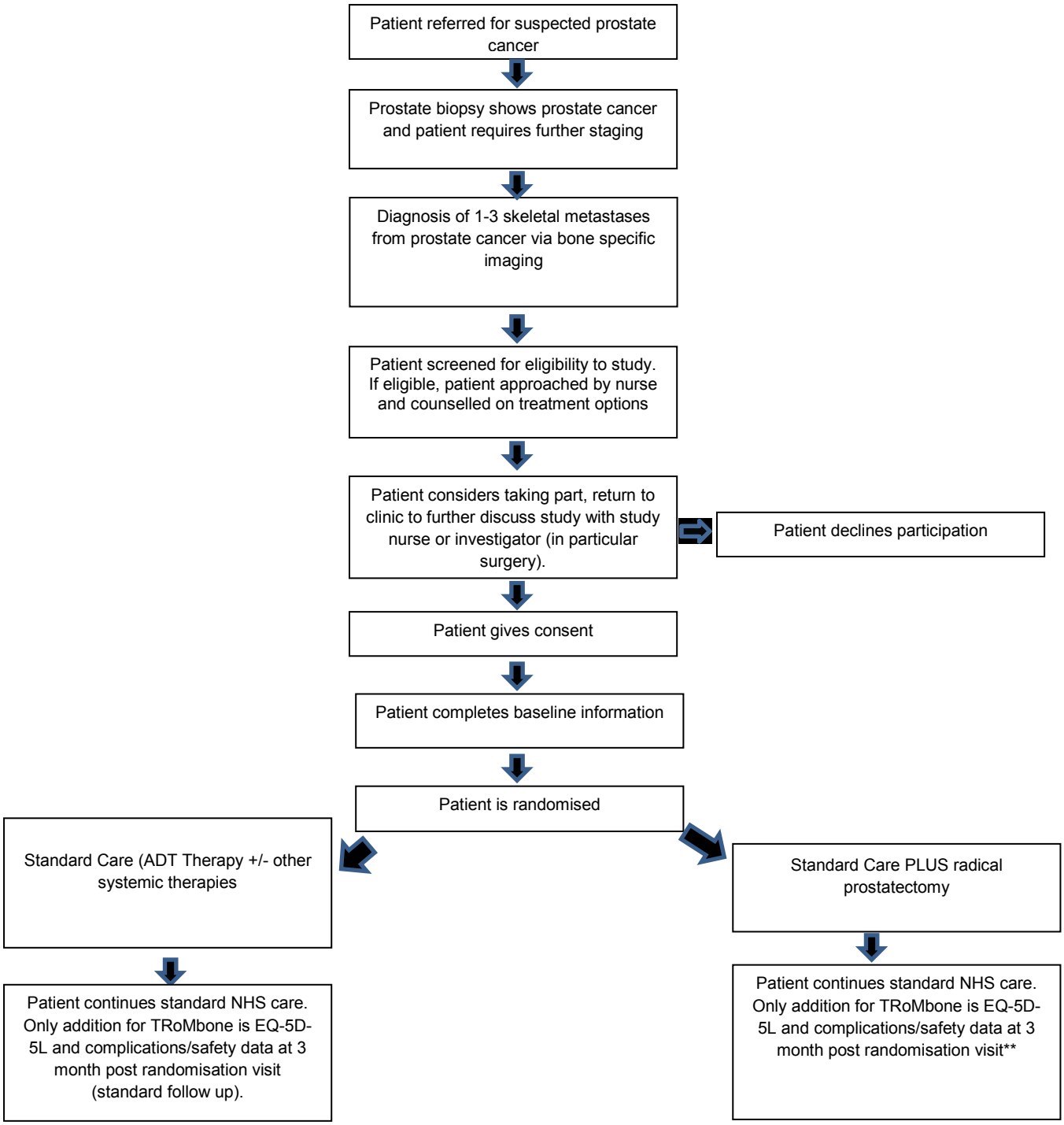
If eligible, patients will be approached by a specialist nurse and counselled on treatment options. All eligible patients will receive a Patient Information Leaflet (PIL). A research nurse will call patients approximately one week following their initial visit. They will ascertain if the patient is potentially interested in taking part in TRoMbone, and if so book them in to return to the clinic. Patients will be invited to return to clinic following their initial visit (where they receive the diagnosis of oligo-metastatic prostate cancer), where they will be given any further information they require about the trial. It is at this visit they will be asked to give their consent. Consenting patients will complete baseline assessments (demographics, medical history, concomitant medication, vital signs and routine bloods) and be randomised in a 1:1 fashion between the intervention and comparator. Post-treatment allocation follow up will not differ from routine clinical care for either group. Patients will be seen every 3 months for the first year. QoL follow up will be conducted during routine NHS care follow-up visits at 3 months. Safety data and complication data will be collected at this visit.

