PIVOTALboost

A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost

PROTOCOL

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The PIVOTALboost trial has been scientifically approved by Cancer Research UK's Clinical Research Committee and is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. A copy of the current membership of the TMG can be obtained from the PIVOTALboost Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Prof Isabel Syndikus (Chief Investigator)		6th July 2023

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

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

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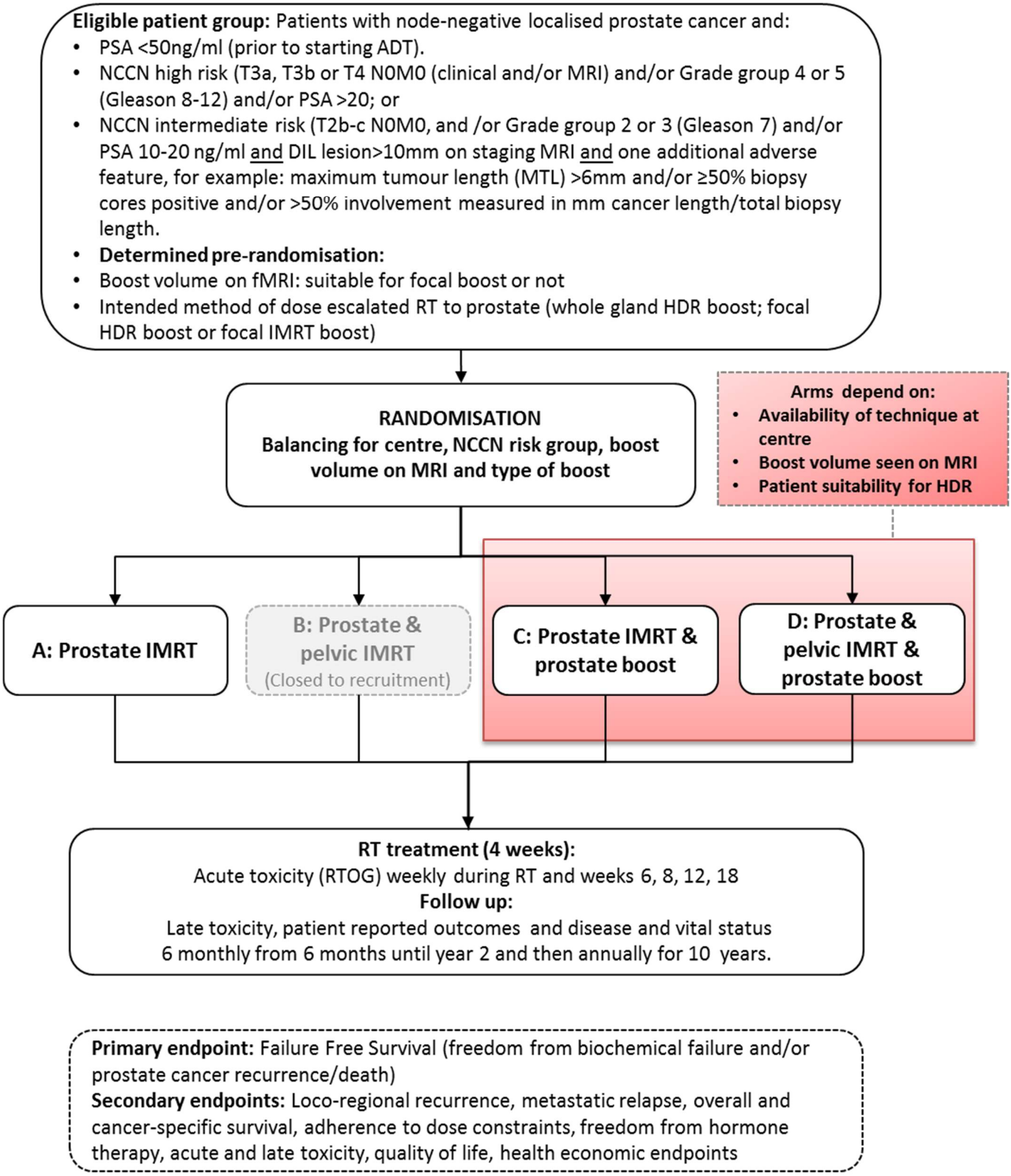
TRIAL SUMMARY

PROTOCOL TITLE	PIVOTALboost: A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost
TARGET DISEASE	1. Histologically confirmed, previously untreated, non-metastatic adenocarcinoma of the prostate; 2. PSA <50ng/ml (prior to starting ADT) 3. NCCN localised high risk or locally advanced disease • T3a, T3b or T4 N0M0 (clinical and/or MRI) and/or • Grade group 4 or 5 (Gleason 8-10) and/or • PSA >20; or 4. NCCN intermediate risk disease • T2b-c N0M0, and /or Grade group 2 or 3 (Gleason 7) and/or PSA 10-20 ng/ml and • DIL lesion >10mm on staging MRI and • One additional adverse feature, for example: maximum tumour length (MTL) >6mm and/or ≥50% biopsy cores positive and/or >50% involvement measured in mm cancer length /total biopsy length.
STUDY OBJECTIVES	The primary objective of PIVOTALboost is to assess whether pelvic lymph node radiotherapy with or without dose escalation to the prostate with HDR, HDR incorporating a focal boost or focal boost IMRT can lead to improved failure free survival with similar levels of bladder (genitourinary) and bowel (gastrointestinal) side effects experienced by patients.
STUDY DESIGN	Multicentre four-arm phase III randomised controlled trial
TRIAL POPULATION	Patients receiving radical radiotherapy for localised, node negative prostate cancer.
RECRUITMENT TARGET	2229 patients (following closure of arm B)
TRIAL TREATMENT	Patients will be allocated to one of the following treatment arms: • A: Prostate alone IMRT • B: Prostate and pelvic IMRT (closed to recruitment) • C: Prostate IMRT and prostate boost • D: Prostate and pelvic IMRT and prostate boost. Randomisation into arms C and D will depend on the boost volume identified by MRI (suitable for focal boost or not), availability of focal HDR or IMRT and patient suitability in case of HDR (see section 10 and 13 for further details).
NEOADJUVANT AND ADJUVANT HORMONE THERAPY	Patients in the intermediate risk group will receive 6 -12 months of ADT, and patients in the high risk group may receive 2-3 years of ADT; in selected high risk patients, shorter duration hormone therapy (6 months) is acceptable. patients ideally undergo planning after 2-4 months (maximum 11) of neo-adjuvant ADT and commence radiotherapy at a maximum of 12 months.

	Patients receiving extended ADT to permit safe delay of radiotherapy as a result of the COVID19 pandemic will be permitted to enter (see 1.1.11).
PRIMARY ENDPOINT	Failure-free survival (FFS), defined by the time to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence, distant metastases or death due to prostate cancer.
SECONDARY ENDPOINTS	• Time to loco-regional recurrence; time to biochemical failure or prostate recurrence; metastatic relapse free survival; overall and prostate cancer specific survival; time to recommencement of androgen deprivation therapy. • Adherence to dose constraints. • Acute bladder and bowel toxicity at 18 weeks. • Late toxicity. • Quality of life. • Health economic endpoints.
FOLLOW UP	**RT treatment (1-18 weeks):** • Acute toxicity (RTOG, CTCv4.0) assessed during radiotherapy week 1-4, week 6, 8 12, and 18 plus QL from start of RT. **Follow up:** *time points from start of RT* • Late toxicity and PSA at 6, 12, 18, 24 months annually for 5 years • Annual follow-up for PSA and recurrence at least until 10 years.

TRIAL SCHEMA



1. INTRODUCTION

1.1. Background

1.1.1. Standard treatment for prostate cancer

Patients with intermediate and high risk prostate cancer and those with locally advanced disease which has not spread elsewhere are recommended to have either radical prostatectomy or radical radiotherapy (RT) [1]. Whilst recent data from the CHHiP trial (CRUK/06/016) suggests patients at lower risk of recurrence/progression have 5-year progression free rates (freedom from biochemical failure or prostate cancer recurrence) in excess of 85%, local, lymph node and/or biochemical failure in the higher risk group is around 20-30% [2]. Dose escalation to the whole prostate of 78Gy or higher using intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT) improves biochemical control but can cause increases in urinary and bowel toxicity [3-5]. There are two dose escalation techniques available that limit this increase in normal tissue toxicity. High dose rate brachytherapy (HDR) minimises bowel and bladder irradiation [6-10] by delivering radiation directly to the prostate gland via probes placed under anaesthetic. Focal dose escalation can be used to target dominant intraprostatic tumour or lesion (DIL) within the prostate and is suitable for patients with tumour volumes which do not occupy the majority of the prostate (as seen on the staging MRI). A focal boost can be delivered using IMRT or HDR [11-13] and may avoid the excess toxicity of dose escalation to the whole gland using IMRT because the high dose volume is located inside the prostate and only 10-30% of the prostate surface is treated to a high dose, resulting in a lower dose to the adjacent normal tissues than IMRT boost to the whole prostate

1.1.2. Modest hypofractionation (20 fraction schedule)

In the last few years, hypofractionated external beam radiotherapy (EBRT) has gained increasing popularity for prostate cancer treatment; prostate cancer has a low α/β ratio, lower than that of the surrounding organs at risk and thus there is a potential therapeutic benefit of using larger fraction size. Hypofractionation saves treatment time, health care resources and improves patients' experience. Contemporary randomised studies have reported encouraging results of tumour control without an increase of relevant side effects, especially late toxicity [14-16]. The phase III CHHiP trial (CRUK/06/016, ISRCTN:97182923) included 3216 patients, 73% of whom had intermediate risk prostate cancer. The standard fractionation of 74Gy in 37 fractions (f) was compared to moderately hypofractionated regimens of 60Gy/20f and 57Gy/19f. After a median follow up of 62.4 months, the 20f schedule was found to be non-inferior to the standard schedule (hazard ratio (HR): 0.83 (90% Confidence Interval (CI): 0.68, 1.02), with 5-year progression free rates of 90.5% (95% CI: 88.4–92.2) for 20f and 88.3% (86.0-90.2) for 37f. Acute RTOG bowel toxicity was higher for patients receiving 20f (Mann-Whitney: $p<0.001$; grade2+: 74Gy: 176/715 (24.6%); 60Gy: 277/720 (38.5%)); however late toxicity profiles were similar between groups [2]. The incidence of patient-reported bowel symptoms was low and similar between patients in the control group and hypofractionated groups up to 5 years after radiotherapy [17]. As a result, and in line with the anticipated change in UK standard practice, a hypofractionated 60Gy/20f IMRT schedule will be the basis for all RT delivered within PIVOTALboost.

1.1.3. Image guided radiotherapy (IGRT)

Movements of the prostate between and during treatment fractions are common, with a large inter-patient variability. Unless these shifts are corrected before each treatment the dose to the treatment volumes is reduced and conversely the dose to the rectum and bladder increased. The high dose gradients and small boost volumes for focal boost IMRT require more accuracy compared to standard prostate IMRT [18]. IGRT includes use of cone beam CT (CBCT), tomotherapy and fiducial markers and allows visualisation of the prostate, or a surrogate thereof, in the treatment room prior to delivery, enabling more precise targeting of the prostate. Use of image guidance has become increasingly widespread in the delivery of prostate RT and it is anticipated that its use will be incorporated into guideline-based practice.

