



## Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: TRoMbone trial

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Keywords:	prostate cancer, oligometastatic, surgery, robot-assisted, radical prostatectomy
Abstract:	<p><b>Objectives</b></p> <p>To test feasibility of randomisation to radical prostatectomy plus pelvic lymphadenectomy (RP) in addition to standard-of-care (SOC) systemic therapy in men with newly diagnosed oligo-metastatic prostate cancer.</p> <p><b>Patients and methods</b></p> <p>A prospective, randomised, non-blinded, feasibility clinical trial with an</p>

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	<p>embedded QuinteT Recruitment Intervention (QRI) to optimise recruitment was conducted in nine tertiary-care nationwide centres undertaking high-volume robotic surgery. We aimed to randomise 50 men with synchronous oligo-metastatic prostate cancer within an 18-month recruitment period to SOC systemic therapy versus SOC plus RP (intervention arm).</p> <p>The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.</p> <p>Results</p> <p>51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.</p> <p>Discussion</p> <p>It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.</p>
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3 **Feasibility and safety of radical prostatectomy for oligo-metastatic prostate**  
4 **cancer: TRoMbone trial**  
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6 **(Testing Radical prostatectomy in men with prostate cancer and oligo-Metastases to the bone)**  
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## **Abstract**

### **Objectives**

To test feasibility of randomisation to radical prostatectomy plus pelvic lymphadenectomy (RP) in addition to standard-of-care (SOC) systemic therapy in men with newly diagnosed oligo-metastatic prostate cancer.

### **Patients and methods**

A prospective, randomised, non-blinded, feasibility clinical trial with an embedded QuinteT Recruitment Intervention (QRI) to optimise recruitment was conducted in nine tertiary-care nationwide centres undertaking high-volume robotic surgery. We aimed to randomise 50 men with synchronous oligo-metastatic prostate cancer within an 18-month recruitment period to SOC systemic therapy versus SOC plus RP (intervention arm).

The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.

### **Results**

51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.

### **Discussion**

It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.

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4 Prostate cancer; oligo-metastatic; radical prostatectomy; robot-assisted; surgery  
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For Peer Review

## Introduction

Prostate cancer is the most common cancer and the second most frequent cause of cancer death in Western men.(1) Patients presenting with metastatic disease have a median survival of 42.1 months,(2) and until recently, the standard-of-care has been initial androgen deprivation therapy (ADT) alone. Contemporary data from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial demonstrate a survival benefit for supplementing ADT with docetaxel chemotherapy for men presenting with metastatic prostate cancer.(3) Evidence from other tumour types as well as prostate cancer supports the concept of a transitory phenotype between localised/locally advanced cancer and widely disseminated disease, otherwise called the 'oligo-metastatic' state.(4) There is continuing controversy as to whether chemotherapy should be given in men presenting with oligo-metastatic prostate cancer where the disease burden is less than widespread metastases. The AJCC TNM staging system of prostate cancer categorises all skeletal-metastatic patients as M1b,(5) and there are no official statistics of numbers presenting with newly-diagnosed oligo-metastatic disease. There is also a lack of international consensus on the definition of oligo-metastatic prostate cancer; nonetheless, 1-3 skeletal metastases without any visceral metastases is a widely-utilised definition.(6)

The 'seed and soil' hypothesis postulates that a receptive micro-environment ('soil') allows dissemination of malignant cells ('seed') to form metastases, with soil development driven by factors secreted by the primary tumour.(7) Primary tumours can seed to distant sites which can further seed the primary lesion, leading to a vicious cycle of metastasis;(8) this 'self-seeding' phenomenon is dependent on the presence of an intact primary cancer focus.(9) Furthermore, disseminated tumour cells in men with clinically localised prostate cancer before prostatectomy confer a five-fold increased risk of future metastasis, but these same cells detected after surgery do not increase such risk.(10-12) Collectively, these biological data suggest that an intact primary lesion drives metastatic progression beyond early spread of circulating tumour cells. Further, population-based data of men with likely metastatic or micro-metastatic prostate cancer showed that those who underwent initial systemic therapy without radical therapy were approximately three-fold more likely to die of prostate cancer than those that had radical therapy.(13) The STAMPEDE randomised trial investigated the role of local therapy using prostate radiotherapy rather than surgery due to safety concerns, in men presenting with metastatic prostate cancer. A sub-group analysis demonstrated a relative survival advantage of 32% at 3 years for men with oligo-metastatic disease who underwent radical radiotherapy in addition to systemic therapy. However, no survival benefit was seen in those with a high burden of metastases in the total cohort.(14) Although the sub-group analysis fulfils nine out of ten criteria for credibility of sub-group analyses,(15) it has not yet been widely adopted internationally to include prostate radiotherapy as standard-of-care for men with oligo-metastatic disease. This is partly because another similar trial, HORRAD, has not shown a benefit for local radiotherapy in men with metastatic prostate cancer, including those with lower metastatic burden.(16) Hence, the role of local therapy with radiotherapy remains controversial in the presence of oligo-metastatic disease, with conclusive evidence that it has no benefit in those with high metastatic loads.

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3 Surgical removal of the prostate (radical prostatectomy) is an equivalent alternative  
4 to radiotherapy in men with organ-confined disease,(17) and hence represents  
5 another potential local radical therapy in the multi-modality approach to oligo-  
6 metastatic disease. There are a number of uncontrolled observational series  
7 investigating peri-operative outcomes of radical prostatectomy in men with  
8 metastatic disease, but these are limited by retrospective data collection as well as  
9 confounding indications in which only highly select men undergo surgery with poorly-  
10 defined eligibility criteria. (18, 19) Hence, there remains an urgent unmet need for  
11 randomised trials specifically examining the role of surgery in oligo-metastatic  
12 prostate cancer. However, lack of surgical experience in operating on oligo-  
13 metastatic disease mandate the need for stringent safety assessments in any such  
14 trial. Also, randomisation to surgical trials is fraught with difficulty and a number of  
15 high-profile prostate cancer trials have failed to recruit. Hence, most UK funders will  
16 not support a full surgical trial without a feasibility study confirming ability to  
17 randomise and safety of any novel intervention. One major success in recruitment  
18 terms was the Prostate Testing for Cancer and Treatment ( ProtecT) study which  
19 employed a QuinteT Recruitment Intervention (QRI) that has been subsequently  
20 shown to improve recruitment in a further 13 challenging RCTs, including the recent  
21 PART prostate cancer feasibility trial.(20-23) We therefore integrated a QRI as well  
22 as robust safety assessments within this randomised controlled feasibility trial of  
23 surgery plus standard-of-care (SOC) systemic therapy versus SOC alone in men  
24 with newly-diagnosed oligo-metastatic prostate cancer (1-3 skeletal metastases from  
25 prostate cancer, no visceral metastases); the TRoMbone trial.

26  
27 Our aims were: 1] to test the feasibility of recruiting and randomising men in the UK  
28 to a trial investigating radical prostatectomy (RP) in oligo-metastatic prostate cancer,  
29 with a view to launching a major trial; 2] to understand recruitment challenges and  
30 inform optimal recruitment strategies for a main trial through the QRI; and, 3] to  
31 collect quality-of-life and early oncological/safety/functional outcomes in these men.

## 32 33 34 35 36 37 38 39 **Subjects/patients and methods**

### 40 41 Trial design

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43 The TRoMbone study was a prospective, randomised, controlled feasibility trial:  
44 *population*- men aged less than 75 years presenting with newly-diagnosed oligo-  
45 metastatic, locally-resectable prostate cancer and Eastern Co-operative Group  
46 performance status (ECOG PS) 0-1; *intervention*- radical prostatectomy (RP) plus  
47 standard-of-care (SOC); *comparator*- SOC, currently ADT+/-docetaxel  
48 chemotherapy; *outcome*- 50 participants recruited over 18 months after an initial  
49 three-month set-up period. Randomisation was stratified by site and allocation set in  
50 parallel on a 1:1 ratio. The randomisations were blocked within site using variable  
51 block sizes of two and four. The study was not blinded. Given that this is a feasibility  
52 study, no quantitative analysis was planned and descriptive statistics were used to  
53 inform a future possible full trial.

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57 The study opened to recruitment initially in three centres. In QRI Phase 1,  
58 recruitment barriers were investigated in the initial three-month period through  
59 analysis of monthly screening log data and data collected through semi-structured  
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3 interviews with surgeons, oncologists, research and specialist nurses, and audio-  
4 recorded recruitment appointments. Findings were presented and discussed with the  
5 Chief Investigator (CI) and Trial Management Group (TMG), and a plan of actions  
6 was agreed to optimise recruitment in Phase 2, including changes to the eligibility  
7 criteria, opening new centres, and feedback and 'tips' to support recruiters.  
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## 10 Subjects

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12 Inclusion criteria at the start of the trial were: participant willing and able to give  
13 informed consent for participation in the study; male aged 18-74 years; diagnosed  
14 with oligo-metastatic prostate cancer (defined as 1-3 skeletal lesions on bone  
15 imaging, no visceral metastases); locally-resectable tumour (clinical/radiological  
16 stage T1-T3; ECOG PS 0-1; suitable for radical prostatectomy (RP) within three  
17 months of starting SOC. As a result of the Phase 1 QRI results (see below), the final  
18 eligibility criterion was changed to extend the maximum time from start of SOC to RP  
19 from three to 12 months. Exclusion criteria did not change during the trial and were:  
20 participants with contra-indications to RP; visceral metastases; prior radiotherapy to  
21 the abdomen/pelvis or to skeletal metastases; current involvement in other  
22 interventional research.  
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26 Three UK cancer centres were initially opened to recruitment. As a result of the  
27 Phase 1 QRI results, this was expanded to nine UK cancer centres selected based  
28 on geographical diversity. Potential participants were identified as part of routine  
29 clinical care, either from individual surgical/oncology clinics or via cancer multi-  
30 disciplinary team (MDT) meetings. Those found to have oligo-metastatic prostate  
31 cancer on staging investigations were screened for trial eligibility. Staging  
32 investigations included bone scintigram, MRI, CT, and PET depending on local  
33 practice, with some patients undergoing multiple staging tests. Recruiting sites chose  
34 the type of staging imaging they performed based on their standard clinical practice  
35 so the trial outcomes would be generalisable across the UK. Oligo-metastatic sites  
36 were not confirmed with biopsy, as this is invasive and not standard practice in the  
37 UK.  
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41 Eligible patients were approached by a specialist nurse, oncologist, or surgeon, and  
42 received a Patient Information Leaflet (PIL). Patients were given sufficient time to  
43 make a decision on whether they wanted to join the trial, and if so, were invited to  
44 give written consent. Consenting patients became subjects and completed baseline  
45 assessments (demographics, medical history, concomitant medication, vital signs,  
46 and routine bloods), and were then randomised by the Registration/Randomisation  
47 and Management of Product (RRAMP) software on the OpenClinica online platform  
48 of the Oxford Clinical Trials Research Unit (OCTRU):  
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50 <https://www.ndorms.ox.ac.uk/octru>. Post-treatment allocation follow-up was as per  
51 routine clinical care for both groups, with patient-reported quality-of-life (QOL)  
52 collected from the EQ-5D-5L descriptive and visual analogue scale questionnaires  
53 before randomisation and 3-month post-randomisation visits. For the surgical  
54 participants, standard peri-operative and outcomes data including  
55 safety/complications/functional outcomes were also recorded until six months post-  
56 surgery.  
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## 60 Interventions