The schedule of assessments are given in the Table below.

Assessment		**Pre-screen**	**(Visit 1) Baseline (Randomisation)**	**Procedure**	**(Visit 2) 3 months post Randomisation**
Diagnosis and confirmation of prostate cancer		X			
Bone specific imaging to confirm oligo-metastatic prostate cancer		X			
Eligibility assessment			X		
Informed consent			X		
Demographics/Medical History/Concomitant Medication			X		
Vital signs/Routine Bloods			X		
(Standard Care)	ADT +/- other systemic therapies			X	x
	Study Follow Up				X
	Standard Follow Up				X
	EQ-5D (QoL)		X		X
Standard Care + Surgery Arm	**Surgery**			X*	
	ADT +/- other systemic therapies			x	X
	Study Follow Up				X*
	Standard Follow Up				X*
	EQ-5D (QoL)		X		X

**Please note that clinical follow-up for surgery will occur at the 3 month visit (post randomisation). It is anticipated that this visit will be approximately 6 weeks post-surgery, given current NHS waiting times for radical prostatectomy. If the 6 week post-surgery and 3 month post randomisation visits do not coincide then patients randomised to receive surgery will receive their standard 6 week visit in addition to the 3 month visit (also standard for patients receiving ADT +/- other systemic therapies).*

The patient pathway is shown below.



***Note: We understand that in some sites patients will receive chemotherapy as part of their 'systemic therapy treatment'. In this situation it is the decision of the Oncologist responsible for their care as to whether they receive this chemotherapy before or after surgery (if randomised to the standard care PLUS radical prostatectomy arm). If the patient is either partway (e.g. 0-4 months) through their chemotherapy course or prescribed their chemotherapy prior to surgery; then they have to complete this course before they can proceed with surgery. Therefore the surgical follow up data may not be complete at 3 months.*

However, sites will complete the 3 month post randomisation visit as per protocol (i.e. obtain EQ-5D-5L and follow-up data).

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants aged less than 75 years presenting with newly diagnosed oligo-metastatic, locally resectable prostate cancer, and who are deemed fit for radical prostatectomy based on an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male aged 18-74 years.
- Diagnosed with oligo-metastatic prostate cancer (1-3 skeletal lesions on bone specific imaging, no visceral metastases).
- Locally resectable tumour (clinical/radiological stage T1-T3).
- ECOG performance status 0-1.
- Suitable for radical prostatectomy within 12 months of starting standard care.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Contraindications to radical prostatectomy
- Visceral metastases
- Prior radiotherapy to the abdomen/pelvis or to skeletal metastases
- Any systemic therapy of prostate cancer (including standard care) for 12 or more months prior to enrolment
- Current involvement in other interventional research

7. STUDY PROCEDURES

7.1. Recruitment

For this feasibility trial, we plan to randomised 50 patients to either standard care, or radical prostatectomy plus standard care (please refer to Section 5 - Study Design for more details).

If eligible, patients will be approached by a specialist nurse and counselled on treatment options for oligo-metastatic prostate cancer. The researcher will take verbal consent to audio-record future research consultations. All eligible patients will receive a patient information leaflet. A research nurse will call

patients approximately one week following their initial visit. They will ascertain if the patient is potentially interested in taking part in TRoMbone, and if so book them in to return to the clinic. Patients will be invited to return to clinic following their initial visit (where they receive the diagnosis of oligo-metastatic prostate cancer), where they will be given any further information they require about the trial.