1.1.4. Pelvic lymph node RT

Our multicentre phase II trial of standard prostate IMRT (74Gy/37f) versus prostate plus pelvic node IMRT

(74Gy and 60Gy/37f) (PIVOTAL, CRUK/10/022) recruited 124 participants with locally advanced (very high risk) node negative prostate cancer and demonstrated that a standardised treatment delivery protocol [19] was associated with low rates of grade 2+ lower GI toxicity at 18 weeks (prostate alone: 3.3% (95% CI: 0.4-11.3); prostate + pelvis: 4.8% (1.0-13.5)) [20]. However it remains uncertain whether a high risk group would benefit from pelvic node irradiation [21] and whether dose escalation to the prostate is also required. In clinically node-negative patients with high risk localised prostate cancer, surgical series have demonstrated high rates of pathological positive nodes [22], but three randomised trials which included low and intermediate risk participants did not demonstrate a benefit of pelvic node irradiation in these patient groups [23-25] It is not clear whether high risk patients derive more benefit [21]. Interim data from a randomised trial demonstrated that a 20f schedule to the pelvic nodes is tolerated with similar toxicity to that seen in PIVOTAL [26] and we believe there is sufficient evidence that hypofractionated schedules including pelvic nodes have acceptable toxicity profiles [27]. In a survey of UK centres (conducted to inform trial development), out of 29 responding UK sites, 10 sites used pelvic irradiation in all high risk patients; 5 of those also on selected intermediate patients, 11 for selected high risk patients only and 8 centres did not offer it routinely to any node negative high risk patient. There is thus considerable variation in practice that a phase III UK trial, building on PIVOTAL, would seek to harmonise.

1.1.5. Dose escalation

Phase III studies [28-31] which used lower prostate boost doses than those proposed within PIVOTALboost have shown better biochemical control with dose escalation, but similar overall survival [1] and increased toxicity [32]. A linear relationship between biochemical control and radiation dose has been found: increasing dose by 1Gy reduces failure risk by 1.8% ($p<0.04$) in the dose range between 64-79.6Gy [14]. Furthermore, improvements in cancer specific survival have been recorded in cohort studies with longer follow-up and in the CHHiP trial with moderate hypofractionation [2,33,34]. In a large series of 1530 patients treated with 3D conformal RT (CRT) and doses of <70Gy to >80Gy (4 dose groups), biochemical control improved with increasing dose group (relative risk 0.94 95%CI: 0.91-0.97) but bowel and urinary toxicity also increased, with a grade 2-3 rectal complication rate which was twice as high for patients treated to 78Gy than to 70Gy five years after treatment (26% vs. 12%) [4]. The limit of conventionally fractionated dose escalation is around 86Gy [5,35,36]. In contrast to dose escalation using EBRT to the entire prostate gland, the two techniques to deliver a tumour boost proposed in PIVOTALboost could confer benefit without unacceptable increases in toxicity.

1.1.6. High dose-rate brachytherapy (HDR)

HDR is a promising technique and one trial in intermediate- and high-risk patients has shown that compared to hypofractionated EBRT (55Gy/20f), combining hypofractionated EBRT (35.75Gy/13f) and a 17.5Gy/2f HDR boost resulted in an improvement in 5-year relapse-free survival from 61% to 75% ($p=0.04$) for high risk patients, however incidence of severe toxicity at five years was relatively high (26% in both arms) [6]. This trial used 3D CRT at lower doses than the IMRT dose proposed within PIVOTALboost so there may be room to improve control rates whilst minimising toxicity. HDR offers the advantage of excellent conformity, rapid dose fall-off outside the target volume and the possibility for dose escalation with sparing of the normal tissues. HDR is particularly suitable for patients with no obvious tumour on the staging MRI scan but positive biopsies (10-15% of high risk patients) or with tumour involvement >50% on the MRI scan [7-10]. HDR is not an option for patients on long-term anticoagulation therapy, recent prostate surgery (transurethral resection, TURP), with a history of recent deep vein thrombosis or pulmonary embolus, significant cardiovascular comorbidity and or patients who are unfit for prolonged general anaesthetic.

1.1.7. Focal boost dose escalation

Compared to dose-escalated EBRT to the entire prostate volume, a more localised, focal boost strategy reduces the risk of late toxicity. The dose is increased only to sub-volumes of the prostate gland containing a significant amount of cancer while the rest receives the standard dose [13-15,37,38]. The method is particularly suitable for high risk patients with locally bulky disease [39-41] who have an increased risk of

local failure, thus tailoring the dose escalation to localisation of the intra-prostatic tumour. This technique requires an accurate localisation of tumour volumes on staging MRI scans [42]. It is estimated that around 80-90% of high risk patients have disease confined to under 50% of the prostate gland (as seen on staging MRI scan) [43] which would be suitable for a targeted focal boost. There is good evidence from planning and dosimetry studies [44] that focal boost escalation could improve the therapeutic ratio compared to dose escalated whole prostate EBRT. Although the results from cohort studies show acceptable toxicity and good early PSA control [13-15,38], it is difficult to know whether these benefits would be apparent in a randomised controlled multicentre trial [45]. IMRT and HDR can be used to deliver the focal boost and are in current clinical use; the biological dose used is similar, but the technique used depends mostly on the experience of the site and the suitability and preference of the patient. Both focal boost techniques can be combined with whole prostate IMRT and used to treat the prostate only or can be combined with pelvic node IMRT.

1.1.8. Focal IMRT boost

A number of single centre studies have been published developing and exploring the technical details of different focal boost approaches [24-26,46]. In the UK, we are leading two single arm phase II studies that evaluate focal boost IMRT and provide pilot data/experience for PIVOTALboost: BIOPROP (NCT02125175) which is running at 2 UK centres and the single centre DELINEATE study (ISRCTN04483921). The study evaluates a focal IMRT boost to 82Gy/37f, equivalent to 66-67 Gy in 20 fractions and has reported toxicity rates comparable to those seen in the CHHiP trial. Acute bowel toxicity was at worst RTOG grade 2 for 18% (8/45); worst grade acute bladder toxicity was grade 2: 69% (31/45) and grade 3: 7% (3/45). By 18 weeks bowel and bladder toxicities had resolved to grade 1. Late bowel toxicity was reported by 7 patients (grade 1: 5; grade 2: 7) and late bladder toxicity by 5 patients (grade 1: 4; grade 2: 1). Cumulative RTOG grade 2 or worse toxicity rates at 12 months were 7% for bladder and 0% for bowel [47]. In the first BIOPROP20 cohort, the dose schedule (boost dose 68Gy/20f, prostate dose 60Gy/20f), acute bowel toxicity was at worst RTOG grade 1 for 7% (2/28); worst grade acute bladder toxicity was grade 2: 11% (3/28) and no grade 3. By 18 weeks bowel and bladder toxicities had resolved to grade 1, one patient still had grade 2 bladder toxicity. With a medium follow up of 38 months, late bowel toxicity was reported by 3 patients (grade 1: 3) and late bladder toxicity by 7 patients (grade 1: 7; grade 2: 2). Cumulative CTCAEv4 grade 2 or worse toxicity rates at 36 months were 7% for bladder and 0% for bowel [48]. In 2021, the results from the FLAME trial (NCT01168479) were published [49] which concluded that the addition of focal boost IMRT improved biochemical disease-free survival for patients with localized intermediate- and high-risk prostate cancer without impacting toxicity and quality of life. The focal boost arm received an additional simultaneous integrated focal boost up to 95 Gy (fractions up to 2.7 Gy), higher than in PIVOTALboost which uses standard doses.

1.1.9. Focal HDR boost

Focal HDR boost has been evaluated in single centre cohort studies [50-525]. A cohort study confirmed an excellent coverage of the boost volume; the study demonstrated that the closeness to the urethra and rectum was limiting the boost dose in 4 out of 25 patients [50], a finding which was confirmed by a two planning studies for 16 and 9 patients, where the urethral dose limited boost volume doses [51,52]. PIVOTALboost will build on this experience in a multicentre randomised setting. The treatment is similar to HDR to the whole prostate, with the whole gland CTV treated to 15Gy and the dose to the boost volume increased to 19 Gy, whilst respecting normal tissue constraints. Localisation of the focal boost is defined using functional MRI as with focal IMRT boosts. Compared to the staging MRI scan, the shape and volume of the prostate (and the boost volume) changes during the needle insertion at the beginning of the implant. The boost volume can be transferred by cognitive fusion or fusion with the planning CT/MRI or planning ultrasound. An alternative technique is to use sector optimisation [53]. In sector optimisation the prostate is divided into anatomical sectors and those sectors involved with tumour on pre-treatment functional MRI are then boosted without additional margins.

1.1.10. MRI Imaging

Multi- parametric MRI imaging will be performed according to the PI RADS guidelines [54]. Based on histo-pathological correlation with prostatectomy specimens, T2-weighted sequences combined with DW MRI sequences, or DW combined with DCE MRI sequences, have sensitivities and specificities of 70% to 87% [55]. The comparisons of imaging with histopathology studies use 16-32 segments for the analysis and many cohorts include low risk patients or small (<5mm) lesions; hence the findings are not directly applicable to PIVOTALboost. An imaging sub-study of DELINEATE (n=26) has demonstrated that the diagnostic accuracy (compared to template mapping biopsies) of functional MRI to detect and localise tumour for the purpose of radiation boosts has a sensitivity 85-86%, specificity 93-98%; (2) agreement between readers on DIL volumes outlined on the MRI and (3) correlation between DIL volumes and pathology (length core involvement) [47]. Similar findings were reported in a cohort study, including patients with low to intermediate risk patients [42]. However, as there are uncertainties in outlining boost volumes [56-58], a 3mm intra-prostatic margin is recommended for the focal IMRT boost volume; for the focal HDR boost, the segment(s) involved on the staging MRI defines the boost volume.

1.1.11. Androgen Deprivation Therapy

In a meta-analysis, neo-adjuvant, concurrent and adjuvant androgen deprivation therapy (ADT) combined with radiotherapy and demonstrated a better survival (HR 1.3; 95% CI: 1.2-1.41; $p < 0.00001$), disease free survival (HR 2.51; 95% CI: 1.32-4.76; $p = 0.005$) and metastases–free survival (HR 2.53; 95% CI: 1.75-3.67; $p < 0.00001$) in the combined group [59]. The total duration of adjuvant ADT in the CHHiP trial was 6 months; in the high risk group, the 5-year biochemical disease free survival was 84.5% and compares favourably with other randomised trials with longer-term ADT in this risk group (unpublished data). In EORTC 22961, a 36-month ADT regimen was compared with a 6-month ADT regimen. ADT used for 36 months achieved better 5-year overall survival rates than a 6-month ADT (85% *vs.* 81%, respectively, HR 1.42, 95% CI: 1.09-1.85). Longer duration had a detrimental effect on quality of life and sexual function [60]. In a recent review of the evidence, 28-36 months of ADT is recommended for patients in the localised high risk group [61]. In PIVOTALboost, patients in the intermediate risk group will receive 6-12 months of ADT, and patients in the high risk group may receive 2-3 years of ADT; in selected high risk patients, shorter duration hormone therapy (6 months) is acceptable. Patients undergo planning after 2-4 months (maximum 11) of neo-adjuvant ADT and commence radiotherapy at a maximum of 12 months. Use of Androgen Receptor Target Agents (e.g. Enzalutamide [62], Abiraterone [63], Darolutamide or Apalutamide [64] will also be permitted, provided this is in accordance with national/devolved nation guidelines.