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4 All participants received SOC systemic therapy-ADT+/-docetaxel. Expected adverse  
5 effects of systemic therapy (e.g. reduced or absent libido, impotence, hot flashes)  
6 were recorded. Participants in the intervention arm underwent robot-assisted radical  
7 prostatectomy plus pelvic lymphadenectomy consistent with international guidelines  
8 for high-risk prostate cancer.(24) Excised nodal packets included obturator, external  
9 iliac, internal iliac, common iliac, and fossa of Marcille. Standard pre-operative (e.g.  
10 Gleason score, PSA, clinical stage), intra-operative (e.g. operative time, need for  
11 blood transfusion), and post-operative (e.g. Clavien-Dindo grade,(25) 21 individual  
12 complications)(26) parameters were recorded until six months post-operatively. The  
13 timing of surgery in the intervention arm was initially within three months of starting  
14 SOC but then amended via Protocol Amendment to within 12 months of starting  
15 SOC, as a result of the Phase 1 QRI results (as stated above).  
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### 19 Outcomes

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21 The intervention arm in this feasibility trial received radical prostatectomy. The  
22 procedure is well established in the treatment of localised and locally-advanced  
23 prostate cancer, but here we investigated its use in oligo-metastatic disease.  
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26 The primary outcome of the feasibility study of randomisation was to recruit and  
27 randomise 50 participants, 18 months after the opening of the first site, optimised by  
28 a QRI. Secondary outcomes were quality-of-life assessment at baseline and three  
29 months post-randomisation (using EQ-5D-5L), and peri-operative outcomes  
30 including operative data (type of surgery, operative time, console time, need for  
31 blood transfusion, outcome of the procedure, return to theatre, length of hospital  
32 stay, successful catheter removal, peri-operative complications by Clavien-Dindo  
33 grade and assessment of 21 pre-specified complications), early oncological data  
34 (positive surgical margins (PSM), length of PSM, final pathological stage, lymph  
35 nodes removed, lymph nodes positive, 3-month and 6-month post-operative PSA),  
36 and early functional data (1-month, 3-month, and 6-month post-operative erectile  
37 function and continence recovery).  
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### 41 Sample size

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43 A sample size of 50 participants was chosen as a result of a preliminary scoping  
44 exercise across 14 UK prostate cancer centres suggesting an average of two eligible  
45 patients per month per site for the trial. We thus estimated that 50 participants were  
46 a realistic target given we intended to open three sites with a total recruitment period  
47 of 18 months (assuming roughly one-half of eligible patients would accept  
48 randomisation, predicted from QRI results from other surgical trials).  
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51 No interim analyses were planned but a Trial Management Group (TMG) monitored  
52 safety data and had the ability to stop the trial early if the intervention was deemed  
53 unsafe. Reporting of adverse events followed standard Oxford Clinical Trials  
54 Research Unit (OCTRU) procedures.  
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### 57 Randomisation and masking

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3 Randomisation was performed using the web-based secure randomisation system  
4 provided by OCTRU. Participants were randomised on a 1:1 basis and stratified by  
5 site with block sizes of two and four. There was no blinding in the trial, and clinicians  
6 and participants were fully aware of the treatment allocation. Research/specialist  
7 nurses and surgeons at the sites were responsible for enrolling participants, and  
8 followed the web-based system with regards assigning participants to study arms.  
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### 10 Analytical methods

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12 All randomised participants were included. No participant withdrew consent prior to  
13 treatment allocation. Outcomes data were summarised across the two randomised  
14 groups (Tables 1-3).  
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18 A QuinteT Recruitment Intervention (QRI) was used to understand the recruitment  
19 process and how it operates in all TRoMbone recruiting centres, so that sources of  
20 recruitment difficulties could be identified and suggestions made to improve  
21 recruitment(21). QRI findings and suggested changes were fed-back to the Chief  
22 Investigator (CI), site Principal Investigators (PI), and trial research staff. The QRI  
23 was conducted in two phases:  
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26 *Phase 1- understanding recruitment:* to understand the recruitment process as it  
27 occurred, and to identify and investigate sources of recruitment difficulty. Site  
28 screening logs were collected to provide data about eligibility assessment, and  
29 recruitment processes using the SEAR framework,(27) which identifies points at  
30 which patients continue or drop out of the trial. In-depth, semi-structured interviews  
31 were conducted and audio-recorded with: (i) members of the TMG, including the CI  
32 and those closely involved in trial co-ordination; (ii) clinical and recruitment staff  
33 across the three initial sites; (iii) subjects eligible for recruitment, including those who  
34 accepted or rejected randomisation; (iv) subjects after treatment allocation or receipt  
35 to discuss perceptions regarding their treatment and care while on the trial. The QRI  
36 researcher also attended investigator meetings between the CI, TMG, and clinical  
37 investigators, to gather further information about specific recruitment issues  
38 encountered. Recruiting staff audio-recorded appointments with potential subjects,  
39 such that the QRI researcher could provide feedback to recruiters in Phase 2 to  
40 optimise their recruitment technique. Study documentation (PILs and consent forms)  
41 were also reviewed and compared with the interviews and recorded appointments, to  
42 identify any disparities or improvements that could be made. All audio-recorded  
43 transcripts and notes were analysed thematically by the QRI researcher, using  
44 constant comparison and case-study approaches including targeted conversation  
45 analysis.(28)  
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50 *Phase 2- feedback to CI/TMG and plan of action:* after three months, the QRI  
51 researcher (CW) presented anonymised findings to the CI and TMG, identifying  
52 factors that appeared to be hindering recruitment. A plan of action was then  
53 formulated by the QRI team, CI, and TMG, in order to improve recruitment. The  
54 impact of this plan of action was evaluated by assessing the numbers of eligible  
55 patients, percentages of those approached about the trial, and numbers that  
56 consented to be randomised and accepted or rejected the treatment allocation, both  
57 before and after the first three-month period, and at regular intervals after  
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3 implementation. Ongoing interviews with recruiters also provided qualitative  
4 information about the acceptability of the plan of action and its impact.  
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### 6 Trial registration

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9 International Standard Randomised Controlled Trial Number (ISRCTN) 15704862.  
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## 11 **Results**

### 12 Feasibility of randomisation and Quintet Recruitment Intervention

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15 71/176 (40.3%) screened patients were eligible; 51/71 (71.8%) were randomised  
16 (Figure 1). Low recruitment rates were significantly improved with the QRI plan of  
17 action implemented in Phase 2 after three months (Figure 2). Phase 1 of the QRI  
18 identified the commonest causes of non-recruitment: inability to identify eligible  
19 patients; lack of clinician equipoise; and, inability to receive docetaxel chemotherapy  
20 pre-operatively.  
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25 During Phase 1, 12 potentially eligible patients were screened at MDT, of whom ten  
26 were deemed eligible. Screening data demonstrated lower than expected eligible  
27 patient numbers, most often due to systemic treatment more than three months prior  
28 to enrolment as a result of oncologists' strong preference for men with oligo-  
29 metastatic prostate cancer to be offered docetaxel chemotherapy within twelve  
30 weeks of starting ADT. Given that the chemotherapy course is six cycles  
31 administered three weeks apart, it was not possible for participants to undergo  
32 surgery within three months of starting ADT if they were to be given chemotherapy  
33 pre-operatively. As clinical practice changed from the period when the trial was set  
34 up to increasing usage of chemotherapy, this became an early barrier to recruitment.  
35 Hence, the plan of action stated that a further six geographically-diverse centres  
36 should be opened to recruitment and subject eligibility should be widened to those  
37 suitable for radical prostatectomy within 12 months of starting ADT, to allow for  
38 docetaxel chemotherapy before surgery in the intervention arm. It also became  
39 apparent that eligible patients were not being referred from outside the normal  
40 catchment areas, so it was suggested that the trial be publicised in urological and  
41 oncological forums, press outlets, and patient groups.  
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46 31 in-depth interviews were conducted with 13 surgeons, eight oncologists, and ten  
47 research/specialist nurses. 32 subjects had their consultations recorded with 11  
48 recruiters (seven surgeons, two oncologists, and two research nurses) at five  
49 centres. 15 randomised subjects from six centres were also interviewed; eight were  
50 allocated SOC and seven intervention. 6/7 subjects in the intervention arm were  
51 interviewed after surgery. Most interviews and appointment recordings during Phase  
52 1 demonstrated a lack of clinician equipoise. Hence, the plan of action included  
53 individual recruiter feedback to optimise recruitment consultations and share  
54 recruitment tips with all sites. Recruitment tips and feedback were individualised and,  
55 as in prior studies(21, 22), follow-up interviews with recruiters found them helpful in  
56 explaining randomisation and uncertainty, as well as fully informing patients about  
57 the potential consequences of study participation. From the outset, clinician  
58 equipoise was delicately balanced between the long-term hope of potential survival  
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3 benefits and the more immediate known side-effects of surgery, but surgeons found  
4 it difficult to express this to patients. They became more confident about expressing  
5 equipoise as concerns about the risks and side-effects of surgery were alleviated by  
6 successful surgeries, feedback from men keen to join the study, and the growing  
7 numbers of randomisations.  
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10 From the screening logs and recruiter interviews it also became apparent that many  
11 eligible patients present to oncologists rather than urologists. Hence, individual site-  
12 specific strategies were employed, including direct booking of surgical appointments  
13 by oncologists, joint surgeon-oncologist consultations, use of nurse specialists to co-  
14 ordinate patient pathways, and pre-recruitment remote consultations for patients that  
15 would otherwise have to travel significant distances. These changes resulted in  
16 improved communication between surgeons and oncologists, with joint decision-  
17 making regarding optimal timing of chemotherapy and surgery after starting ADT for  
18 individual patients.  
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21 As a result of the plan of action implemented in Phase 2 of the study, the TRoMbone  
22 trial recruited to completion, demonstrating feasibility of randomisation. Although the  
23 recruitment rate for the TRoMbone study ranged from 60-83 percent in centres which  
24 randomised more than one patient, three centres did not recruit. These centres were  
25 open for a shorter time (median three months) compared to the six recruiting centres  
26 (median nine months) and did not manage to re-configure their pathways to  
27 implement the plan of action devised from the QRI.  
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### 30 Safety and early outcomes