QuinteT Recruitment Investigation (QRI)

A QuinteT Recruitment Investigation (QRI) will be used to understand the recruitment process and how it will operate in all TRoMbone recruiting centres, so that sources of recruitment difficulties can be identified and suggestions made to change aspects of design, conduct, organisation or training that could then lead on to improvements in recruitment. All findings and any suggested changes are fed back first to the Chief Investigator (CI), Principal Investigators (PI), and research staff involved in the trial.

The data from the QRI will be discussed in the Trial Management Group (TMG). The QRI will be conducted in two phases:

Phase I: understanding recruitment

The aim of Phase I is to understand the recruitment process as it occurs. There are several distinct parts that can provide information about recruitment as it happens, and to identify and investigate the sources of recruitment difficulties.

1. Patient pathway through eligibility and recruitment

A comprehensive process of logging of potential Randomised Controlled Trial (RCT) participants through screening and eligibility phases is helpful for monitoring recruitment. It can provide some basic data about levels of eligibility and recruitment, and identify points at which patients opt in or opt out of the RCT.

2. In-depth interviews

In-depth, semi-structured interviews will be conducted and audio-recorded with some or all of the following groups:

(a) Members of the TMG, including the CI and those most closely involved in the design, management, leadership and coordination of the trial

(b) Clinical and recruitment staff across the three clinical centres involved in the feasibility RCT.

(c) Participants eligible for recruitment to the RCT, including those who accept or reject randomisation.

In addition, telephone interviews with TRoMbone study patients will be conducted by the QRI researcher to discuss their treatment and care whilst on the TRoMbone study.

3. Observations of investigator meetings

The CI, TMG and clinical investigators will meet occasionally or have telephone conferences about progress with the RCT. The QRI researcher may observe and audio-record these meetings, with permission. The aim will be to gather further information about specific issues that may have a bearing on recruitment.

4. Audio-recording of recruitment appointments

Recruiting staff will audio-record appointments where they provide information to patients and approach them about trial participation. The QRI researcher will listen to appointments, document relevant details and provide an account to be fed back to the RCT CI anonymously.

5. Study documentation

Patient information sheets (PIS) and consent forms will be compared and contrasted with the interviews and recorded appointments, to identify any disparities or improvements that could be made.

Research methods for Phase I

Interviews and meetings will be audio-recorded and transcribed with consent. Transcripts and notes will be analysed thematically by the QRI researcher, using techniques of constant comparison and case-study approaches including targeted conversation analysis. Findings will be documented and synthesised for presentation to the CI.

Phase II: Feedback to CI/TMG and plan of action

The QRI researcher will present summaries of anonymised findings to the RCT CI and TMG, identifying the factors that appear to be hindering recruitment with supporting evidence. If the CI/TMG agree that particular factors are amenable to change, a plan of action will then be drawn up to try to improve recruitment. The plan for the RCT and the activities of the QRI research team will be focused on the issues emerging from the QRI. It is likely that some aspects will be generic, such as how to explain randomisation and deal with patient preferences and issues related to the specific RCT. In previous studies, such things have included: re-drafting of study information, advice about presenting the study, and changing aspects of organisation in clinical centres. In previous studies, these have been addressed by new study information, changes to the protocol, or training for recruiters.

Evaluation of the impact of the plan

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving. Interviews with recruiters will ask about the acceptability of the QRI and any changes that occur.

7.1. Screening and Eligibility Assessment

All men that are found to be eligible for the feasibility trial will have routine clinical baseline assessments to check fitness for surgery; this includes routine bloods plus data on demographics, medical history, and concomitant medication (please refer to Section 5 - Study Design for more details).

Patients will be sent a copy of the PIL about the audio-recording and interview study (QRI) in the post. Recruiters will check if the patient has any questions about the recording process at the first recruitment appointment, and then seek written consent to record the discussion. Patients who agree will sign a one-off consent form that seeks permission to record future discussions about the trial in the lead up to the patient making their decision about participation. They will also be asked for consent to be contacted about an interview by a researcher at the University of Bristol. If patients have not received the written information about the recording process or main RCT in advance, patients will be asked to provide verbal consent for the recruiters to record the initial appointment, and will be provided with the relevant patient information sheets about the recording process and RCT. Patients who agree to their appointments being recorded will provide written consent in their subsequent appointment with the recruiting clinician/nurse. If patients do not provide written consent to their appointments being audio-recorded, the recording of their initial appointment will be deleted, and no further recordings made.