During the COVID19 pandemic (starting in the UK ~March 2020) treatment recommendations based on expert opinion were to extend the length of time prostate cancer patients are on ADT prior to radiotherapy beyond 6 months in order to mitigate against a delayed start to radiotherapy. For patients recruited to the trial and affected by the COVID-19 pandemic, they should start radiotherapy within 12 months of starting ADT [70-71]. Other reasonable causes resulting in delay to the start of radiotherapy to up to 12 months from starting ADT, should be discussed in the first instance with the PIVOTALboost Trial Manager at the ICR-CTSU.

1.2. Known risks and benefits

1.2.1. Potential benefits

It is anticipated that the use of dose escalation within the prostate adapted to the patient specific tumour characteristics on the staging MRI and or the treatment of pelvic lymph nodes will improve loco-regional tumour control. This should lead to benefits for patients in terms of improved PSA control, reduction in local, regional and metastatic disease relapse and reduced need for long-term hormone therapy.

1.2.2. Potential risks

The toxicity of the prostate boost schedules may be higher than of the prostate alone schedules, however the tumour boost dose has been determined based on early phase UK studies described above. The pelvic node IMRT technique has been demonstrated to be safe within the PIVOTAL trial, which ruled out grade2+ gastrointestinal toxicity rates larger than 20%, so we expect similar outcomes in this study in the pelvic node

group (arm B). The shorter fractionation schedule (60Gy/20f) may lead to a moderate increase in acute gastrointestinal toxicity, but is not expected to increase late toxicity. Acute toxicity will be reviewed in each of the experimental arms (B, C and D) once a minimum of 119 patients per arm have completed the 18 weeks acute toxicity follow up assessment (see section 13). As the recruitment pattern for arm B is different to arms C and D this analysis will be carried out as the data for each of the experimental arms matures. Adverse event data will be collected prospectively and rates will be monitored by the IDMC throughout the study.

Some participating centres will have limited experience of the boost techniques prior to opening PIVOTALboost, however centres' delivery of treatment techniques will undergo Radiotherapy Trials Quality Assurance (RTTQA) accreditation prior to opening and throughout the trial's duration to maintain a quality standard in accordance with the trial specific RT planning and delivery guidelines. It is anticipated that ongoing central monitoring of safety data throughout the trial will mitigate any potential risks to patients, who may benefit from improvements in disease control by participation in PIVOTALboost.

1.3. Description of population

PIVOTALboost will recruit patients with high risk or intermediate risk (with adverse features) localised prostate cancer who opt to have radiotherapy as radical treatment.

1.4. Study rationale

Following the CHHiP trial, hypofractionated image-guided radiotherapy is anticipated to become the new standard of care for patients with localised prostate cancer undergoing RT. The PIVOTALboost trial will evaluate the need for pelvic node radiotherapy, and depending on staging MRI imaging, of whole gland or focal dose escalation.

2. TRIAL OBJECTIVES

2.1. Primary objective

The primary objective of PIVOTALboost is to assess whether pelvic lymph node radiotherapy with or without dose escalation to the prostate with HDR, HDR incorporating a focal boost or focal boost IMRT when delivered at multiple centres can lead to improved failure free survival with similar levels of bladder (genitourinary) and bowel (gastrointestinal) side effects experienced by patients.

2.2. Secondary objectives

Secondary objectives of PIVOTALboost are to assess:

- Acute bladder and bowel toxicity of hypofractionated prostate radiotherapy at 18 weeks
- Late toxicity
- Quality of life
- Time to loco-regional recurrence, time to biochemical or clinical failure, metastatic relapse free survival, overall survival and prostate cancer specific survival; time to recommencement of androgen deprivation therapy
- Health economic endpoints.

2.3. Exploratory and translational objectives

PIVOTALboost will assess the usefulness of functional MRI imaging to select patients for different randomisation streams. Boost volumes (staging MRI scan), planning boost volumes and dose volume histograms will be analysed and compared with toxicity outcomes. In addition, and subject to successful funding applications the following sub-studies are proposed:

- Imaging sub-studies to explore the role of PSMA PET imaging for staging and boost volume outlining.

- Translational projects to include a genetic signature analysis to evaluate risk group stratification and collaboration with RAPPER project.

3. TRIAL DESIGN

PIVOTALboost is a multicentre randomised controlled phase III trial in patients with localised prostate cancer, with a 4-arm parallel design. Patients will be allocated to one of the following treatment arms:

- A: Prostate alone IMRT
- B: Prostate and pelvic IMRT
- C: Prostate IMRT and prostate boost.
- D: Prostate and pelvic IMRT and prostate boost.

This parallel group design will allow pair-wise comparisons of each of the experimental arms (B, C or D) with the control arm (A). Randomisation into arms C and D will depend on the boost volume identified by MRI (suitable for focal boost or not), availability of focal HDR or IMRT, and patient suitability for focal IMRT or HDR (see section 10 for further details). Treatment allocation will be by minimisation (with a random component) within each randomisation option (see section 10 and 13 for further details).

Box 1. Suitable focal boost volume

In summary, a **suitable focal boost** volume is defined as:

On the **pre-biopsy** staging multiparametric MRI (mpMRI) scan, a dominant intra-prostatic lesion (DIL) has:

- A score 3-5 lesion (clinical significant cancer is likely or highly likely to be present) according to the (PI-RADS (v.2) guidelines. Both T2 and DWI are important, and this depends on tumour location in the gland.
- DIL >5mm axial dimension – minimum (>10mm if patient is NCCN intermediate risk).
- Total DIL volume estimated to be <50% total prostate volume. If there are 2 or 3 DILs, add the individual volumes. Volumes can be estimated with measurement of dimension in 3 directions.

Patients with **post-biopsy MRI** won't be eligible for a focal boost, but can receive a whole gland boost if suitable for HDR.

Patients will be assessed weekly during RT, then at 6, 8, 12, 18 weeks; 6, 12, 18 and 24 months, then annually up to 10 years from the start of RT. RT side effects and patient reported outcomes will be assessed up to 5 years. Longer-term follow-up will include PSA levels (routine testing) and details of disease recurrence and deaths.

For certain time period/s during the COVID19 pandemic recruitment may be suspended, restricted or focussed to certain (otherwise eligible) patient groups (e.g. to those geographically close to treatment centres). Details of these changes to the eligible population will be circulated to all open centres and included in the Trial Master File.

4. STUDY ENDPOINTS

4.1. Primary endpoint

Failure-free survival (FFS), defined by the time from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence, distant metastases or death due to prostate cancer.

Biochemical (PSA) failure is defined following the RTOG-ASTRO Phoenix Consensus definition: an increase in serum PSA ≥2ng/ml greater than the post-treatment nadir.

In addition, it is recognised that after high dose radiotherapy a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years. In some cases the magnitude of the bounce is high enough for the patient to be incorrectly classified as a PSA failure. To prevent this, PSA failure before 24 months will require 3 consecutive rises in PSA (not less than 6 weeks apart) resulting in a clinical diagnosis of failure, or commencement of further treatment (e.g. ADT). After 24 months, the definition of PSA failure for patients receiving radiotherapy will revert to the Phoenix definition described above (i.e. nadir+2 ng/ml).

4.2. Secondary endpoints

- Time (from randomisation) to loco-regional recurrence (local or lymph node/pelvic recurrence);
- Time (from randomisation) to biochemical or clinical failure, defined by the time from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence or distant metastases
- Metastatic relapse free survival (time from randomisation to distant metastases or prostate cancer death);
- Overall survival and prostate cancer specific survival;
- Time to recommencement of androgen deprivation therapy;
- Adherence to dose constraints
- Acute bladder and bowel toxicity at 18 weeks;
- Late toxicity;
- Quality of life;
- Health economic endpoints.

Secondary outcome measures have been selected to comprehensively assess the treatment techniques whilst minimising as far as possible the burden of data collection for participating centres. Though COMET guidelines for localised prostate cancer are not yet available [65], we have taken into account recommendations from the International Consortium for Health Outcomes Measurement (ICHOM) [66

].

4.3. Exploratory endpoints

- Number of patients with no boost volume, boost volume and boost volume >50% identified on the staging MRI;
- Type of MRI sequence (T2W, DWI, DCE or other) and timing (pre-biopsy or post biopsy)

Subject to separate funding application are sub-study endpoints relating to PSMA PET CT staging scans and translational studies.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of participants

Original calculations required 1952 patients: 517 allocated to Arm A, 517 to Arm B, 459 to Arm C and 459 to Arm D with relative numbers between treatment groups 9:9:8:8. The allocation ratio will be monitored and adjusted during the trial to account for number of sites open, and what type of boost is available at each site.

Following closure of Arm B changes to the sample size requirements were made. Recruitment will now be

complete when 847 patients have been randomised to Arms A and C and 847 patients have been randomised to Arms A and D. Overall, the total recruitment across all four arms will be 2229 (see section 13 and appendix 4, for details).

5.2. Source of participants

Participants will be recruited from participating sites in the UK. Patients will be approached about participation in PIVOTALboost if they are considered (e.g. at multi-disciplinary team meetings) to be fit for radical radiotherapy and fulfil the eligibility criteria. International recruitment from quality assured sites outside the UK may be considered by the Trial Management Group subject to Sponsor and ethics approval and adequate funding.

ICR-CTSU encourages investigators to consider equality, diversity and inclusion when recruiting participants into its trials.

5.3. Inclusion criteria

1. Histologically confirmed, previously untreated, non-metastatic adenocarcinoma of the prostate using the Gleason scoring or grade group system (histological confirmation can be based on tissue taken at any time, but a re-biopsy should be considered if the biopsy is more than 12 months old).

2. PSA <50ng/ml prior to starting ADT.

3.1. NCCN localised high risk or locally advanced disease

- T3a, T3b or T4 N0M0 (clinical and/or MRI) and/or
- Grade group 4 or 5 (Gleason 8-10) and/or
- PSA >20;

or

3.2. NCCN intermediate risk disease

- T2b-c N0M0, and/or Grade group 2 or 3 (Gleason 7) and /or PSA 10-20 ng/ml

and

- DIL lesion >10mm on staging MRI

and

- One additional adverse feature, for example: Maximum tumour length (MTL) >6mm and/or ≥50% biopsy cores positive and/or >50% involvement measured in mm cancer length /total biopsy length.