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33 The baseline characteristics of the subjects are shown in Table 1. 36/50 (72%)  
34 subjects had Gleason score 8-10, 45/50 (90%) had clinical T3 disease, and 6/50  
35 (12%) had co-morbidities. Most subjects had erectile dysfunction at baseline; the  
36 median IIEF-5 score in the SOC arm was 18.5 (mild ED) and 13.0 (mild-to-moderate  
37 ED) in the intervention group. No participant had urinary incontinence at baseline.  
38 Quality-of-life (QOL) scores were high in both groups at baseline, with median EQ-  
39 5D-5L visual analogue scale (VAS) scores of 85.0 and 90.0 in the SOC and  
40 intervention cohorts, respectively. There were no clinically significant differences in  
41 any baseline characteristics between study groups.  
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44 For the intervention participants, peri-operative data are summarised in Table 2. All  
45 patients were on ADT before surgery with a median time (range) of three (1-9)  
46 months; 11/24 (45.8%) had docetaxel chemotherapy pre-operatively; all completed  
47 six cycles before surgery. All surgeries were completed successfully using robot-  
48 assisted surgery without conversion. One subject in the intervention arm felt too  
49 unwell to undergo surgery post-chemotherapy. One subject suffered a rectal injury  
50 which was diagnosed and repaired intra-operatively; this patient stayed in hospital  
51 for seven days without further complication. One subject suffered a post-operative  
52 infected lymphocele for which he was re-admitted for percutaneous drainage; he  
53 then developed septic pericarditis and underwent a pericardiocentesis during the  
54 same re-admission, before recovering fully. One subject suffered a post-operative  
55 urinary tract infection and one had a post-operative wound infection. Erectile function  
56 was not preserved in any subject post-operatively. 4/24 (16.7%) patients remained  
57 incontinent (>1 pad/24h) six months after surgery. The positive margin rate was  
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3 10/24 (41.7%), with 19/23 (82.6%) having Gleason 8-10 on final pathology, and  
4 21/24 (87.5%) having extra-prostatic (pT3) disease. 19/23 (82.6%) patients had a 6-  
5 month post-operative PSA<1 ng/ml.  
6

7  
8 Table 3 summarises the outcomes of the TRoMbone trial three months post-  
9 randomisation and shows that PSA levels were uniformly low due to systemic  
10 therapy. Commonly known side-effects of systemic therapy were reported in  
11 expected frequencies in both groups with no inter-group differences: reduced/absent  
12 sexual desire; shrinkage of testes and/or penis; hot flushes; breast tenderness and  
13 growth of breast tissue; osteoporosis; anaemia; decreased mental sharpness; loss of  
14 muscle mass; weight gain; fatigue; increased cholesterol; depression. Subjects were  
15 impotent with similar low IIEF-5 scores in both groups (median 5.0). SOC  
16 participants maintained their continence, while median pad use was two per day in  
17 the intervention arm. QOL scores were high and comparable between SOC and  
18 intervention groups, with no differences in EQ-5D-5L descriptive scores and clinically  
19 insignificant differences in VAS scores (median 84.0 vs. 90.0 in SOC and  
20 intervention arms, respectively).  
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## 25 Discussion

26  
27 This trial has demonstrated feasibility to randomise men in the UK presenting with  
28 newly-diagnosed oligo-metastatic prostate cancer to standard-of-care (SOC)  
29 systemic therapy versus SOC plus radical prostatectomy with pelvic  
30 lymphadenectomy. As surgeons became more familiar with operating on metastatic  
31 patients, UK oncology and urology communities gained confidence in its safety and  
32 recruitment accelerated. The randomisation rate (randomised/eligible) was high as  
33 men with oligo-metastatic prostate cancer were supportive of research on radical  
34 local treatment and optimistic that surgery might help. However, eligible participants  
35 were fewer than expected from the preliminary scoping exercise, and careful  
36 identification and pathway optimisation for men with oligo-metastatic prostate cancer  
37 were required using the SEAR framework(27) to recruit successfully.  
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41 Robot-assisted laparoscopic surgery for randomised men in the intervention arm was  
42 technically feasible and appeared safe in those men who had been treated with  
43 ADT+/- docetaxel chemotherapy pre-operatively. Operative times, length of stay,  
44 complications, surgical margin rates, and early biochemical outcomes were all  
45 similar to radical prostatectomy series for standard indication.(26) Urinary continence  
46 outcomes were also similar to standard surgery. The surgical group did not suffer  
47 worse quality-of-life (QOL) compared to the SOC cohort.  
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50  
51 This is the world-first randomised clinical trial examining the feasibility of radical  
52 surgery to the primary tumour in men with newly-diagnosed oligo-metastatic prostate  
53 cancer, with rigorous data collection of its primary and secondary outcomes. It  
54 represents one of few surgical trials that have recruited successfully, largely due to  
55 the embedded QuinteT Recruitment Intervention.(21) Multiple cancer centres across  
56 the UK were able to successfully recruit subjects, demonstrating generalisability of  
57 the feasibility methods. In addition, the trial has shown the safety of robot-assisted  
58 surgery for men with oligo-metastatic prostate cancer.  
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3 The lack of consistency in imaging modalities to define eligibility may have caused  
4 heterogeneity in the study cohort. This is especially so as some participants had their  
5 oligo-metastatic state defined by PSMA-PET and others by conventional imaging.  
6 While this might mean that the study population was heterogeneous in its burden of  
7 disease, this pragmatism however follows the UK current standard practice and  
8 increases the study's generalisability. Quality-of-life (QOL) impact was measured by  
9 a generic tool rather than specific prostate cancer-related QOL instruments which  
10 might have better captured urinary and sexual health domains. In our surgical  
11 feasibility study, we have also not examined the role of stereotactic body  
12 radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main  
13 study as other investigators have shown this to be an effective approach in oligo-  
14 recurrent prostate cancer.(29)  
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17  
18 Other studies have shown safety and technical feasibility of surgery in men with  
19 metastatic prostate cancer,(19) but none in the UK population and none to date in a  
20 randomised trial setting. Other ongoing randomised trials investigate radical surgery  
21 in metastatic disease, but do not specifically examine the role of surgery in addition  
22 to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has  
23 demonstrated that this is the optimal population of men with metastatic prostate  
24 cancer worth considering for local radical treatment.(14) TRoMbone now shows it is  
25 safe and feasible to investigate surgery in this setting. A future definitive trial is likely  
26 to accrue in the UK; recruitment is likely to be faster than in this feasibility study  
27 because an increasing number of surgeons will have experience and confidence in  
28 undertaking these operations as well as QRI-informed improved recruitment  
29 strategies.  
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## Legends to figures

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53 Figure 1. CONSORT flow diagram

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55 Figure 2. Recruitment

## Legends to tables

1  
2  
3 Table 1. Baseline subject characteristics. (a) categorical variables; (b) continuous  
4 variables  
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6  
7 Table 2. Peri-operative data in intervention subjects  
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9 Table 3. PSA, functional, and quality-of-life outcomes in study groups at three  
10 months post-randomisation  
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For Peer Review

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3 **Feasibility and safety of radical prostatectomy for oligo-metastatic prostate**  
4 **cancer: TRoMbone trial**  
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6 **(Testing Radical prostatectomy in men with prostate cancer and oligo-Metastases to the bone)**  
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## Abstract

### Objectives

To test feasibility of randomisation to radical prostatectomy plus pelvic lymphadenectomy (RP) in addition to standard-of-care (SOC) systemic therapy in men with newly diagnosed oligo-metastatic prostate cancer.

### Patients and methods

A prospective, randomised, non-blinded, feasibility clinical trial with an embedded QuinteT Recruitment Intervention (QRI) to optimise recruitment was conducted in nine tertiary-care nationwide centres undertaking high-volume robotic surgery. We aimed to randomise 50 men with synchronous oligo-metastatic prostate cancer within an 18-month recruitment period to SOC systemic therapy versus SOC plus RP (intervention arm).

The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.

### Results

51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.

### Discussion

It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.

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### Keywords

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Prostate cancer; oligo-metastatic; radical prostatectomy; robot-assisted; surgery

For Peer Review

## Introduction

Prostate cancer is the most common cancer and the second most frequent cause of cancer death in Western men.(1) Patients presenting with metastatic disease have a median survival of 42.1 months,(2) and until recently, the standard-of-care has been initial androgen deprivation therapy (ADT) alone. Contemporary data from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial demonstrate a survival benefit for supplementing ADT with docetaxel chemotherapy for men presenting with metastatic prostate cancer.(3) Evidence from other tumour types as well as prostate cancer supports the concept of a transitory phenotype between localised/locally advanced cancer and widely disseminated disease, otherwise called the 'oligo-metastatic' state.(4) There is continuing controversy as to whether chemotherapy should be given in men presenting with oligo-metastatic prostate cancer where the disease burden is less than widespread metastases. The AJCC TNM staging system of prostate cancer categorises all skeletal-metastatic patients as M1b,(5) and there are no official statistics of numbers presenting with newly-diagnosed oligo-metastatic disease. There is also a lack of international consensus on the definition of oligo-metastatic prostate cancer; nonetheless, 1-3 skeletal metastases without any visceral metastases is a widely-utilised definition.(6)

The 'seed and soil' hypothesis postulates that a receptive micro-environment ('soil') allows dissemination of malignant cells ('seed') to form metastases, with soil development driven by factors secreted by the primary tumour.(7) Primary tumours can seed to distant sites which can further seed the primary lesion, leading to a vicious cycle of metastasis;(8) this 'self-seeding' phenomenon is dependent on the presence of an intact primary cancer focus.(9) Furthermore, disseminated tumour cells in men with clinically localised prostate cancer before prostatectomy confer a five-fold increased risk of future metastasis, but these same cells detected after surgery do not increase such risk.(10-12) Collectively, these biological data suggest that an intact primary lesion drives metastatic progression beyond early spread of circulating tumour cells. ~~As well as the biological rationale~~Further, population-based data of men with likely metastatic or micro-metastatic prostate cancer showed that those who underwent initial systemic therapy without radical therapy were approximately three-fold more likely to die of prostate cancer than those that had radical therapy.(13) The STAMPEDE randomised trial investigated the role of local therapy using prostate radiotherapy rather than surgery due to safety concerns, in men presenting with metastatic prostate cancer. A sub-group analysis demonstrated a relative survival advantage of 32% at 3 years for men with oligo-metastatic disease who underwent radical radiotherapy in addition to systemic therapy. However, no survival benefit was seen in those with a high burden of metastases in the total cohort.(14) Although the sub-group analysis fulfils nine out of ten criteria for credibility of sub-group analyses,(15) it has not yet been widely adopted internationally to include prostate radiotherapy as standard-of-care for men with oligo-metastatic disease. This is partly because another similar trial, HORRAD, has not shown a benefit for local radiotherapy in men with metastatic prostate cancer, including those with lower metastatic burden.(16) Hence, the role of local therapy with radiotherapy remains controversial in the presence of oligo-metastatic disease, with conclusive evidence that it has no benefit in those with high metastatic loads.