7.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form (ICF) before any study-specific procedures are performed.

Eligible patients will receive a TRoMbone Patient Information Leaflet (PIL) and TRoMbone Informed Consent Form (ICF) either at the screening visit, or via post and/or electronically by email beforehand. These detail the purpose of the study, what participation will involve and the risks of the trial arms and study participation. Patients will be asked for their permission to have appointments audio-recorded where their treatment options are discussed. Eligible patients will also receive a QRI Patient Information Leaflet. If patients agree to this, they will be asked to sign a QRI Patient Consent form. Staff involved in recruiting patients into TRoMbone will also be provided with a QRI Staff Information Leaflet and QRI Staff Consent form to sign.

If patients have agreed to take part in the QRI part of the study, but decline to participate in TRoMbone study, they may still be approached by a Qualitative Researcher to discuss their decision. These men will also be free to withdraw from the QRI at any point.

Staff will be approached and provided with the QRI Staff Information Sheet at the earliest possible point after the document has obtained all necessary approvals (HRA and REC etc.). Staff will have been informed of the project from the start of all communication with the site. We would expect the staff information sheet to be given at the site initiation visit (SIV). Ideally, staff will sign the consent form before their first patient is recruited at their site, but if this is less than 24 hours after the SIV, then audio recordings of consultations will not happen for that patient. Staff at the site, will also be invited to attend an interview with a Qualitative Researcher from the University of Bristol. These will be optional. Interviews are undertaken during the active recruitment phase so that findings can be reviewed and action taken to improve recruitment techniques.

All participation in the QRI section of TRoMbone is voluntary and staff can withdraw their consent to continue at any point.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will have as much time as needed to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant, a copy placed in the participant's medical records. The original signed form will be retained at the study site (within the Investigator Site File, ISF).

7.3. Randomisation, blinding and code-breaking

Randomisation will be performed using the web-based secure randomisation system provided by the Oxford Clinical Trials Research Unit (OCTRU). Participants will be randomised on a 1:1 basis and will be stratified by site. There will be no blinding with the TRoMbone study, clinicians and participants will be fully aware of the treatment allocation.

7.4. Visit 1 (Baseline)

Following consent the patient will be asked to complete the EQ-5D-5L quality of life questionnaire, and a baseline CRF will be completed by the research team. Some of the information for the baseline CRF will be taken from the patient's medical notes.

Patients will be randomised using the web-based system, Standard Care or Standard Care plus radical prostatectomy. Patients will receive the ADT +/- other systemic therapies as is routine care and those randomised to radical prostatectomy will be listed for surgery. Patients will follow routine NHS care and will receive ADT +/- other systemic therapies through the usual NHS procedures.

Visit 1a – Interview (QRI)

Patients who have been approached for TRoMbone (including decliners) may be invited to an interview with a Qualitative Researcher from the University of Bristol if they consented to take part in the QRI. Here they will discuss why and how they made their decision. This interview will inform the recruitment techniques used during the study.

7.5. Visit 2 (3 months +/- 2 weeks, post randomisation)

There will be no TRoMbone specific study visits for participants. Patients will be followed through standard NHS clinic visits. These occur every three months after a patient is prescribed ADT +/- other systemic therapies (which is prescribed at randomisation if not already started). During the first 3 month visit,

patients will be asked to complete the EQ-5D-5L, and will be asked about complications/side effects. Safety data will also be recorded.

7.6. Staff Interviews

Staff interviews will take place with consent during the active phase of recruitment. These will inform recruitment techniques for the study. Feedback will be given at TMG meetings and disseminated to the trial site staff.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent
- Loss to follow up

If a participant is withdrawn from the study, data collected until that point will still be used for analysis, unless the participant withdraws consent to do so. If participants withdraw from the study after they have received a study treatment (either standard care or radical prostatectomy), then they will not be replaced. Participants that withdraw after randomisation and before treatment is received will be replaced. The reason for withdrawal will be recorded in the CRF.