4. Age ≥18 years.

5. Signed, written informed consent.

6. WHO performance status 0-2 (Appendix 1).

5.4. Exclusion criteria

1. Prior radiotherapy to the prostate or pelvis.
2. Prior radical prostatectomy.

   Prior ADT for > 6 months at randomisation. Radiotherapy should start within 6 months of starting ADT. *For patients receiving extended ADT to permit safe delay of radiotherapy as a result of the COVID19 pandemic, the duration of ADT must be less than 12 months prior to commencing radiotherapy.*

3. Adjuvant docetaxel chemotherapy.
4. Radiologically suspicious or pathologically confirmed lymph node involvement, as confirmed by radiological assessment (see section 8.1 screening assessments).

5. Evidence of metastatic disease, as confirmed by radiological assessment (see section 8.1 screening assessments).
6. Life expectancy <5 years.
7. Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts and would make pelvic node planning more difficult.
8. For patients having fiducials inserted: Anticoagulation therapy/ bleeding tendency making fiducial placement unsafe in the opinion of the clinician.
9. For patients being considered for randomisation options C2 and D2 only and are undergoing a planning MRI scan: Contraindication to undergo a MRI scan.
10. For undergoing HDR brachytherapy: long-term anticoagulation therapy which cannot be temporarily stopped, prostate surgery (TURP) with a significant tissue cavity, a history of recent deep vein thrombosis or pulmonary embolus, significant cardiovascular comorbidity, unfit for prolonged general anaesthetic.
11. Medical conditions likely to make radiotherapy inadvisable e.g. inflammatory bowel disease, significant urinary symptoms.
12. Previous malignancy within the (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival.
13. Any other contraindication to external beam radiotherapy to the pelvis.

5.5. Lifestyle guidelines

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

6. SCREENING

6.1. Screening log

, All participating sites will be required to keep a log of all participants who are considered fit for radical radiotherapy (following discussion at the MDT) and are potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Details of suitability for boost (if applicable)
- Trial ID (if applicable)

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

6.2. Procedure for obtaining informed consent

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

No protocol required assessments should be conducted until the PIVOTALboost consent form has been signed and dated by both the patient and the PI or delegated clinician, unless they are performed routinely as part of standard patient care.

Patients who consent to PIVOTALboost will be asked to consent to participate in the Patient Reported Outcomes (PRO) and future translational sub-studies. Patients should be made aware that participation in the sub-studies is entirely voluntary. Refusal to participate in the sub-studies will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

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

6.3. Participation in other research

Patients who fulfil the eligibility criteria will be given the opportunity to participate in PIVOTALboost even if they have participated in other research prior to recruitment. Participation in other research will be considered on a case-by-case basis by the Trial Management Group.

Participation in the ICR-CTSU study within a trial investigating electronic collection of patient reported outcomes, SPRUCE, is permitted.

7. RANDOMISATION

Patients must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by

emailing **randomisation-icrctsu@icr.ac.uk** to request a call back

09.00-17.00 (UK time) Monday to Friday

Randomisation should take place as close to the start of radiotherapy treatment as possible. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant and person randomising patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies;
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number
- Randomisation option , NCCN risk group (intermediate or high), If high risk, treatment with androgen receptor target agents e.g. Enzalutamide, Abiraterone, Darolutamide or Apalutamide (yes or no), boost volume identified at staging MRI (suitable for a focal boost or not) and, type of boost planned if allocated to arms C or D (whole gland HDR or focal HDR or focal IMRT). **Please note**- If there is no suitable volume for boost identified at the staging MRI and if a centre is only offering focal IMRT boost, then the patient is not eligible to enter the trial. However, if a centre offers both HDR (whole gland and focal) and focal IMRT and if there is no suitable volume for boost identified at the staging MRI, then the patient is eligible to enter the whole gland HDR- AC1D1 arm (please see the decision tree flowchart on page 28 of the protocol)

The site will be given the patient's unique randomisation number (Trial ID) and treatment allocation over the phone (see section 14.2).

ICR-CTSU will send written confirmation (via email) of trial entry to the data management contact at the recruiting centre.

PIVOTALboost arm B closed to recruitment in Q2 2022.

8. TRIAL ASSESSMENTS

8.1. Screening assessments

The following screening assessments should be conducted prior to randomisation

- Complete history.
- DRE and physical examination (only if clinically indicated).
- Assessment of performance status, using WHO scale (see Appendix 1).
- Assessment of fitness using the Adult Comorbidity Evaluation (ACE-27) scale and American Society of Anaesthesiologists (ASA) scale (see Trial Guidance Notes).
- Eligibility for A vs B, and A vs B vs C1 vs D1:
  Radiological assessment of prostate cancer. Ideally within 2 months and within a maximum of 12 months prior to randomisation and 6 months prior to starting ADT; this includes a mpMRI scan of the prostate and pelvis and at least one of the following: bone scan, WB MRI, MRI spine, Choline PET, PSMA PET. If patients are longer than 6 months on ADT because of the COVID-19 pandemic, the imaging needs to be performed in 6 months prior to starting ADT.

  PIVOTALboost arm B closed to recruitment in Q2 2022.

- Eligibility for A vs B vs C2 vs D2:
  Radiological assessment of prostate cancer. Ideally within 2 months and within a maximum of 12 months prior to randomisation and starting ADT; this includes a mpMRI scan of the prostate and pelvis and at least one of the following: bone scan, WB MRI, MRI spine, Choline PET, PSMA PET. If the patient is offered the boost randomisation arms (A vs B vs C2 vs D2) **a pre-biopsy mpMRI is mandatory.** If the pre-biopsy mpMRI has occurred more than 6 months prior to randomisation or starting ADT a repeat mpMRI is strongly recommended prior to treatment to exclude progressive disease in the interim. If patients are longer than 6 months on ADT because of the COVID-19 pandemic, the imaging needs to be performed in 6 months prior to starting ADT; a pre biopsy mpMRI remains mandatory. Please see definition of a suitable focal boost volume on page 16, Box 1.

  PIVOTALboost arm B closed to recruitment in Q2 2022.

- PSA test prior to the commencement of ADT (as per eligibility criteria should be <50ng/ml)
- Full blood count, Urea & Electrolytes. For patients affected by the COVID-19 pandemic, results taken prior to or at planning are acceptable.
- Baseline symptoms will be assessed using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 4 and RTOG bladder and bowel toxicity scoring (conducted within 4 weeks prior to randomisation).
- If the patient has consented to the PRO sub study, completion of the following questionnaires (within 4 weeks prior to randomisation).:
  - ALERT-B (Assessment of Late Effects of RadioTherapy - Bowel) screening tool.
  - Gastrointestinal Symptom Rating Scale (GSRS)
  - IIEF-5 Questionnaire (SHIM)
  - International Prostate Symptom Score (IPSS)
  - Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire

- EQ-5D

Where participating sites are taking part in the SPRUCE study (REC Ref: 21/WM/0223) PIVOTALboost participants should be approached about SPRUCE and enrolled following completion of the PIVOTALboost baseline booklet and randomisation into PIVOTALboost. All PIVOTALboost follow up QL questionnaires will be administered directly to participants by ICR-CTSU for patients participating in SPRUCE.

8.1.1. Staging multiparametric MRI scan

A minimum of T1W, T2W and one other functional sequence should be performed up 12 months prior to randomisation. All images should be acquired using a 1.5 Tesla (or higher) MRI scanner with a body coil. Whether the staging MRI has been done pre or post biopsy will be collected.

8.2. Pre-treatment assessments

The following assessments should be conducted within 14 days prior to or at RT planning:

- Assessment of pre-treatment symptoms (RTOG, CTCAE v4)
- PSA and testosterone (at least 2 months after starting ADT and prior to starting radiotherapy. For patients who have had multiple PSAs whilst on ADT, prior to starting radiotherapy, please record the one closest to the radiotherapy start date.
- For patients randomised to HDR, ECG and clotting required.

8.3. On-treatment assessments

- Acute toxicity assessment (RTOG, CTCAE v4) weekly during treatment
- IPSS (at the end of week 4 of treatment).

8.4. Post radiotherapy assessments

Any follow up visits may be done as a telephone consultation, at the discretion of the treating clinician.

8.4.1. 6, 8 and 12 weeks from first external beam radiotherapy fraction

- Acute toxicity assessment (RTOG, CTCAE v4)
- IPSS

8.4.2. 18 weeks from first external beam radiotherapy fraction

- Acute toxicity assessment (RTOG, CTCAE v 4)
- IPSS
- QL questionnaires (EPIC-26 & EQ-5D).

8.4.3. 6, 12, 18, 24, 36, 48 and 60 months (from first radiotherapy fraction)

- Late toxicity assessment (CTCAE v 4 and RTOG)
- QL questionnaires (EPIC-26, EQ-5D, ALERT-B, GSRS, IIEF). These will be sent to the patient's home address direct from ICR-CTSU, once patient status is ascertained.
- PSA
- NHS resource usage assessment.

8.4.4. Annually thereafter

Patients will not be required to undergo any trial specific investigations; however, data will be requested annually from standard follow up visits relating to:

- Assessment of disease status

- PSA
- Survival
- Second primary cancers
- NHS resource usage assessment.

These data items may also be obtained, with patient consent, through linkage to routine data sources e.g. to datasets held by the National Cancer Registration and Analysis Service (NCRAS).

8.5. Procedure at PSA failure or disease recurrence

At PSA failure or recurrence participants should be treated according to the local Principal Investigator's clinical judgement. It is recommended to observe PSA failure initially. If appropriate and / or the patient is considered for local salvage therapies, local control should be assessed by mpMRI imaging, PSMA PET and / or biopsies. Staging with bone scan, MRI and CT scan is recommended prior to re-commencing hormone therapy if either the PSA doubling time is <6 month and PSA >2ng/ml, or PSA >10-20ng/ml.

8.6. Discontinuation from study treatment

Participants may discontinue from study treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for withdrawal should be documented and may include:

- Disease recurrence or PSA failure
- Unacceptable toxicity
- Co-morbidities

Participants who discontinue treatment should continue to be followed up in accordance with the protocol.

8.7. Discontinuation from follow-up

If a patient withdraws from further follow-up a trial deviation form should be submitted to ICR-CTSU stating whether the patient has withdrawn consent for information to be sent to the ICR-CTSU or whether they simply no longer wish to attend trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

9. SCHEDULE OF ASSESSMENTS

Visit/Assessment	Screening (pre-randomisation)	Pre-treatment	External beam treatment week 1-4	Week 6, 8, 12	Week 18	6, 12, 18, 24, 36, 48, 60 months	Annually thereafter	PSA failure or disease recurrence
Histological confirmation of prostate cancer	X							
Complete history and physical examination (physical examination & DRE if clinically indicated)	X							
WHO PS, ASA score, ACE-27 score	X							
Radiological assessment (multi-parametric MRI scan, and one of the following: bone scan, WB MRI, MRI spine, Choline PET, PSMA PET	X[1]							
PSA	X	X[4]				X	X	X
FBC, U+E	X							
Testosterone		X[4]						
Clotting and ECG		X[2]						
Baseline signs & symptoms (RTOG, CTCAE v.4)	X	X						
Acute toxicity assessment (RTOG, CTCAE v.4)		X	X	X	X			
QL questionnaires – IPSS	X		X[3]	X	X			
QL questionnaires – EPIC & EQ-5D	X				X	X		
QL questionnaires – ALERT-B, GSRS, IIEF-5 (SHIM)	X					X		
Late toxicity assessment (RTOG, CTCAE v.4)						X		
Assessment of disease status						X	X	X

[1]Screening radiological assessment should take place ideally within 2 months and within a maximum of 12 months prior to randomisation AND no more than 6 months prior to starting ADT. For details how patients are screened and assessed during the COVID pandemic, please refer to section 8.1 and 8.2

[2]Only for patients randomised to HDR.