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3 Surgical removal of the prostate (radical prostatectomy) is an equivalent alternative  
4 to radiotherapy in men with organ-confined disease,(17) and hence represents  
5 another potential local radical therapy in the multi-modality approach to oligo-  
6 metastatic disease. There are a number of uncontrolled observational series  
7 investigating peri-operative outcomes of radical prostatectomy in men with  
8 metastatic disease, but these are limited by retrospective data collection as well as  
9 confounding indications in which only highly select men undergo surgery with poorly-  
10 defined eligibility criteria. (18, 19) Hence, there remains an urgent unmet need for  
11 randomised trials specifically examining the role of surgery in oligo-metastatic  
12 prostate cancer. However, lack of surgical experience in operating on oligo-  
13 metastatic disease mandate the need for stringent safety assessments in any such  
14 trial. Also, randomisation to surgical trials is fraught with difficulty and a number of  
15 high-profile prostate cancer trials have failed to recruit. Hence, ~~before commencing a~~  
16 ~~full trial, it is imperative to assess the feasibility of such a study and the safety of the~~  
17 ~~operative intervention. most UK funders will not support a full surgical trial without a~~  
18 ~~feasibility study confirming ability to randomise and safety of any novel intervention.~~  
19 One major success in recruitment terms was the Prostate Testing for Cancer and  
20 Treatment ( ProtecT) study which employed a QuinteT Recruitment Intervention  
21 (QRI) that has been subsequently shown to improve recruitment in a further 13  
22 challenging RCTs, including the recent PART prostate cancer feasibility trial.(20-23)  
23 We therefore integrated a QRI as well as robust safety assessments within this  
24 randomised controlled feasibility trial of surgery plus standard-of-care (SOC)  
25 systemic therapy versus SOC alone in men with newly-diagnosed oligo-metastatic  
26 prostate cancer (1-3 skeletal metastases from prostate cancer, no visceral  
27 metastases); the TRoMbone trial.

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33 Our aims were: 1] to test the feasibility of recruiting and randomising men in the UK  
34 to a trial investigating radical prostatectomy (RP) in oligo-metastatic prostate cancer,  
35 with a view to launching a major trial; 2] to understand recruitment challenges and  
36 inform optimal recruitment strategies for a main trial through the QRI; and, 3] to  
37 collect quality-of-life and early oncological/safety/functional outcomes in these men.  
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## 41 **Subjects/patients and methods**

### 42 Trial design

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45 The TRoMbone study was a prospective, randomised, controlled feasibility trial:  
46 *population-* men aged less than 75 years presenting with newly-diagnosed oligo-  
47 metastatic, locally-resectable prostate cancer and Eastern Co-operative Group  
48 performance status (ECOG PS) 0-1; *intervention-* radical prostatectomy (RP) plus  
49 standard-of-care (SOC); *comparator-* SOC, currently ADT+/-docetaxel  
50 chemotherapy; *outcome-* 50 participants recruited over 18 months after an initial  
51 three-month set-up period. Randomisation was stratified by site and allocation set in  
52 parallel on a 1:1 ratio. The randomisations were blocked within site using variable  
53 block sizes of two and four. The study was not blinded. Given that this is a feasibility  
54 study, no quantitative analysis was planned and descriptive statistics were used to  
55 inform a future possible full trial.  
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3 The study opened to recruitment initially in three centres. In QRI Phase 1,  
4 recruitment barriers were investigated in the initial three-month period through  
5 analysis of monthly screening log data and data collected through semi-structured  
6 interviews with surgeons, oncologists, research and specialist nurses, and audio-  
7 recorded recruitment appointments. Findings were presented and discussed with the  
8 Chief Investigator (CI) and Trial Management Group (TMG), and a plan of actions  
9 was agreed to optimise recruitment in Phase 2, including changes to the eligibility  
10 criteria, opening new centres, and feedback and 'tips' to support recruiters.  
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### 13 Subjects

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16 Inclusion criteria at the start of the trial were: participant willing and able to give  
17 informed consent for participation in the study; male aged 18-74 years; diagnosed  
18 with oligo-metastatic prostate cancer (defined as 1-3 skeletal lesions on bone  
19 imaging, no visceral metastases); locally-resectable tumour (clinical/radiological  
20 stage T1-T3; ECOG PS 0-1; suitable for radical prostatectomy (RP) within three  
21 months of starting SOC. As a result of the Phase 1 QRI results (see below), the final  
22 eligibility criterion was changed to extend the maximum time from start of SOC to RP  
23 from three to 12 months. Exclusion criteria did not change during the trial and were:  
24 participants with contra-indications to RP; visceral metastases; prior radiotherapy to  
25 the abdomen/pelvis or to skeletal metastases; current involvement in other  
26 interventional research.  
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30 Three UK cancer centres were initially opened to recruitment. As a result of the  
31 Phase 1 QRI results, this was expanded to nine UK cancer centres selected based  
32 on geographical diversity. Potential participants were identified as part of routine  
33 clinical care, either from individual surgical/oncology clinics or via cancer multi-  
34 disciplinary team (MDT) meetings. Those found to have oligo-metastatic prostate  
35 cancer on staging investigations were screened for trial eligibility. Staging  
36 investigations included bone scintigram, MRI, CT, and PET depending on local  
37 practice, with some patients undergoing multiple staging tests. Recruiting sites chose  
38 the type of staging imaging they performed based on their standard clinical practice  
39 so the trial outcomes would be generalisable across the UK. Oligo-metastatic sites  
40 were not confirmed with biopsy, as this is invasive and not standard practice in the  
41 UK.  
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45 Eligible patients were approached by a specialist nurse, oncologist, or surgeon, and  
46 received a Patient Information Leaflet (PIL). Patients were given sufficient time to  
47 make a decision on whether they wanted to join the trial, and if so, were invited to  
48 give written consent. Consenting patients became subjects and completed baseline  
49 assessments (demographics, medical history, concomitant medication, vital signs,  
50 and routine bloods), and were then randomised by the Registration/Randomisation  
51 and Management of Product (RRAMP) software on the OpenClinica online platform  
52 of the Oxford Clinical Trials Research Unit (OCTRU):  
53 <https://www.ndorms.ox.ac.uk/octru>. Post-treatment allocation follow-up was as per  
54 routine clinical care for both groups, with patient-reported quality-of-life (QOL)  
55 collected from the EQ-5D-5L descriptive and visual analogue scale questionnaires  
56 before randomisation and 3-month post-randomisation visits. For the surgical  
57 participants, standard peri-operative and outcomes data including  
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3 safety/complications/functional outcomes were also recorded until six months post-  
4 surgery.  
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### 6 Interventions

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9 All participants received SOC systemic therapy-ADT+/-docetaxel. Expected adverse  
10 effects of systemic therapy (e.g. reduced or absent libido, impotence, hot flashes)  
11 were recorded. Participants in the intervention arm underwent robot-assisted radical  
12 prostatectomy plus pelvic lymphadenectomy consistent with international guidelines  
13 for high-risk prostate cancer.(24) Excised nodal packets included obturator, external  
14 iliac, internal iliac, common iliac, and fossa of Marcell. Standard pre-operative (e.g.  
15 Gleason score, PSA, clinical stage), intra-operative (e.g. operative time, need for  
16 blood transfusion), and post-operative (e.g. Clavien-Dindo grade,(25) 21 individual  
17 complications)(26) parameters were recorded until six months post-operatively. The  
18 timing of surgery in the intervention arm was initially within three months of starting  
19 SOC but then amended via Protocol Amendment to within 12 months of starting  
20 SOC, as a result of the Phase 1 QRI results (as stated above).  
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### 23 Outcomes

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26 The intervention arm in this feasibility trial received radical prostatectomy. The  
27 procedure is well established in the treatment of localised and locally-advanced  
28 prostate cancer, but here we investigated its use in oligo-metastatic disease.  
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31 The primary outcome of the feasibility study of randomisation was to recruit and  
32 randomise 50 participants, 18 months after the opening of the first site, optimised by  
33 a QRI. Secondary outcomes were quality-of-life assessment at baseline and three  
34 months post-randomisation (using EQ-5D-5L), and peri-operative outcomes  
35 including operative data (type of surgery, operative time, console time, need for  
36 blood transfusion, outcome of the procedure, return to theatre, length of hospital  
37 stay, successful catheter removal, peri-operative complications by Clavien-Dindo  
38 grade and assessment of 21 pre-specified complications), early oncological data  
39 (positive surgical margins (PSM), length of PSM, final pathological stage, lymph  
40 nodes removed, lymph nodes positive, 3-month and 6-month post-operative PSA),  
41 and early functional data (1-month, 3-month, and 6-month post-operative erectile  
42 function and continence recovery).  
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### 45 Sample size

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48 A sample size of 50 participants was chosen as a result of a preliminary scoping  
49 exercise across 14 UK prostate cancer centres suggesting an average of two eligible  
50 patients per month per site for the trial. We thus estimated that 50 participants were  
51 a realistic target given we intended to open three sites with a total recruitment period  
52 of 18 months (assuming roughly one-half of eligible patients would accept  
53 randomisation, predicted from QRI results from other surgical trials).  
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57 No interim analyses were planned but a Trial Management Group (TMG) monitored  
58 safety data and had the ability to stop the trial early if the intervention was deemed  
59 unsafe. Reporting of adverse events followed standard Oxford Clinical Trials  
60 Research Unit (OCTRU) procedures.

## Randomisation and masking

Randomisation was performed using the web-based secure randomisation system provided by OCTRU. Participants were randomised on a 1:1 basis and stratified by site with block sizes of two and four. There was no blinding in the trial, and clinicians and participants were fully aware of the treatment allocation. Research/specialist nurses and surgeons at the sites were responsible for enrolling participants, and followed the web-based system with regards assigning participants to study arms.