7.8. Definition of End of Study

The end of study will be the date of the last visit of the last participant (LVLP).

8. INTERVENTIONS

The intervention arm will receive a well-established surgical procedure, radical prostatectomy, plus standard care. The radical prostatectomy will be done within 12 months from the start of standard care.

University College Hospital London, Royal Surrey County Hospital, and Oxford University Hospitals have been initially chosen as the feasibility sites (more sites will be added if required) as these sites have a track record of working together on prostate cancer surgical studies and have surgeons who have demonstrated expertise in radical prostatectomy, as evidenced by an annual individual case volume of at least 100 cases and the recent British Association of Urological Surgeons (BAUS) radical prostatectomy audit (www.baus.org.uk). All sites will conduct pelvic lymph node dissection during radical prostatectomy, extrapolating from European Association of Urology guidelines in high-risk localised prostate cancer[36], and will include the following nodal packets: obturator, external iliac, internal iliac (hypogastric), common iliac (up to the ureteric crossing), and fossa of Marcille.

A quality assurance programme will be instituted to ensure a median nodal count of at least 15 nodes per case. Standard pre-operative (e.g. Gleason score, PSA, clinical stage), intra-operative (e.g. operative time, estimated blood loss), and post-operative parameters (e.g. Clavien-Dindo complications[37]) will be recorded as per standard clinical practice.

Participants in the intervention arm (radical prostatectomy plus standard care) may be approached at a later date for other ethically-approved clinical research if they are deemed eligible. However, other studies will not be part of this feasibility trial and participants will not be obliged to take part in other studies.

9. SAFETY REPORTING

The intervention arm in this feasibility trial will receive radical prostatectomy. This procedure has become well established in the treatment of localised and locally advanced prostate cancer over the past four decades. What is being investigated here is its use in oligo-metastatic prostate cancer. In other words, this is a conventional therapy being evaluated in an unconventional setting. There is no reason to suspect that the safety profile of radical prostatectomy will be different in oligo-metastatic disease than in localised or locally advanced prostate cancer, and we have published preliminary data to confirm its safety in a multi-institutional cohort outside the UK[27]. However, we will collect Clavien-Dindo complications data and assess individual complications across all relevant domains for radical prostatectomy as per our prior publication[26].

9.1. Expected Adverse Events

Androgen deprivation therapy (ADT) is known to have the following possible adverse events:

- Reduced or absent libido (sexual desire)
- Impotence (erectile dysfunction)
- Shrinkage of testicles and penis
- Hot flashes, which may get better or even go away with time
- Breast tenderness and growth of breast tissue
- Osteoporosis (bone thinning), which can lead to broken bones
- Anaemia (low red blood cell counts)
- Decreased mental sharpness
- Loss of muscle mass
- Weight gain
- Fatigue
- Increased cholesterol
- Depression

Radical prostatectomy (RP) is known to have the following possible complications:

- Bleeding, which can lead to blood transfusion
- Readmission
- Reoperation
- Neurovascular injuries
- Organ injuries
- Ileus

- Thromboembolism
- Pneumonia
- Myocardial infarction
- Haematoma
- Lymphocoele
- Anastomotic leakage
- Fistula
- Bladder neck/anastomotic stricture
- Sepsis
- Wound infection

These adverse events will be monitored and managed according to standard clinical practice.

9.2. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.3. Reporting Procedures for Serious Adverse Events

Trial centres will use a standardised safety reporting form to inform the Trial Manager of SAEs within twenty-four hours of becoming aware of them (initial report); this can be done via email to the trial office or by fax. For the purpose of the TRoMbone study, SAEs are defined as being "unexpected, related to the study intervention and serious". Events which are serious, related and expected, as listed above, will be reported as complications, using the TRoMbone complications form.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form. All SAEs, will be reviewed by the Chief Investigator, to determine whether the SAE is "*related"* and "*unexpected"* as defined by the HRA guidance. These will then be assessed by the nominated independent safety data reviewer.