[3]IPSS questionnaire to be completed only at the end of week 4.

[4]at least 2 months after starting ADT and prior to starting radiotherapy. For patients who have had multiple PSAs whilst on ADT, prior to starting radiotherapy, please record the one closest to the radiotherapy start date.

10. TREATMENT

10.1. Randomisation options

Patients will be eligible for entry into one of the following randomisation options according to:

- boost volume (whether the tumour volume identified on the staging MRI is suitable for focal boost or not),
- suitability and availability of HDR (e.g. patient not suitable for HDR brachytherapy or any other clinical reason) and,
- type of focal boost (IMRT or HDR brachytherapy).
- Suitability and availability of focal IMRT boost.

In centres with no access to HDR or focal IMRT boost, all patients will enter randomisation option 1 (irrespective of having a suitable boost or not). Randomisation option 1 closed to recruitment on 1st April 2022

Randomisation Option 1 (Pelvic node randomisation): No suitable focal boost volume on the staging MRI* and not suitable for HDR brachytherapy:

Arm	Radiotherapy treatment area	
	Prostate dose	Pelvic node dose
A	60Gy/20#	
B	60Gy/20#	47Gy/20#

**this includes patients with post-biopsy MRI and patients with pre-biopsy MRI not fulfilling conditions for suitable boost*

Randomisation Option 2a (Pelvic node and whole gland boost): No suitable focal boost volume on the staging MRI* and suitable for HDR:

Arm	Radiotherapy treatment area		
	Prostate dose	Pelvic node dose	Whole gland HDR
A	60Gy/20#		
B**	*60Gy/20#*	*47Gy/20#*	
C1	37.5Gy/15#		15Gy/1#
D1	42Gy/20#	47Gy/20#	15Gy/1#

**this includes patients with post-biopsy MRI and patients with pre-biopsy MRI not fulfilling conditions for suitable boost.*

this also includes patients who have a suitable boost volume on MRI at a HDR centre where only **whole gland HDR is RTQA is approved.*

***Arm B closed to recruitment* in Q2 2022

Randomisation Option 2b (Pelvic node and focal boost randomisation): Suitable focal boost volume

Arm	Radiotherapy treatment area			
	Prostate dose	Pelvic node dose	Focal Boost dose	
			Focal IMRT**	Focal HDR**
A	60Gy/20#			
B***	*60Gy/20#*	*47Gy/20#*		
C2	60Gy/20#		67Gy/20#	
C2	37.5Gy/15#			15Gy/1# *(whole prostate)* 19Gy/1# *(tumour boost dose)*
D2	60Gy/20#	47Gy/20#	67Gy/20#	

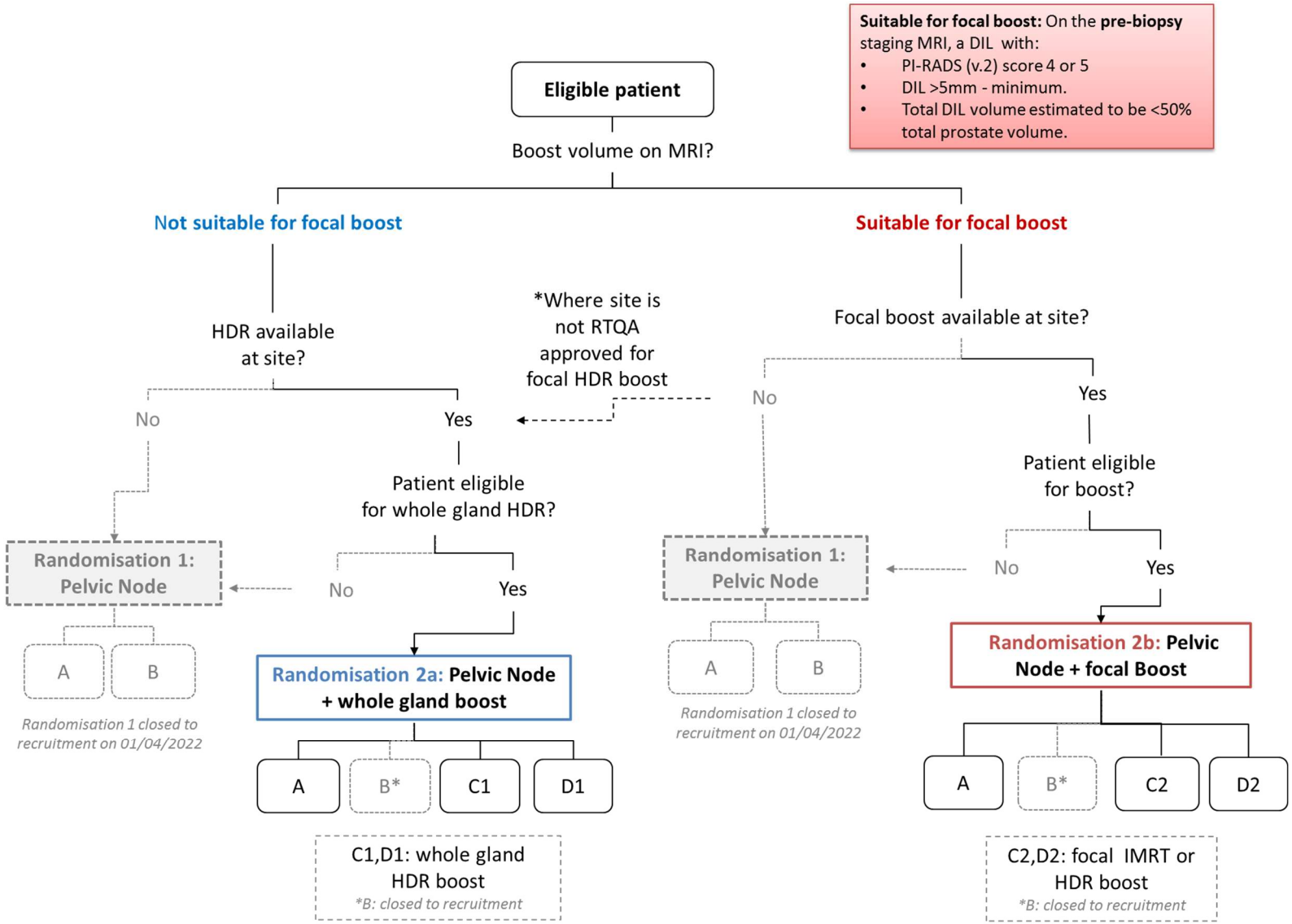
D2	42Gy/20#	47Gy/20#		15Gy/1# (whole prostate) 19Gy/1# (tumour boost dose)

*** use of focal HDR or focal boost IMRT determined for each patient prior to randomisation.*

See figure 1 (next page) for the decision algorithm to determine what randomisation option corresponds to each patient.

*** *Arm B closed to recruitment* in Q2 2022

Figure 1. Decision tree algorithm to allocate a patient into the appropriate randomisation option



10.2. Treatment timelines

Radiotherapy treatment should commence ideally within 8 weeks following randomisation and within 6 months of starting hormone therapy (see 10.3). Delays to radiotherapy (with extended ADT) due to COVID19 clinical management strategies or other reasonable causes, are permitted and should be documented (details of how to do this are given in the Trial Guidance notes).

10.3. Hormone therapy

Hormone therapy (ADT) will typically commence after completion of the staging investigations. If choline PET CT scans or PSMA PET CT scans are used for assessment, these should be arranged prior to commencement of ADT.

Patients in the intermediate risk group will receive 6 -12 months of ADT, and patients in the high risk group may receive 2-3 years of ADT; patients undergo planning ideally after 2-4 months (maximum 6) of neo-adjuvant ADT and commence radiotherapy at a maximum of 6 months.

For patients affected by the COVID-19 pandemic, there is no restriction on length of time patients can be on ADT prior to randomisation, however the duration of ADT must be less than 12 months prior to radiotherapy starting. Other reasonable causes resulting in delay to the start of radiotherapy to up to 12 months from starting ADT, are also permitted but should be discussed in the first instance with the PIVOTALboost Trial Manager at the ICR-CTSU.

LHRH antagonists or LHRH agonists with short-term androgen blockade are standard of care; bicalutamide daily or cyproterone acetate for 1 to 2 weeks is given initially to prevent possible 'tumour flare' phenomenon. ADT is part of routine care; therefore drugs will be provided by standard local arrangements.

In addition to ADT therapy which is mandated for PIVOTALboost, patients classified as high risk at randomisation can receive androgen receptor target agents (e.g. abiraterone, apalutamide, enzalutamide, or darolutamide) where this is part of local routine care. Treatment should be prescribed as per local practice and drugs should be provided by standard local arrangements.

Bicalutamide monotherapy can be used if patients have significant cardiovascular co-morbidity or wish to maintain sexually active. Troublesome gynaecomastia or breast pain should be treated with radiotherapy to the breast tissue or tamoxifen may be given.

10.4. Image guided radiotherapy

Daily imaging and online correction (kV, CBCT, CT on rails, tomotherapy or MR-guided RT) are mandatory for all arms. Fiducial markers or soft tissue imaging can be used for IGRT. For fiducial marker insertion a minimum of three fiducial markers are inserted into the prostate as per standard care. Markers should ideally be separated 20mm apart. This can be undertaken before the HDR implant if appropriate, depending on the type of marker, an appropriate time prior to external beam planning should be scheduled.

10.5. Radiotherapy planning and delivery

All participants will be planned to receive 15 or 20 fractions of radiotherapy delivered daily. External beam radiotherapy planning will ideally be performed during month 2-4 (maximum 6) of ADT and radiotherapy treatment will commence within 6 months of ADT. Delays to radiotherapy (with extended ADT) due to COVID19 clinical management strategies are permitted and should be documented (details of how to do this are given in the Trial Guidance Notes).

If participants are allocated to a HDR implant, the HDR implant will be scheduled 14-21 days before starting EBRT (EBRT will consist of 15 fractions for arm C1 or C2 and 20 fractions for arm D1 or D2). EBRT planning will be carried out before or after the HDR implant. EBRT is started two to three weeks after the HDR (day 0). However, if it is standard protocol in the unit, HDR implant can be scheduled 2-3 weeks after completion of EBRT subject to RTQA approval. The first acute toxicity assessment occurs during week 1 of EBRT.