## Analytical methods

All randomised participants were included. No participant withdrew consent prior to treatment allocation. Outcomes data were summarised across the two randomised groups (Tables 1-3).

A QuinteT Recruitment Intervention (QRI) was used to understand the recruitment process and how it operates in all TRoMbone recruiting centres, so that sources of recruitment difficulties could be identified and suggestions made to improve recruitment(21). QRI findings and suggested changes were fed-back to the Chief Investigator (CI), site Principal Investigators (PI), and trial research staff. The QRI was conducted in two phases:

*Phase 1- understanding recruitment:* to understand the recruitment process as it occurred, and to identify and investigate sources of recruitment difficulty. Site screening logs were collected to provide data about eligibility assessment, and recruitment processes using the SEAR framework,(27) which identifies points at which patients continue or drop out of the trial. In-depth, semi-structured interviews were conducted and audio-recorded with: (i) members of the TMG, including the CI and those closely involved in trial co-ordination; (ii) clinical and recruitment staff across the three initial sites; (iii) subjects eligible for recruitment, including those who accepted or rejected randomisation; (iv) subjects after treatment allocation or receipt to discuss perceptions regarding their treatment and care while on the trial. The QRI researcher also attended investigator meetings between the CI, TMG, and clinical investigators, to gather further information about specific recruitment issues encountered. Recruiting staff audio-recorded appointments with potential subjects, such that the QRI researcher could provide feedback to recruiters in Phase 2 to optimise their recruitment technique. Study documentation (PILs and consent forms) were also reviewed and compared with the interviews and recorded appointments, to identify any disparities or improvements that could be made. All audio-recorded transcripts and notes were analysed thematically by the QRI researcher, using constant comparison and case-study approaches including targeted conversation analysis.(28)

*Phase 2- feedback to CI/TMG and plan of action:* after three months, the QRI researcher (CW) presented anonymised findings to the CI and TMG, identifying factors that appeared to be hindering recruitment. A plan of action was then formulated by the QRI team, CI, and TMG, in order to improve recruitment. The impact of this plan of action was evaluated by assessing the numbers of eligible patients, percentages of those approached about the trial, and numbers that

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3 consented to be randomised and accepted or rejected the treatment allocation, both  
4 before and after the first three-month period, and at regular intervals after  
5 implementation. Ongoing interviews with recruiters also provided qualitative  
6 information about the acceptability of the plan of action and its impact.  
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### 8 9 Trial registration

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11 International Standard Randomised Controlled Trial Number (ISRCTN) 15704862.  
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## 13 14 **Results**

### 15 16 Feasibility of randomisation and Quintet Recruitment Intervention

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18 71/176 (40.3%) screened patients were eligible; 51/71 (71.8%) were randomised  
19 (Figure 1). Low recruitment rates were significantly improved with the QRI plan of  
20 action implemented in Phase 2 after three months (Figure 2). Phase 1 of the QRI  
21 identified the commonest causes of non-recruitment: inability to identify eligible  
22 patients; lack of clinician equipoise; and, inability to receive docetaxel chemotherapy  
23 pre-operatively.  
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27 During Phase 1, 12 potentially eligible patients were screened at MDT, of whom ten  
28 were deemed eligible. Screening data demonstrated lower than expected eligible  
29 patient numbers, most often due to systemic treatment more than three months prior  
30 to enrolment as a result of oncologists' strong preference for men with oligo-  
31 metastatic prostate cancer to be offered docetaxel chemotherapy within twelve  
32 weeks of starting ADT. Given that the chemotherapy course is six cycles  
33 administered three weeks apart, it was not possible for participants to undergo  
34 surgery within three months of starting ADT if they were to be given chemotherapy  
35 pre-operatively. As clinical practice changed from the period when the trial was set  
36 up to increasing usage of chemotherapy, this became an early barrier to recruitment.  
37 Hence, the plan of action stated that a further six geographically-diverse centres  
38 should be opened to recruitment and subject eligibility should be widened to those  
39 suitable for radical prostatectomy within 12 months of starting ADT, to allow for  
40 docetaxel chemotherapy before surgery in the intervention arm. It also became  
41 apparent that eligible patients were not being referred from outside the normal  
42 catchment areas, so it was suggested that the trial be publicised in urological and  
43 oncological forums, press outlets, and patient groups.  
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48 31 in-depth interviews were conducted with 13 surgeons, eight oncologists, and ten  
49 research/specialist nurses. 32 subjects had their consultations recorded with 11  
50 recruiters (seven surgeons, two oncologists, and two research nurses) at five  
51 centres. 15 randomised subjects from six centres were also interviewed; eight were  
52 allocated SOC and seven intervention. 6/7 subjects in the intervention arm were  
53 interviewed after surgery. Most interviews and appointment recordings during Phase  
54 1 demonstrated a lack of clinician equipoise. Hence, the plan of action included  
55 individual recruiter feedback to optimise recruitment consultations and share  
56 recruitment tips with all sites. Recruitment tips and feedback were individualised and,  
57 as in prior studies(21, 22), follow-up interviews with recruiters found them helpful in  
58 explaining randomisation and uncertainty, as well as fully informing patients about  
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3 the potential consequences of study participation. From the outset, clinician  
4 equipoise was delicately balanced between the long-term hope of potential survival  
5 benefits and the more immediate known side-effects of surgery, but surgeons found  
6 it difficult to express this to patients. They became more confident about expressing  
7 equipoise as concerns about the risks and side-effects of surgery were alleviated by  
8 successful surgeries, feedback from men keen to join the study, and the growing  
9 numbers of randomisations.  
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12 From the screening logs and recruiter interviews it also became apparent that many  
13 eligible patients present to oncologists rather than urologists. Hence, individual site-  
14 specific strategies were employed, including direct booking of surgical appointments  
15 by oncologists, joint surgeon-oncologist consultations, use of nurse specialists to co-  
16 ordinate patient pathways, and pre-recruitment remote consultations for patients that  
17 would otherwise have to travel significant distances. These changes resulted in  
18 improved communication between surgeons and oncologists, with joint decision-  
19 making regarding optimal timing of chemotherapy and surgery after starting ADT for  
20 individual patients.  
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24 As a result of the plan of action implemented in Phase 2 of the study, the TRoMbone  
25 trial recruited to completion, demonstrating feasibility of randomisation. Although the  
26 recruitment rate for the TRoMbone study ranged from 60-83 percent in centres which  
27 randomised more than one patient, three centres did not recruit. These centres were  
28 open for a shorter time (median three months) compared to the six recruiting centres  
29 (median nine months) and did not manage to re-configure their pathways to  
30 implement the plan of action devised from the QRI.  
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### 32 33 Safety and early outcomes

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35 The baseline characteristics of the subjects are shown in Table 1. 36/50 (72%)  
36 subjects had Gleason score 8-10, 45/50 (90%) had clinical T3 disease, and 6/50  
37 (12%) had co-morbidities. Most subjects had erectile dysfunction at baseline; the  
38 median IIEF-5 score in the SOC arm was 18.5 (mild ED) and 13.0 (mild-to-moderate  
39 ED) in the intervention group. No participant had urinary incontinence at baseline.  
40 Quality-of-life (QOL) scores were high in both groups at baseline, with median EQ-  
41 5D-5L visual analogue scale (VAS) scores of 85.0 and 90.0 in the SOC and  
42 intervention cohorts, respectively. There were no clinically significant differences in  
43 any baseline characteristics between study groups.  
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47 For the intervention participants, peri-operative data are summarised in Table 2. All  
48 patients were on ADT before surgery with a median time (range) of three (1-9)  
49 months; 11/24 (45.8%) had docetaxel chemotherapy pre-operatively; all completed  
50 six cycles before surgery. All surgeries were completed successfully using robot-  
51 assisted surgery without conversion. One subject in the intervention arm felt too  
52 unwell to undergo surgery post-chemotherapy. One subject suffered a rectal injury  
53 which was diagnosed and repaired intra-operatively; this patient stayed in hospital  
54 for seven days without further complication. One subject suffered a post-operative  
55 infected lymphocoele for which he was re-admitted for percutaneous drainage; he  
56 then developed septic pericarditis and underwent a pericardiocentesis during the  
57 same re-admission, before recovering fully. One subject suffered a post-operative  
58 urinary tract infection and one had a post-operative wound infection. Erectile function  
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3 was not preserved in any subject post-operatively. 4/24 (16.7%) patients remained  
4 incontinent (>1 pad/24h) six months after surgery. The positive margin rate was  
5 10/24 (41.7%), with 19/23 (82.6%) having Gleason 8-10 on final pathology, and  
6 21/24 (87.5%) having extra-prostatic (pT3) disease. 19/23 (82.6%) patients had a 6-  
7 month post-operative PSA<1 ng/ml.  
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10 Table 3 summarises the outcomes of the TRoMbone trial three months post-  
11 randomisation and shows that PSA levels were uniformly low due to systemic  
12 therapy. Commonly known side-effects of systemic therapy were reported in  
13 expected frequencies in both groups with no inter-group differences: reduced/absent  
14 sexual desire; shrinkage of testes and/or penis; hot flushes; breast tenderness and  
15 growth of breast tissue; osteoporosis; anaemia; decreased mental sharpness; loss of  
16 muscle mass; weight gain; fatigue; increased cholesterol; depression. Subjects were  
17 impotent with similar low IIEF-5 scores in both groups (median 5.0). SOC  
18 participants maintained their continence, while median pad use was two per day in  
19 the intervention arm. QOL scores were high and comparable between SOC and  
20 intervention groups, with no differences in EQ-5D-5L descriptive scores and clinically  
21 insignificant differences in VAS scores (median 84.0 vs. 90.0 in SOC and  
22 intervention arms, respectively).  
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## 27 Discussion