The trial co-ordinating centre is responsible for reporting SAEs, where appropriate, to the Sponsor and ethics committee within required timelines. An SAE occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was

'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse events form. OCTRU safety reporting procedures will be followed at all times.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

We aim to randomise 50 men from 3-10 centres over an 18-month timeframe. We expect 100-120 eligible men to present to the 3 initial set-up centres over this time period based on our preliminary scoping exercise of presenting patients; hence, an accrual rate of 50% would achieve the primary outcome.

10.2. Analysis of Outcome Measures

Analysis of primary outcome data will be narrative. All participants that are randomised and receive the study intervention or standard care will be included. Participants that withdraw consent prior to treatment allocation will not be counted towards the feasibility target of 50 participants. Baseline data will be summarised across the two randomised groups. The secondary outcomes of quality of life and time to castrate resistance will not be reported as part of this feasibility study. It is envisioned that the secondary outcome data from the feasibility study participants would be included in an analysis of the full trial, subject to feasibility of recruitment being demonstrated and further funding for the main trial being received.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Recording and Record Keeping

The patient data will be entered onto a validated installation of OpenClinica (www.openclinica.com), the data is held in a Postgres database and can only be accessed by authorised users via the OpenClinica application. The OpenClinica application resides on a webserver hosted and managed by Oxford University's Medical Services Division IT Services department (http://www.imsu.ox.ac.uk/). The server is on the university's backbone network and is backed up nightly to a secure off-site location. Consent will be obtained from the patients to be able to share information and prior to sharing, data will be anonymised. In addition, any indirect identifiers that may lead to deductive disclosures will be removed to reduce the risk of identification. After closure of the trial and data analyses, the data will be made publicly available at the time of publication. The data types obtained will be preserved for 10 years from the end of the study. Paper resources will be archived.

All audio-recorded data will be transferred to the University of Bristol to be used for research and training. Only the researchers and those employed on the study will have access to the recordings. Responsible members of the University of Oxford or the host NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are following regulations.

Audio-recordings will be stored on a password protected computer for the duration of this study and up to a maximum of 10 years, after which they will be wiped.

12. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the Standard Operating Procedures of the UKCRC registered unit overseeing the study (OCTRU). A risk assessment will be undertaken of the trial and a proportionate monitoring plan will be put in place to decide on the extent and nature of any on-site monitoring. Central monitoring of incoming data and operational aspects of the trial will be done by the Trial Manager (or delegated person) according to the central monitoring plan.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Chief Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information leaflet and any proposed advertising material will be submitted to the Research Ethics Committee (REC) for approval.

The Chief Investigator will submit and, where necessary, obtain approval from the REC for all amendments to the original approved documents.

13.4. Reporting

The Chief Investigator shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, Sponsor, and host organisation if requested. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by Prostate Cancer Foundation (PCF), via a Young Investigator award to the Chief Investigator and The Urology Foundation Medal and Research Scholarship.

14.2. Insurance

The University has indemnity insurance in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.
NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Prostate Cancer Foundation. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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16. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2.0	21Jul2017	Neelam Hassanali	Change in terminology from treatment-as-usual to standard care. Clarification of standard care treatment in the comparator arm Update of the recruitment time frame from 12 to 18 months Update to the inclusion and exclusion to allow for systemic therapy to be used within 12 months Removal of specific names of TRoMbone recruiting sites, to allow for any new sites that may be included The secondary objectives have been updated to clarify that the secondary outcome measures will be collected for all men in the study The wording of the statistical analysis for the study was amended. The reason for this was that the feasibility study was not designed to do this and on reflection this should not have been included. For example, the sample size was not chosen to ensure sufficient statistical power to undertake such an analysis. They (secondary objectives) have been amended to allow for collection and not comparison.
2	V3.0	30Oct2017	Jo Cook and Surjeet Singh	General grammatical changes made throughout the protocol. Minor changes to Abbreviation table. Clarification in Section 4 (Objectives and Outcome Measures) Clarification in Section 5 (Schedule of assessments and Patient Pathway flow)

				Clarification in Section 7 (QRI changes and also use of post and email to send study documentation) Clarification in Section 8 (Intervention). The radical prostatectomy will be done within 12 months from the start of standard care.