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

10.6. EBRT treatment scheduling and gaps

Treatment can start on any day of the week other than a Monday and is given daily, 5 fractions per week; overall duration should be 28-33 days. A gap of up to 5 days is acceptable in the event of machine service, breakdown or re-planning but further delays should be avoided. Patients should not be started prior to a bank holiday period if this would prolong treatment for more than 7 days. If there is a delay for more than 5 days, please add details including the length of overall treatment time and the reason (radiotherapy toxicity, intercurrent illness, technical issues related to radiotherapy delivery, technical issues related to patient factors e.g. re-planning) on the CRF.

10.7. Supportive care guidelines

In the event of patient catheterisation during the course of treatment it is expected that the participant will continue and complete radiotherapy in accordance with their allocated treatment group. As the bladder requires filling prior to treatment delivery, the catheter must be clamped or a flip-valve is used.

Participants' symptoms should be managed according to local practice, although the following are suggestions for patient care:

- Slow flow and frequency: tamsulosin or alfuzosin are often helpful.
- Dysuria/Frequency: Check for evidence of infection and treat if present with appropriate antibiotics, anticholinergics (eg oxybutynin, tolterodine, solifenacin), NSAIDs, analgesics.
- Diarrhoea: Loperamide or opioid
- Proctitis: suppository +/- local anaesthetics (e.g. sheriproct, proctosedyl)

10.8. Concomitant therapy

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication), must be recorded in the patient's notes, and if applicable also on the appropriate pages of the CRF.

10.9. Non-permissible medications/therapies

Non-permissible concurrent medications/therapies include:

- Adjuvant chemotherapy is not considered standard of care in this patient population as per NHS guidance.

11. RADIOTHERAPY QUALITY ASSURANCE (QA)

A comprehensive QA programme for the PIVOTALboost trial will be designed and implemented by the NCRI Radiotherapy Clinical Trials Quality Assurance (NCRI RTTQA) group. This will include pre-trial and on-trial components and full details are provided in the Radiotherapy Planning and Delivery Guidelines document.

11.1. Pre-trial quality assurance programme

The following will need to be completed by participating centres prior to site activation.

1. Facility questionnaire
2. Benchmark outlining cases
3. Benchmark planning cases
4. MRI QA questionnaire

11.2. On-trial quality assurance programme

On-trial QA may be streamlined with previous pelvic trials, to be advised by the RTQA team on a site-by-site basis, and includes:

1. Prospective and/or retrospective case reviews
2. Collection of staging MRI imaging
3. Review of HDR implant parameters (see RTQA document for details)
4. Dosimetry site visit (subject to prior RTQA dosimetry accreditation)
5. DICOM data collection for all patients

12. SAFETY REPORTING

12.1. Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a research procedure; events do not necessarily have a causal relationship with the procedure.

12.2. Serious adverse event (SAE)

An SAE is any untoward medical occurrence that occurs after the commencement of study treatment (including fiducial marker/HDR implant) and within 30 days of the last treatment administration and:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.
- Additionally, RTOG Grade≥3 acute or late radiation side effects i.e. related to study treatment, occurring within 5 years after radiotherapy treatment will be regarded as an SAE.

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

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

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

12.3. Serious Adverse Reaction (SAR)

A serious adverse reaction is an SAE that is suspected as having a causal relationship to the research procedure, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table). Definitions of causality:

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

12.4. Related Unexpected Serious Adverse Event

An adverse event that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see section 12.7)

12.5. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE. All AEs must be reported on the relevant toxicity, sign or symptom eCRF.

The severity of AEs should be graded according to CTCAE v4 and RTOG criteria. For each toxicity/sign/symptom, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

12.6. Reporting Serious Adverse Events to ICR-CTSU

Any SAE (except those in section 12.7) that occurs after the commencement of study treatment (including fiducial marker/HDR implant) and up to 30 days following the last administration of study treatment must be reported and RTOG grade ≥3 acute or late radiation side effects occurring within 5 years after radiotherapy treatment should be reported to ICR-CTSU as described below.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event by completing the PIVOTALboost SAE form. The completed SAE form should be sent by email to **sae-icr@icr.ac.uk**

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

All SAE forms must be completed signed and dated by the Principal Investigator or designated representative.

The Site SAE log should be completed and the SAE form filed in the Site Investigator File.

12.7. Expected Adverse Events

The following adverse events are considered expected if grade ≤3 and are exempt from expedited reporting to ICR-CTSU but should be reported using the appropriate CRF.

- Haematuria
- Dysuria/frequency
- Nausea/vomiting
- Prostate spasms or pain
- Diarrhoea
- Abdominal pain
- Urinary tract infection
- Urinary/clot retention
- Erectile Dysfunction (≤grade 3)

12.8. Review of Serious Adverse Events

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

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see section 13.7).

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

12.9. Expedited Reporting of Related Unexpected SAEs

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

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

12.10. Follow up of Serious Adverse Events

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

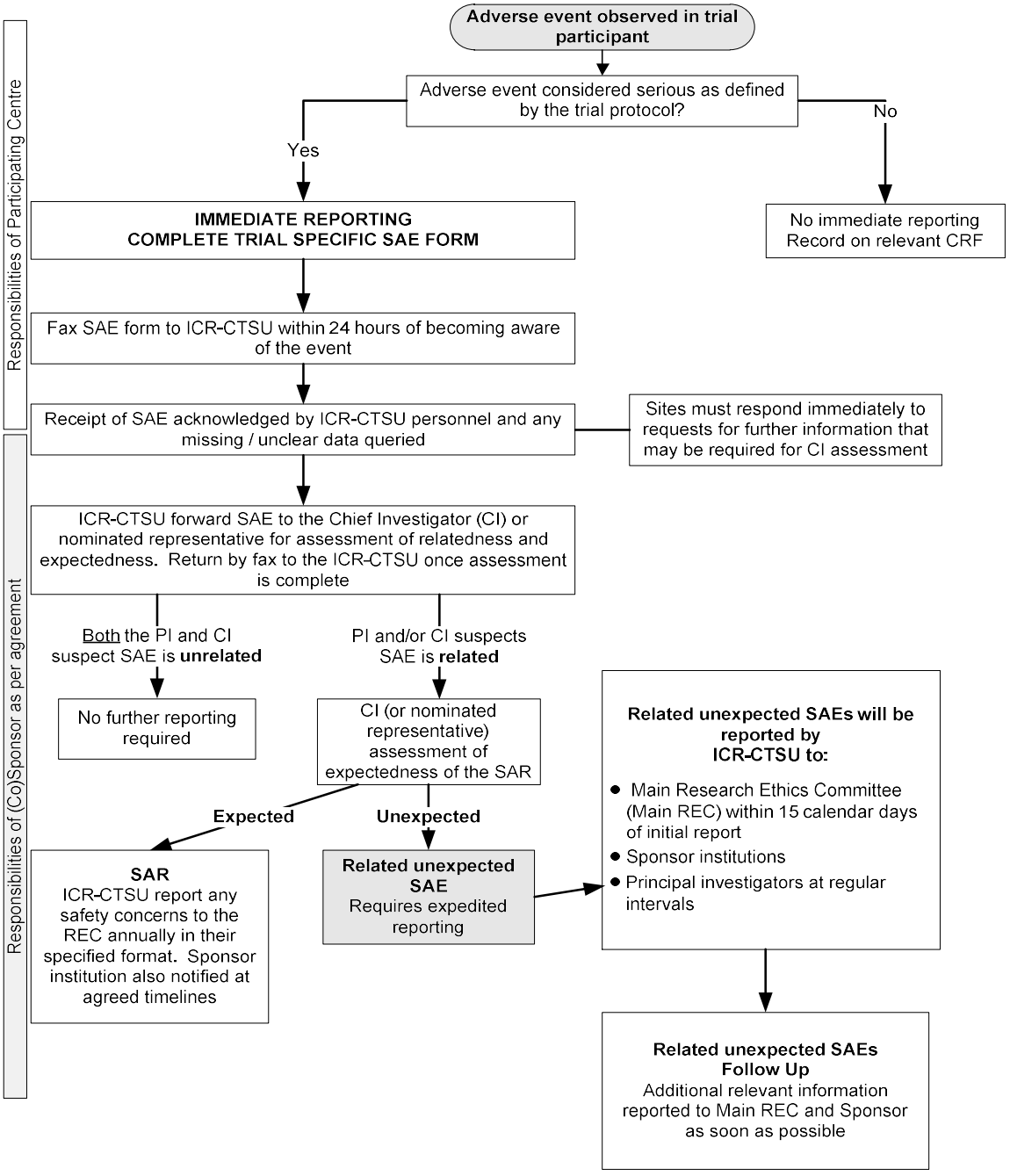
12.11. Annual reporting of safety considerations

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor, if applicable, the collaborative group in each participating country at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

12.12. Reporting pregnancies

If any trial participants' partner becomes pregnant whilst the trial participant is receiving trial treatment or up to 90 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 2: Flow diagram for SAE reporting and action following report



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

13. STATISTICAL CONSIDERATIONS

13.1. Statistical design and sample size

It is assumed that Failure Free Survival (FFS) at 5 years in the control arm (A) will be 80%. This estimate is based on unpublished data from high risk patients in CHHiP, which showed 5-year biochemical progression free rates of 84.4% [2]. Results from the M0 control cohort of the STAMPEDE trial [67] (a higher risk group than planned for PIVOTALboost), i.e. a FFS of 75% at 5 years in a subgroup of M0 N0 patients with planned RT (n=121) have also been considered.

Initial sample size calculation:
The study was powered to detect a 7% difference in 5-year FFS for each experimental arm compared to A (B, C or D) from 80% to 87%. This difference corresponds to a hazard ratio (HR) of 0.624 for each experimental arm as compared to A. This HR was chosen as sufficient to warrant a change in practice in the knowledge that more extreme effects have been reported in similar settings e.g. HR=0.47 in the ASCENDE trial [68]. In order to adjust for multiplicity [69] the 2-sided significance level for each comparison is set to 0.017 (0.05/3). As it was acknowledged that it could be easier to recruit more patients in the A vs. B comparison (see section 13.2 below), we allowed for more patients in the A vs. B comparison:

- to achieve 85% power to detect a 7% difference in 5 year FFS between A and B, 517 patients per group are needed (502 per group to observe 217 events, plus 3% for loss to follow-up).
- to achieve 80% power to detect a 7% difference in 5 year FFS between A and C (or A vs. D), a total of 918 patients are needed (a total of 892 to observe 193 events, plus 3% for loss to follow-up). The overall sample size for A vs C (A vs D) remains the same when the allocation ratio A:C (A:D) is 2:3 or 1:1.

Treatment allocation will be by minimisation. For the 2 way randomisation (A vs B) the ratio will be 1:1. Treatment allocation in the 4 arm randomisation was based on using a 2:2:3:3 ratio initially as it was expected fewer sites will be able to offer boost treatment groups (C and D). The plan was to closely monitor recruitment and adjust the allocation ratio in the 4 arm randomisation to 1:1:1:1 to ensure 9:9:8:8 (517:517:459:459) final relative numbers. The overall sample size was therefore **1952** patients.