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29 This trial has demonstrated feasibility to randomise men in the UK presenting with  
30 newly-diagnosed oligo-metastatic prostate cancer to standard-of-care (SOC)  
31 systemic therapy versus SOC plus radical prostatectomy with pelvic  
32 lymphadenectomy. As surgeons became more familiar with operating on metastatic  
33 patients, UK oncology and urology communities gained confidence in its safety and  
34 recruitment accelerated. The randomisation rate (randomised/eligible) was high as  
35 men with oligo-metastatic prostate cancer were supportive of research on radical  
36 local treatment and optimistic that surgery might help. However, eligible participants  
37 were fewer than expected from the preliminary scoping exercise, and careful  
38 identification and pathway optimisation for men with oligo-metastatic prostate cancer  
39 were required using the SEAR framework(27) to recruit successfully.  
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43 Robot-assisted laparoscopic surgery for randomised men in the intervention arm was  
44 technically feasible and appeared safe in those men who had been treated with  
45 ADT+/- docetaxel chemotherapy pre-operatively. Operative times, length of stay,  
46 complications, surgical margin rates, and early biochemical outcomes were all  
47 similar to radical prostatectomy series for standard indication.(26) Urinary continence  
48 outcomes were also similar to standard surgery. The surgical group did not suffer  
49 worse quality-of-life (QOL) compared to the SOC cohort.  
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52 This is the world-first randomised clinical trial examining the feasibility of radical  
53 surgery to the primary tumour in men with newly-diagnosed oligo-metastatic prostate  
54 cancer, with rigorous data collection of its primary and secondary outcomes. It  
55 represents one of few surgical trials that have recruited successfully, largely due to  
56 the embedded QuinteT Recruitment Intervention.(21) Multiple cancer centres across  
57 the UK were able to successfully recruit subjects, demonstrating generalisability of  
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3 the feasibility methods. In addition, the trial has shown the safety of robot-assisted  
4 surgery for men with oligo-metastatic prostate cancer.  
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7 The lack of consistency in imaging modalities to define eligibility may have caused  
8 heterogeneity in the study cohort. This is especially so as some participants had their  
9 oligo-metastatic state defined by PSMA-PET and others by conventional imaging.  
10 While this might mean that the study population was heterogeneous in its burden of  
11 disease, this pragmatism however follows the UK current standard practice and  
12 increases the study's generalisability. Quality-of-life (QOL) impact was measured by  
13 a generic tool rather than specific prostate cancer-related QOL instruments which  
14 might have better captured urinary and sexual health domains. In our surgical  
15 feasibility study, we have also not examined the role of stereotactic body  
16 radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main  
17 study as other investigators have shown this to be an effective approach in oligo-  
18 recurrent prostate cancer.(29)  
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22 Other studies have shown safety and technical feasibility of surgery in men with  
23 metastatic prostate cancer,(19) but none in the UK population and none to date in a  
24 randomised trial setting. Other ongoing randomised trials investigate radical surgery  
25 in metastatic disease, but do not specifically examine the role of surgery in addition  
26 to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has  
27 demonstrated that this is the optimal population of men with metastatic prostate  
28 cancer worth considering for local radical treatment.(14) TRoMbone now shows it is  
29 safe and feasible to investigate surgery in this setting. A future definitive trial is likely  
30 to accrue in the UK; recruitment is likely to be faster than in this feasibility study  
31 because an increasing number of surgeons will have experience and confidence in  
32 undertaking these operations as well as QRI-informed improved recruitment  
33 strategies.  
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50 and especially the participants of this investigational research trial.  
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## Legends to figures

Figure 1. CONSORT flow diagram

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4 Figure 2. Recruitment  
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8 **Legends to tables**  
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10 Table 1. Baseline subject characteristics. (a) categorical variables; (b) continuous  
11 variables  
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13 Table 2. Peri-operative data in intervention subjects  
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16 Table 3. PSA, functional, and quality-of-life outcomes in study groups at three  
17 months post-randomisation  
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For Peer Review

## Response to Reviewers

Referee: 1

We thank the referee for his/her detailed review of our manuscript. We address the specific points below:

1. The manuscript reports primarily on feasibility: will men with oligometastatic prostate cancer accept randomization to SOC or SOC + RP. The Introduction, however, focuses on what is SOC (paragraph 1), a rather convoluted discussion of the rationale for adding local to systemic therapy (paragraph 2), and then a mention of the study aims (paragraph 3). The Introduction should be devoted to the concept of the difficulty to randomize men to a SOC versus SOC + RP trial [which is the primary (I would argue the only) aim of the study]. Why was a feasibility study needed; is there prior evidence that there would be difficulty enrolling to such a trial; what were the expected obstacles and how did you plan to address these?

We feel that the Introduction sets the scene well and would refer to the positive comments of the other reviewers in this regard. We have substituted one clause in the second para with “*Further*” to reduce the word count, but feel the rest of the content is important for the reader.

The rationale for a feasibility study is well described in the third para of the Introduction and we have made this even more explicit by changing a line in that para to:

*“Hence, most UK funders will not support a full surgical trial without a feasibility study confirming ability to randomise and safety of any novel intervention.”*

In the third para, we have stated that multiple prostate cancer surgical trials have failed to recruit in the past, that there is a lack of surgical experience in operating on oligo-metastatic disease, and that we utilized a tried-and-tested QRI as used in the ProtecT trial to inform us on the obstacles and the plan to address them. The purpose of the QRI was to independently interrogate the challenges to recruitment and then to propose solutions. We did not pre-judge what the QRI would find. Due to a limited word count, we have provided all the references the reader would require if they wish to have further details of the QRI rationale and methodology (no change to the original manuscript):

*“One major success in recruitment terms was the Prostate Testing for Cancer and Treatment (ProtecT) study which employed a QuinteT Recruitment Intervention (QRI) that has been subsequently shown to improve recruitment in a further 13 challenging RCTs, including the recent PART prostate cancer feasibility trial. (20-23) We therefore integrated a QRI as well as robust safety assessments within this randomised controlled feasibility trial of surgery plus standard-of-care (SOC) systemic therapy versus SOC alone in men with newly-diagnosed oligo-metastatic prostate cancer (1-3 skeletal metastases from prostate cancer, no visceral metastases); the TRoMbone trial.”*

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4 2. While the patients had oligometastatic prostate cancer, a requirement was  
5 locally resectable disease in a surgically fit patient. It should come as no surprise  
6 that the outcome from RP was no different than in men without oligometastatic  
7 cancer. Multiple studies have shown the safety of RP in men receiving neoadjuvant  
8 ADT, neoadjuvant chemotherapy, and the combination. I'm not sure why UK men  
9 would be any different than men in other parts of Europe and America or in men  
10 randomized to RP rather than having it electively. There is nothing new in this study  
11 to add to what has already been extensively published.  
12  
13

14 We thank the reviewer with this comment but would humbly disagree. While there  
15 are studies that have examined surgery in metastatic prostate cancer (indeed our  
16 team has been involved in some of them), none of these are devoid of confounding  
17 by indication bias. These studies were retrospective and subject to selection bias,  
18 and our study examines for the first time whether it is safe to conduct surgery in this  
19 population without such selection biases. We are not claiming that UK men are  
20 different to men in other parts of Europe and America but it is true that men  
21 randomised to RP may be different to men having it "electively" as they will be  
22 subject to fewer selection biases. We therefore disagree that there is nothing new in  
23 this study or to what has been already extensively published. There has never been  
24 a randomised study published examining surgery for de novo oligo-metastatic  
25 prostate cancer, and retrospective, observational studies do not provide a high-level  
26 evidence alternative to randomisation. We have discussed the unique characteristics  
27 of our study and compared to the literature in the last para of the Discussion (no  
28 change from the original manuscript):  
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33 *"Other studies have shown safety and technical feasibility of surgery in men with*  
34 *metastatic prostate cancer,(19) but none in the UK population and none to date in a*  
35 *randomised trial setting. Other ongoing randomised trials investigate radical surgery*  
36 *in metastatic disease, but do not specifically examine the role of surgery in addition*  
37 *to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has*  
38 *demonstrated that this is the optimal population of men with metastatic prostate*  
39 *cancer worth considering for local radical treatment.(14) TRoMbone now shows it is*  
40 *safe and feasible to investigate surgery in this setting. A future definitive trial is likely*  
41 *to accrue in the UK; recruitment is likely to be faster than in this feasibility study*  
42 *because an increasing number of surgeons will have experience and confidence in*  
43 *undertaking these operations as well as QRI-informed improved recruitment*  
44 *strategies."*  
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49 3. Per point 2, including information about safety and outcomes in those men  
50 randomized to RP, including Tables 2 and 3, adds nothing to this manuscript. Focus  
51 on the key aim: is it feasible to randomize men with oligometastatic prostate cancer  
52 to SOC versus SOC + RP?  
53

54 As per our reply to point 1, it is important for funders to be reassured that performing  
55 surgery in this novel population is safe. Hence, our TMG were agreed that these  
56 outcomes should be recorded and these assessments are in the study protocol. It  
57 would therefore be unethical to omit these data from the publication. We feel we  
58 have shown both safety and feasibility to randomise.  
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4 4. Is current standard of care for men with oligometastatic prostate cancer not  
5 radiation therapy + radiation rather than systemic therapy alone? Should that not be  
6 the next trial: systemic therapy + XRT versus systemic therapy + RP?  
7

8  
9 We thank the reviewer for this incisive comment. We agree, based on STAMPEDE  
10 and others, that the standard of care for de novo oligo-metastatic prostate cancer  
11 should be systemic therapy + XRT to the primary, and thus the full trial should be a  
12 comparison of surgery to that standard of care. We have now shown that we can  
13 randomise eligible men, and as per referee 3's comments below (and our response),  
14 will plan such a study with the inclusion also of SBRT to the oligo-metastases.  
15

16  
17 As a full study is being planned and will require input from radiotherapists, patient  
18 stakeholders, imaging specialists, and others, we have not discussed the exact  
19 planned design in this manuscript. We have though added in a line in the Discussion  
20 stating that we will include SBRT to the oligo-metastases in the full trial:  
21

22  
23 *"In our surgical feasibility study, we have also not examined the role of stereotactic*  
24 *body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our*  
25 *main study as other investigators have shown this to be an effective approach in*  
26 *oligo-recurrent prostate cancer. (29)"*  
27

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30 Referee: 2

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32 We thank the referee for his/her extremely positive comments about the manuscript  
33 in its original version. We have addressed the other referee comments as best as we  
34 can and hope referee 2 agrees that manuscript has been improved even further.  
35

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38 Referee: 3

39  
40 We thank the referee for his/her positive introductory comments. We address the  
41 specific points below:  
42

- 43  
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45 1. The population seems like a very low risk one given the number of mets/LN  
46 count. I would use CAPRA (and possibly CAPRA S) to better describe the  
47 population  
48

49 We thank the referee for this comment. The CAPRA score includes the following  
50 variables: age, PSA, biopsy Gleason score, clinical T-stage, and percent biopsy  
51 cores involved. It does not include number of mets/ LN count. Also, for clinical T-  
52 stage, it is categorised as T1/T2 or T3a and most of our patients had T3b disease. If  
53 we were to categorise our T3 patients as T3a for the purposes of CAPRA scoring,  
54 then our median CAPRA score in both groups would be 8 and our IQR in both  
55 groups would be 7-8. Instead of a cumulative score like CAPRA we have given the  
56 summary statistics across each variable, which we feel is more informative to the  
57 reader. As pre-operative risk category defined eligibility for this trial we also feel that  
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3 adding in a post-operative cumulative scoring system like CAPRA-S might add  
4 confusion.  
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6 We have therefore not added in CAPRA (or CAPRA-S) scores to Table 1.  
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- 10 2. State more specifically how metastases were detected, bone scan, cross  
11 sectional imaging or both? Were such sites confirmed with biopsy? Was  
12 follow up imaging routinely done?  
13

14 We thank the referee for this comment. Table 1 already contains a section titled  
15 "Distant staging modality" with numbers and percentages of participants who  
16 underwent bone scintigram, MRI, CT, and PET. We have added a line in to the  
17 Methods in the 'Subjects' sub-section to reflect the heterogeneity of staging among  
18 trial participants, reflective of current urological practice:  
19  
20

21 *"Staging investigations included bone scintigram, MRI, CT, and PET depending on*  
22 *local practice, with some patients undergoing multiple staging tests."*  
23  
24

25 We also added a line thereafter:  
26

27 *"Oligo-metastatic sites were not confirmed with biopsy, as this is invasive and not*  
28 *standard practice in the UK."*  
29

30 As all patients received systemic therapy, it was not deemed clinically appropriate or  
31 necessary to do follow up imaging, but rather to monitor PSA. Hence, follow-up  
32 imaging as not done routinely.  
33  
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- 35  
36 3. Given the widespread use of PSMA PET, the authors should discuss how  
37 such imaging technology would impact identification and assessment of such  
38 patients.  
39  
40

41 We thank the reviewer for this comment and fully accept that heterogeneity of  
42 imaging modalities in the study might result in heterogeneity of disease burden in the  
43 study population. However, this reflects current UK (and worldwide) clinical practice,  
44 in which there is no consistency in oligo-metastatic definitions based on defined  
45 imaging modalities. As the purpose of our feasibility study was to evaluate safety and  
46 technical feasibility to randomise men with oligo-metastatic disease, we adopted a  
47 pragmatic approach to eligibility allowing individual cancer centres to use whatever  
48 imaging modalities they routinely did. We have expanded a section in para 4 of the  
49 Discussion to reflect this:  
50  
51

52 *"This is especially so as some participants had their oligo-metastatic state defined by*  
53 *PSMA-PET and others by conventional imaging. While this might mean that the*  
54 *study population was heterogeneous in its burden of disease, [this pragmatism*  
55 *however follows the UK current standard practice and increases the study's*  
56 *generalisability.]"*  
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3 4. What is the role of SBRT to oligometastatic sites? How would this  
4 complement systemic therapy?  
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6

7 Our study was not examining the role of SBRT to oligo-metastatic sites. While there  
8 are data for this approach in oligo-recurrent prostate cancer (e.g. the STOMP trial),  
9 studies using SBRT for de novo (synchronous) oligo-metastatic prostate cancer are  
10 lacking. We plan to investigate this in our main trial and have added the below text to  
11 the penultimate para of the Discussion, along with the STOMP trial reference:  
12

13  
14 *“In our surgical feasibility study, we have also not examined the role of stereotactic  
15 body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our  
16 main study as other investigators have shown this to be an effective approach in  
17 oligo-recurrent prostate cancer.(29)”*  
18

19 The STOMP trial examined time to requiring systemic therapy as its primary  
20 endpoint. As we know that systemic therapy improves survival in de novo metastatic  
21 prostate cancer, we would include it in all arms for our main trial. We have yet to plan  
22 the details of the SBRT arm of this main trial and would require the input of our  
23 radiotherapy colleagues for this, and how SBRT would complement systemic  
24 therapy. As this is beyond the scope of this current paper, and due to a limitation on  
25 word count, we have not discussed this issue further in the text.  
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Figure 1. CONSORT flow diagram

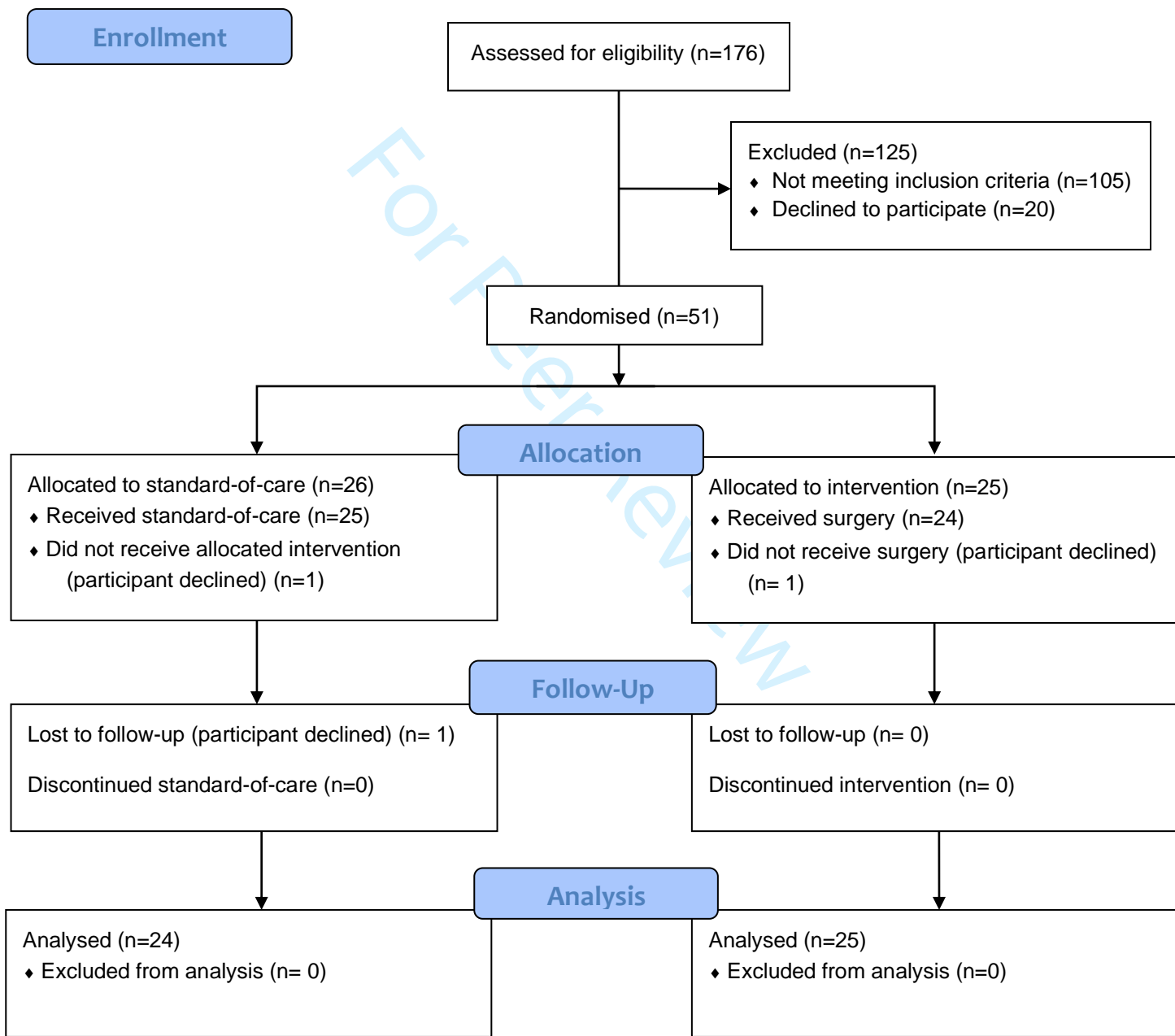
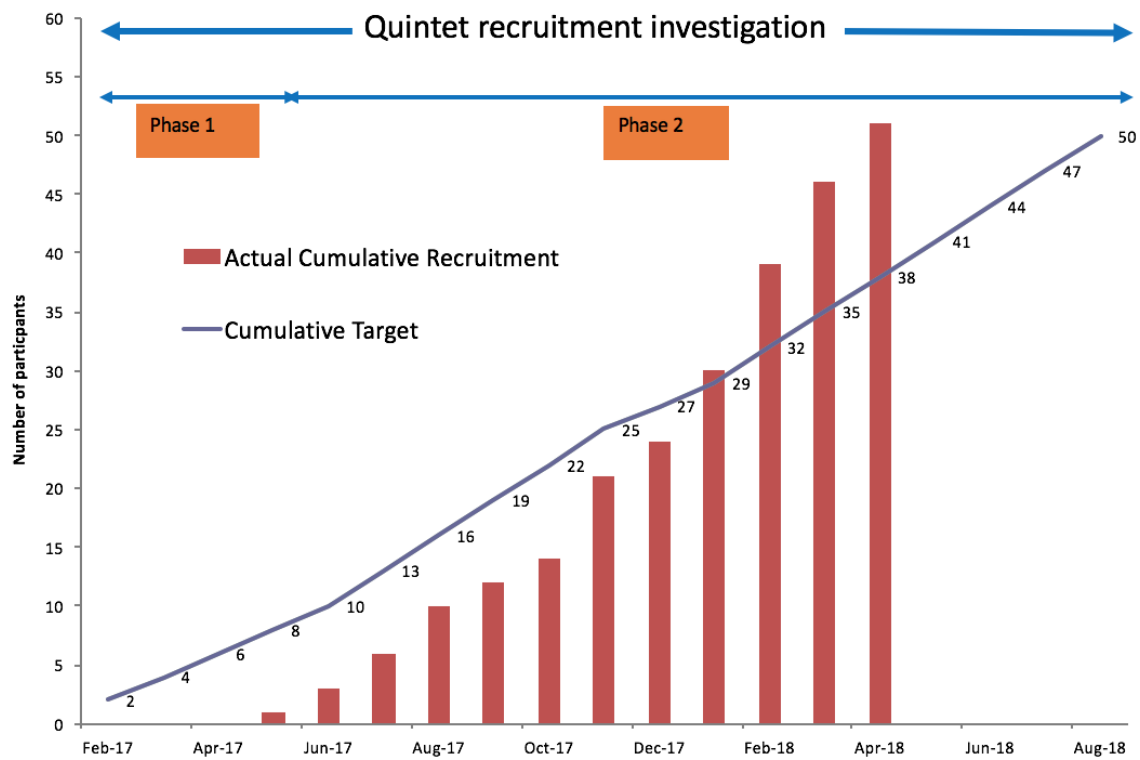


Figure 2. Recruitment



Review

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**Table 1. Baseline subject characteristics****(a) Categorical variables**