Updated sample size calculation:
Recruitment to the 4 arm randomisation was slower than expected and the switch to 1:1:1:1 was not made. This has meant that the sharing of arm A patients for the B comparisons compared to the C and D comparisons is less than expected (from assumed 90% (459:517) it is around 20% (144 shared A's out of 763) by February 2022). This means that recruitment into A vs C vs D needs to continue beyond arm B completing target recruitment.

The sample size for A vs C and A vs D has been revisited under this scenario, keeping the same sample size assumptions, but allowing for the fact that recruitment would not be complete in 4.5 years. With the recruitment period extended by 2 years to 6.5 years and the pattern of staggered recruitment to date used the following is true:

- to achieve 80% power to detect a HR of 0.624 (translating to a 7% difference in 5 year FFS between A and C (or A vs. D), assuming 5 year event free rate of 80% in arm) and retaining a conservative alpha of 0.017, 192 events are required (under 1:1 allocation). This number of events would be observed if 847 patients, (822 plus 3% for loss to follow-up) are recruited over 6.5 years and followed up for 5 years. The overall sample size for A vs C (A vs D) remains the same when the allocation ratio A:C (A:D) is 2:3 or 1:1.

Once arm B has completed target recruitment, the trial will recruit patients to arms A, C and D in the ratio 1:1:1. Recruitment will be complete when 847 patients have been randomised to Arms A and C and 847 patients have been randomised to Arms A and D. Overall, the total recruitment across all four arms will be 2229 (see appendix 4, for details). The revised recruitment target to reach the pairwise comparison sample sizes was initially based on recruitment up to Feb 2022 (recruitment target estimate was 2195) and the current recruitment target is based on numbers when arm B closed and includes actual numbers of shared As and the actual total recruitment to the A vs B.

The sample size calculation is based on the log-rank test using the 'artsurv' command in STATA, incorporating 4.5 years of staggered recruitment and a minimum of 5 years of follow-up.

13.2. Treatment Allocation

During the design of the study, it was acknowledged that recruitment and allocation into the different treatment arms could evolve during the trial, given the number of sites open, and the type of boost available at each site. We ran simulations to explore how this would affect time to complete overall recruitment. Following this, we decided to start the trial using an allocation ratio of 2:2:3:3, so it favours the boost groups C or D in a period where it is expected less sites would be offering the boost treatment groups. The allocation ratio may be adjusted during the trial to ensure 9:9:8:8 final relative numbers. Recruitment will be closely monitored and allocation ratios will be monitored annually. On completing recruitment to AvB comparison, the treatment allocation will be 1:1:1 A:C:D.

Full details on the allocation ratio and simulation study will be provided in the Statistical analysis Plan.

Treatment allocation is by minimisation with a random element; balancing factors will be:

- Randomisation Option 1: centre, NCCN risk group (intermediate, high) and suitable volume for focal boost (yes/no). Randomisation option 1 closed to recruitment on 1st April 2022

- Randomisation Option 2a/2b: centre, NCCN risk group (intermediate, high), If high risk, treatment with androgen receptor target agents (yes/no), suitable boost volume for focal boost (yes/no), type of boost (whole gland HDR, focal HDR or focal IMRT). NCCN risk group and androgen receptor target agents will be combined to include possible categories (i.e. intermediate risk, high risk without androgen receptor target agents and high risk with androgen receptor target agents). Similarly suitable boost volume for focal boost and boost options will be combined (if not suitable for focal boost the option focal boost type is not possible).

13.3. Primary endpoint definition

Failure-free survival (FFS), defined by the time from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence, distant metastases or death due to prostate cancer.

Biochemical (PSA) failure is defined following the RTOG-ASTRO Phoenix Consensus definition: an increase in serum PSA ≥2ng/ml greater than the post-treatment nadir.

In addition, it is recognised that after high dose radiotherapy a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years. In some cases the magnitude of the bounce is high enough for the patient to be incorrectly classified as a PSA failure. To prevent this, PSA failure before 24 months

will require 3 consecutive rises in PSA (not less than 6 weeks apart) resulting in a clinical diagnosis of failure, or commencement of further treatment (e.g. ADT). After 24 months, the definition of PSA failure for patients receiving radiotherapy will revert to the Phoenix definition described above (i.e. nadir+2 ng/ml).

13.4. Secondary endpoint definitions

- Time to loco-regional recurrence (local or lymph node/pelvic recurrence) measured from randomisation; recurrence will be confirmed by radiological evaluation and/or pathological confirmation.
- Time to biochemical or clinical failure, defined by the time from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence or distant metastases, measured from randomisation.
- Metastatic relapse free survival (time from randomisation to distant metastases or prostate cancer death); distant metastases will be confirmed by radiological evaluation and/or pathological confirmation. Site of distant recurrences will be recorded.
- Overall survival; this will include deaths from any cause. Time will be measured from randomisation.
- Prostate cancer specific survival; this will include deaths from prostate cancer only. In general, patients with death recorded as prostate cancer related with no prior recurrence of the disease will be reviewed on a case by case basis. Patients with an unknown cause of death will be assumed to have died from prostate cancer if they have a previously reported progression, otherwise they will be assumed to have died from other causes. Patients dying from other causes will be censored at date of death. Time will be measured from randomisation.
- Time to recommencement of androgen deprivation therapy; date on which anti-androgens or LHRH analogues/antagonists are started or date on which orchidectomy occurs.
- Acute bladder and bowel toxicity at 18 weeks; will be measured using the RTOG and NCI CTCAE scoring systems.
- Acute and late toxicity; will be measured using the RTOG and NCI CTCAE scoring systems.
- Quality of life endpoints (see section 20).
- Health economic endpoints (see section 20).

13.5. Exploratory endpoints

We will record the number of patients with boost volumes on staging fMRI scans, and if the patient is not included in the focal boost randomisation (patient related, tumour / imaging characteristics, resources and availability). The data will help to evaluate the benefit and rule of staging with functional MRI imaging.

13.6. Analysis plan

The principal analysis will occur after a median follow-up of five years or the target numbers of events have been reached, whichever occurs first. For the A vs B comparison the number events required is 217 and for the A vs C comparison (and A vs D) the total number of events required is 193to detect a difference of 7% with 85% (A vs B) or 80% (A vs C, D) power is required. Should the analysis not be event driven, the timing will be subject to approval from the IDMC. . Since arm B has closed to recruitment before the C and D arms, the primary analysis for the A vs B comparison will be undertaken before the boost question (A vs C and A vs D) with permission form the IDMC.

The primary comparisons will compare each of the experimental arms to the standard (i.e. A vs B, A vs C and A vs D) and will include all randomised patients (intention-to-treat analysis). Only contemporaneously randomised controls will be used for the A vs C and A vs D comparisons. As secondary analyses, comparisons between experimental arms will also be reported, as well as the overall impact of prostate IMRT vs prostate and pelvis IMRT (A+C vs B+D) and no prostate boost vs prostate boost (A+B vs C+D). Exploratory analysis of the heterogeneity of treatment effect across whole gland or focal boosts, and type of focal boost (IMRT or HDR) will be performed.

All treatment effects will be presented with 2-sided 95% confidence intervals. Adjustment will be made for multiple testing as appropriate. Time to event endpoints will be summarised presenting estimated Kaplan-Meier curves (by treatment); the time point of primary interest is 5 years from randomisation, which will be presented with 95% CI for each treatment arm. Treatment effects will be estimated and tested for significance by the Cox proportional hazards model, adjusting by stratification factors. Adjusted models will include the duration of ADT prior to starting radiotherapy (as a result of COVID19 related delays to radiotherapy starting). Further models adjusting by other important known prognostic factors will also be fitted. Methods to account for non-proportionality will be used if appropriate. Acute and late side effects will be summarised as frequencies and percentages at each time point. Acute toxicity will also be summarised as worst toxicity reported during radiotherapy. The proportion experiencing grade≥2 side effects will be presented; comparisons between treatment groups will be tested using chi-squared or Fishers exact tests. Logistic regression models will be used to estimate treatment differences (odds ratios). Analysis of QL and health economic endpoints are further detailed in Section 20.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures. The Statistical Analysis Plan will include a section to detail how data impacted by strategies introduced to mitigate risks relating to the COVID19 pandemic will be handled.

Any quality of life data collected from PIVOTALboost participants within the SPRUCE study will be shared with PIVOTALboost for analysis.

13.7. Interim analyses and stopping rules

Adherence to dose volume constraints will be checked after 30 patients are recruited to each experimental arm to ensure treatment can be delivered within safe constraints. Adherence to treatment will be monitored closely during recruitment: in particular any delays or interruptions of more than 5 days of treatment will be escalated to the Trial Management Group.

The IDMC will review emerging safety and efficacy data at regular intervals (at least annually).

Once 119 patients have been recruited to each of the experimental arms (B, C, and D) and completed their week 18 toxicity assessment an interim safety analysis will be conducted to rule out 30% (or more) patients with RTOG grade 2 or worse bladder or bowel complications. The figure has been estimated assuming an expected rate of 20% in the control group (inferred from data for all patients in the PIVOTAL study) and powered (80% power, 0.05 one-sided α) with a one-stage A'Hern design. If 27 or more patients out of 119 in one group developed bladder or bowel complications of grade 2 or more at 18 weeks, consideration will be given to modifying the trial design by dropping the treatment arm. As the recruitment pattern for arm B is different to arms C and D this analysis will be carried out as the data for each of the experimental arms matures.

No formal early stopping rule for futility or efficacy for the primary endpoint (FFS) has been planned.

14. TRIAL MANAGEMENT

14.1. Trial Management Group (TMG)

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

14.2. Trial Steering Committee (TSC)

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

14.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be instigated to monitor the progress of the trial and will comprise a Chairperson and at least two further members with clinical or statistical expertise (at least one member must be a statistician. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

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

The IDMC reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

15. RESEARCH GOVERNANCE

15.1. Sponsor responsibilities

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

15.2. Participating site responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and individual participating site.

16. TRIAL ADMINISTRATION & LOGISTICS

16.1. Site activation

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

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

16.2. Investigator training

Each centre will complete the comprehensive pre-trial section of the quality assurance programme prior to commencing recruitment, as detailed in section 11. In addition to this, prior to trial initiation, a practical workshop will be held to educate Principal Investigators, radiographers and physicists in adaptive radiotherapy techniques. The quality assurance programme will continue throughout the trial, with investigator training as required.

16.3. Data acquisition

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

16.4. Central data monitoring

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

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

16.5. On-site monitoring

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

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

16.6. Completion of the study and definition of study end date

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

16.7. Archiving

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

17. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

17.1. Trial approvals

This trial has been formally assessed for risk by ICR-CTSU.

The trial has received ethical approval from a research ethics committee for multi-centre trials and global R&D approval via the Health Research Authority (HRA). Before entering patients, the Principal

Investigator at each site is responsible for submitting Site Specific Information and gaining local Research and Development approval of this protocol.