<b>Variable</b>	<b>Full cohort</b>	<b>SOC arm</b>	<b>Intervention arm</b>
<b>n (%)</b>	50 (100)	25 (50)	25 (50)
<b>Age</b>			
Less than 60	10 (20)	6 (24)	4 (16)
60-64	12 (24)	5 (20)	7 (28)
65-70	18 (36)	7 (28)	11 (44)
71-74	10 (20)	7 (28)	3 (12)
<b>Ethnicity</b>			
Caucasian	37 (74)	20 (80)	17 (68)
Black African/Caribbean	8 (16)	4 (16)	4 (16)
Asian	5 (10)	1 (5)	4 (16)
<b>Gleason score</b>			
7 (3+4)	3 (6)	2 (8)	1 (4)
7 (4+3)	11 (22)	5 (20)	6 (24)
8	13 (26)	6 (24)	7 (28)
9-10	23 (46)	12 (48)	11 (44)
<b>Clinical stage (DRE)</b>			
T2c	5 (10)	2 (8)	3 (12)
T3	45 (90)	23 (92)	22 (88)
<b>Co-morbidities</b>			
Myocardial infarction	0 (0)	0 (0)	0 (0)
Congestive heart failure	0 (0)	0 (0)	0 (0)
Peripheral vascular disease	0 (0)	0 (0)	0 (0)
Cerebrovascular disease	0 (0)	0 (0)	0 (0)
Dementia	0 (0)	0 (0)	0 (0)
Chronic obstructive pulmonary disease	1 (2)	1 (4)	0 (0)
Rheumatological disease	1 (2)	1 (4)	0 (0)
Connective tissue disorder	0 (0)	0 (0)	0 (0)
Peptic ulcer disease	1 (2)	0 (0)	1 (4)
Mild liver disease	0 (0)	0 (0)	0 (0)
Moderate/severe liver disease	0 (0)	0 (0)	0 (0)
Diabetes mellitus	2 (4)	0 (0)	2 (8)
Diabetes with chronic complications	0 (0)	0 (0)	0 (0)
Moderate/severe chronic kidney disease	0 (0)	0 (0)	0 (0)
Hemiplegia/paraplegia	0 (0)	0 (0)	0 (0)

Leukaemia	0 (0)	0 (0)	0 (0)
Malignant lymphoma	1 (2)	1 (4)	0 (0)
Solid tumour	1 (2)	0 (0)	1 (4)
AIDS	0 (0)	0 (0)	0 (0)
None of the above conditions	44 (88)	23 (92)	21 (84)
<b>Distant staging modality*</b>			
Bone scintigram	41 (82)	19 (76)	22 (88)
MRI	37 (74)	19 (76)	18 (72)
CT	23 (46)	12 (48)	11 (44)
PET	8 (16)	5 (20)	3 (12)
<b>Radiological T-stage</b>			
T2c	4 (8)	1 (4)	3 (12)
T3a	18 (36)	9 (36)	9 (36)
T3b	28 (56)	15 (60)	12 (48)
Missing	1 (2)	0 (0)	1 (4)
<b>Radiological N-stage</b>			
N0	26 (52)	10 (40)	16 (64)
N1	24 (48)	15 (60)	9 (36)
<b>Family history of prostate cancer</b>			
Yes	12 (24)	7 (28)	5 (20)
Missing	4 (8)	4 (16)	0 (0)
<b>Patient on 5-alpha-reductase inhibitor</b>			
Yes	1 (2)	1 (4)	0 (0)
Missing	1 (2)	0 (0)	1 (2)
<b>IIEF-5 category</b>			
7 or less (severe ED)	13 (26)	5 (20)	8 (32)
8-11 (moderate ED)	6 (12)	3 (12)	3 (12)
12-16 (mild-to-moderate ED)	7 (14)	3 (12)	4 (16)
17-21 (mild ED)	11 (22)	8 (32)	3 (12)
22-25 (no ED)	10 (20)	4 (16)	6 (24)
Missing	3 (6)	2 (8)	1 (4)
<b>Incontinence</b>			
No	50 (100)	25 (0)	25 (0)

\*Some participants underwent multiple imaging modalities, as per routine clinical care

## (b) continuous variables

Variable	SOC		Intervention	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
<b>Age</b>	64.7 (6.6)	66.0 (60.2-71.2)	65.3 (5.1)	65.4 (62.5-69.3)
<b>BMI*</b>	28.2 (3.9)	28.2 (25.4-30.4)	31.5 (14.0)	26.4 (24.3-29.9)
<b>PSA</b>	57.0 (117.6)	16.5 (8.2-37.5)	43.3 (79.3)	14.0 (2.7-40.0)
<b>No. of nodal metastases</b>	3.3 (4.3)	1.0 (0.0-10.0)	1.2 (2.8)	0.0 (0.0-1.0)
<b>No. of bone metastases</b>	1.5 (0.7)	1.0 (1.0-2.0)	1.5 (0.8)	1.0 (1.0-2.0)
<b>Prostate volume (cc)**</b>	40.3 (20.3)	40.0 (26.0-50.0)	53.9 (60.7)	38.0 (23.0-60.0)
<b>No. of biopsy cores taken***</b>	11.4 (4.9)	12.0 (10.0-12.0)	13.2 (6.4)	12.0 (10.0-14.0)
<b>No. of biopsy cores positive***</b>	9.1 (4.4)	10.0 (5.0-12.0)	9.0 (3.2)	9.0 (6.0-12.0)
<b>No. of lymph node metastases<sup>+</sup></b>	1.6 (3.0)	0.0 (0.0-2.0)	1.2 (2.8)	0.0 (0.0-1.0)
<b>No. of bone metastases</b>	1.5 (0.8)	1.0 (1.0-2.0)	1.4 (0.7)	1.0 (1.0-2.0)
<b>IIEF-score<sup>++</sup></b>	15.5 (6.8)	18.5 (10.0-21.0)	13.5 (7.6)	13.0 (5.5-21.0)
<b>No. of pads/24h</b>	0 (0)	0 (0)	0 (0)	0 (0)
<b>EQ-5D-5L descriptive score</b>	0.9 (0.1)	1.0 (0.8-1.0)	0.9 (0.1)	1.0 (0.8-1.0)
<b>EQ-5D-5L VAS score</b>	84.7 (11.5)	85.0 (80.0-95.0)	84.7 (13.8)	90.0 (80.0-95.0)

\*BMI had missing data in one SOC and four intervention arm participants

\*\*Prostate volume had missing data in four SOC and two intervention arm participants

\*\*\*No. of biopsy cores taken/positive had missing data in one SOC and one intervention arm participant

<sup>+</sup>No. of lymph nodes metastases had missing data in five SOC and one intervention arm participant

<sup>++</sup>IIEF-5 score had missing data in two SOC and one intervention arm participant

**Table 2. Peri-operative data in intervention subjects\***

<b>Variable</b>	<b>Result</b>
Participants, n	24
PSA at time of surgery, median (IQR)	2.0 (0.79-7.25)
ADT length before surgery (m), median (range)	3 (1-9)
Pre-operative chemotherapy, n (%)	11 (45.8)
Cycles of chemotherapy, median (range)	6 (6-6)
Time from last chemotherapy to surgery (m), median (range)	4 (3-6)
Operative time (min), median (IQR)	185 (165-217)
Console time (min), median (IQR)	150 (129-170)
Intra-operative complications**, n (%)	1 (4.2)
Intra-operative transfusions, n (%)	1 (4.2)
Procedure abandoned, n (%)	0 (0)
Length of stay, median (IQR)	1 (1-2)
Return to theatre during hospital stay, n (%)	0 (0)
Post-operative transfusions, n (%)	1 (4.2)
Failed trial without catheter, n (%)	0 (0)
Pathological Gleason score***, n (%)	
4+3	4 (16.7)
4+4	4 (16.7)
4+5	8 (33.3)
5+4	7 (29.2)
Pathological T-stage, n (%)	
pT2c	3 (12.5)
pT3a	3 (12.5)
pT3b	18 (75.0)
Lymph nodes removed, median (IQR)	11 (7-14)
Lymph node positive, n (%)	11 (45.8%)
Length of catheterisation (d), median (IQR)	14 (10-14)
Post-operative complications within 6m** of surgery, n (%)	3 (12.5)
Erections sufficient for intercourse without invasive aids within 6m of surgery, n (%)	0 (0%)
Incontinence, n (%)	
1m post-operatively	9 (37.5)
3m post-operatively	6 (25.0)
6m post-operatively	4 (16.7)
PSA 3m after surgery <sup>+</sup> , n (%)	
<1 ng/ml	18 (78.3)
≥1 ng/ml	5 (21.7)
PSA 6m after surgery <sup>+</sup> , n (%)	
<1 ng/ml	19 (82.6)
≥1 ng/ml	4 (17.4)
Positive surgical margins, n (%)	10 (41.7%)
Length of positive surgical margins (mm), median (IQR)	7 (2-9)

\*Some of these data were collected as part of routine clinical care with follow-up to 6m after surgery

\*\*21 individual complications were assessed as per Tewari et al.(26)

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\*\*\*In one participant, Gleason grading was not possible due to treatment effect  
+Missing data in one participant

For Peer Review

**Table 3. PSA, functional, and quality-of-life outcomes in study groups at three months post-randomisation**

Variable	SOC (n=25)		Intervention (n=24)*	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
<b>PSA **</b>	2.6 (3.4)	1.2 (0.6-2.9)	1.5 (2.8)	0.4 (0.1-1.4)
<b>IIEF-5 score***</b>	9.0 (3.4)	5.0 (5.0-12.0)	7.7 (5.9)	5.0 (5.0-6.0)
<b>No. of pads/24h</b>	0 (0)	0 (0)	1.8 (0.9)	2 (1.0-2.0)
<b>EQ-5D-5L descriptive score<sup>+</sup></b>	0.9 (0.2)	1.0 (0.8-1.0)	0.9 (0.2)	1.0 (0.8-1.0)
<b>EQ-5D-5L VAS score<sup>++</sup></b>	82.7 (12.3)	84.0 (75.0-90.0)	85.6 (13.5)	90.0 (77.5-96.5)

\*At 3m post-randomisation, 17/25 (68.0%) participants had undergone surgery whereas the others in this arm had still only received SOC

\*\*PSA had missing data in one SOC participant

\*\*\*IIEF-5 score had missing data in three SOC and one intervention arm participants

<sup>+</sup>EQ5D score (UK) had missing data in four SOC and one intervention arm participant

<sup>+</sup>No. of lymph nodes metastases had missing data in five SOC and one intervention arm participant

<sup>++</sup>EQ5D VAS (visual analogue scale) score had missing data in two SOC and one intervention arm participant