17.2. Trial conduct

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

17.3. Informed consent

Patients should be asked to sign the current main REC approved PIVOTALboost consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a delegated clinician. A signature log of delegated responsibilities, listing the designated clinicians and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current main REC approved PIVOTALboost patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

17.4. Patient confidentiality

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

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

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

17.5. Data Protection Act (DPA)

ICR-CTSU will comply with all aspects of the DPA 1998. Any requests from participants for access to their data held at ICR-CTSU will be referred to the Data Protection Officer at the ICR.

17.6. Liability

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements. Inclusion of private patients will be subject to the site ensuring appropriate insurance and indemnity arrangements are in place.

18. FINANCIAL MATTERS

This trial is investigator designed and led and has been approved by the Clinical Research Committee of Cancer Research UK.

ICR has received funding from Cancer Research UK for the central coordination of the trial. In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio. Research Network resources should therefore be made available for the trial to cover UK specific research costs.

19. PUBLICATION POLICY

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

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

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

20. ASSOCIATED STUDIES

20.1. Health Economics

An economic evaluation will be integrated into the design of the trial. This will be supplemented with decision modelling approaches as the benefits of intervention are likely to extend beyond the duration of the trial.

In order to assess the impact of pelvic node radiotherapy, HDR brachytherapy (accounting for pre-operative assessment, anaesthetic time, theatre staff time, medical and physics time and additional imaging with CT and MRI if appropriate) and focal boost IMRT (including fiducial marker placement, MRI planning scan) on daily image guided RT delivery, data relating to treatment planning – including clinician time during outlining and the physics time required to generate plans for each treatment group will be collected. This detailed data collection will take place for a subset of patients/centres.
A cost-utility analysis is planned, estimated using quality-adjusted life-years (QALYs). The analysis will be performed from a NHS and personal social services cost perspective. A health utility tool (EQ5D) will be included in the PRO assessment booklets. Resource use data to be collected alongside the clinical trial will include those relating to the treatment and all aspects of health care in- and outside of the treating centre. Health resources will be valued using nationally available NHS cost data. Regression methods will be used to account for missing trial data and censoring. Results will be presented as mean costs, mean QALYs along with 95% confidence intervals, and the probability that the intervention is cost-effective at different levels of willingness to pay for a QALY gained. Sensitivity analysis will test whether the results are robust to methodological assumptions.

Analysis of health economic data will be undertaken after or in parallel with the primary analysis.

20.2. Quality of Life

In the PRO sub study, quality of life (QL) will be evaluated using the following questionnaires: ALERT-B (Assessment of Late Effects of RadioTherapy - Bowel) screening tool, Gastrointestinal Symptom Rating Scale (GSRS), IIEF-5 Questionnaire, International Prostate Symptom Score (IPSS), Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire.

The ALERT-B questionnaire [1] is a 3 item validated screening tool to detect chronic gastrointestinal symptoms after pelvic radiotherapy in cancer survivors. These symptoms have a significant effect on quality of life. The questionnaire will identify any symptoms that require further discussion with the patient or referral. The GSRS questionnaire [2] (15 items) will be used alongside the ALERT-B questionnaire in order to assess gastrointestinal symptoms after pelvic radiotherapy.

The IIEF-5 questionnaire [3] is a validated diagnostic tool for diagnosing erectile dysfunction and will be used to monitor patients in this study.

The IPSS questionnaire [4] is a validated diagnostic tool (7 items) and will be used to assess urinary and bowel incontinence.

The EPIC questionnaire [5] (in its version with 26 items) was selected as it best represents typical symptoms after radiotherapy in prostate cancer patients. The EPIC domains for urinary incontinence, urinary irritative/obstructive, bowel and sexual have been advocated within the standard set of patient reported outcomes for patients with localised prostate cancer by ICHOM65. The EPIC questionnaire was also introduced in the CHHIP trial and has been used to analyse the above domains.

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

The QL study will be optional for trial participants; however the aim will be to include as many participants as possible to allow full determination of QALYS by treatment arm and to support exploratory analyses by boost technique. QL questionnaires will be completed at baseline, and then (from the start of RT) at 12 and 18 weeks, at 6, 12, 18 and 24 months, and then annually up to 5 years. Given the size of the study, the patient population (localised disease, generally good outcomes) and the use of focused questionnaires, the introduction of web-based data capture direct from participants will be explored. This may provide opportunities for related trial methodology research e.g. comparison of response rates to paper based and web based completion.

An analysis plan will be developed in consultation with the TMG with key endpoints for each questionnaire. Standard algorithms will be used to derive scores and handle missing data in QL questionnaires. Changes from baseline at each time point will be compared within groups as well as between treatment groups (by means of ordinal logistic regressions or ANCOVA models as reported in Wilkins *et al.*17). Analyses to account for the longitudinal nature of the data may be used.

Participation in the ICR-CTSU study within a trial investigating electronic collection of patient reported outcomes, SPRUCE, is permitted.

Quality of Life study references:

1) Taylor S, Byrne A, Adams R, Turner J, Hanna L, Staffurth J, Farnell D, Sivell S, Nelson A, Green J. The Three-item ALERT-B Questionnaire Provides a Validated Screening Tool to Detect Chronic Gastrointestinal Symptoms after Pelvic Radiotherapy in Cancer Survivors. Clin Oncol (R Coll Radiol). 2016 Oct;28(10):e139-47.
2) Svedlund J, Sjödin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129–34.
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20.3. Translational studies

Collection of diagnostic biopsy material to analyse the impact of genetic/genomic signature profiling, scores derived from digital pathology and prediction of response to dose escalation and risk of biochemical relapse, local, regional or metastatic recurrence depending on the signature profiles/scores. As this stage, patients will be asked to provided consent to provide diagnostic samples. Collection will only proceed should suitable funding be secured.

20.4. Additional studies

Subject to funding, several trial related topics will be explored. The list is not limited and additional projects might be added in due course.

1. Prospective evaluation of PET scanning (with different tracers) to evaluate the sensitivity and specificity in a randomised trial.
2. Evaluation of a hypoxic sensitiser as an additional trial arm.
3. Evaluation of new hormone therapy drugs as an additional arm.

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A1. WHO performance status

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

A2. GLOSSARY

ADT	Androgen deprivation therapy
AE	Adverse Event
CBCT	Cone beam CT
CI	Chief Investigator
CI	Confidence interval
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DCF	Data Capture Form
DIL	dominant intraprostatic lesion
DVH	Dose Volume Histogram
DW-MRI	Diffusion-weighted magnetic resonance imaging
EBRT	External beam radiotherapy
f	Fraction
FBC	Full Blood Count
FFS	Failure free survival
GI	Gastrointestinal
GTV	Gross tumour volume
GU	Genitourinary
Gy	Gray
HDR	High dose rate brachytherapy
HR	Hazard ratio
IBDQ	Inflammatory Bowel Disease Questionnaire
ICR	The Institute of Cancer Research
ICR-CTSU	The Institute of Cancer Research Clinical Trials and Statistics Unit
IDMC	Independent Data Monitoring Committee
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
MDT	Multi-disciplinary team
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NCRI RTTQA	NCRI Radiotherapy Clinical Trials Quality Assurance group
NICE	National Institute for Health and Clinical Excellence
PI	Principal Investigator
PI-RADS	Prostate Imaging—Reporting and Data System
PIS	Patient Information Sheet
PRO	Patient Reported Outcomes
PSA	Prostate specific antigen
PSMA-PET	Prostate-specific membrane antigen - positron emission tomography
PTV	Planning target volume
QA	Quality assurance
R&D	Research and Development
REC	Research Ethics Committee
RMH	Royal Marsden Hospital
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
WB MRI	Whole-body magnetic resonance imaging
WHO	World Health Organisation

A3. RTOG Toxicity Scales

Instructions

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused death of the patient.
4. An accurate baseline prior to start of therapy is necessary.

Definitions:

Diarrhoea is defined as a clinical syndrome characterised by frequent loose bowel movements without associated rectal irritation (tenesmus)

Proctitis is defined as a clinical syndrome characterised by rectal irritation or urgency (tenesmus), presence of mucous or blood in the stool and, in some patients, with frequent, sometimes loose bowel movements.

Cystitis is defined as a syndrome characterised by irritative bladder symptoms such as frequency, dysuria and nocturia. Haematuria may or may not be a part of the clinical picture of cystitis.

Acute Toxicity [To be used from baseline to 18 week follow up visit]:

Bladder changes cystitis/frequency:
Grade 0: No symptoms
Grade 1: Frequency of urination or nocturia twice pre-treatment habit/dysuria, urgency not requiring medication.
Grade 2: Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic.
Grade 3: Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/without clot passage.
Grade 4: Haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.
Grade 5: Death directly due to radiation morbidity.

Bowel changes:
Grade 0: No symptoms
Grade 1: Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics.
Grade 2: Diarrhoea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal abdominal pain requiring analgesics.
Grade 3: Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops).
Grade 4: Acute or subacute obstruction, fistula or perforation/GI bleeding requiring transfusion/abdominal pain or tenesmus requiring tube

Late Toxicity [To be used from 6 month follow up visit onwards]:

Grade 0: No symptoms
Grade 1: Minor symptoms requiring no treatment

Grade 2: Symptoms responding to a simple outpatient management, lifestyle (performance status not affected)
Grade 3: Distressing symptoms altering patient's lifestyle (performance status). Hospitalisation for diagnosis or minor surgical intervention (such as urethral dilatation) may be required.
Grade 4: Major surgical intervention (such as laparotomy, colostomy, and cystectomy) or prolonged hospitalisation required.
Grade 5: Fatal complications

A4. Sample size details for updated sample size

Overall sample size and extra number of patients needed.

	Initial sample size
Initial recruitment A vs B:	1034
Initial recruitment C and D:	918
Total initial overall recruitment:	1952
	Updated sample size (6.5 years recruitment)
A vs C (A vs D):	847

Protocol version 7 (dated 16th May 2022)

Estimated numbers recruited based on Feb 2022 recruitment: (A vs B numbers 994 at this date, estimates assumes B completed recruitment)			
Treatment	Randomisation option		
Allocation	1	2	Total
A	373	144	517
B	371	146	517
C		212	212
D		212	212
Total	724	674	1458
Numbers needed to complete: A vs C and A vs D			
Current no A vs C	356		
remainder A vs C	491	(847-356=491)	
remainder A	246		
remainder C	246		
remainder D	246		
Total sample size:			
Total A+C+D	1306	(=144+ 2x212 +3x246)	
A's in A+C+D already counted in AvB	-144*		
Total A+B	1034		
Total overall (A+B+C+D)	2196		
Additional numbers needed:	244	(=2196-1952)	

*These A's are those from the 4-way randomisation option and are included in the A vs B numbers.

Actual numbers recruited at the closing of arm B:			
Treatment	Randomisation option		
Allocation	1	2	Total
A	384	151	535
B	385	151	536
C		227	227
D		226	226
Total	769	755	1524

Numbers needed to complete:		
A vs C and A vs D		
Current no A vs C	378	
remainder A vs C	469	(847-356=491)
remainder A	235	
remainder C	235	
remainder D	235	
Total sample size:		
Total A+C+D	1309	(=151+ 226+227+3x235)
A's in A+C+D already counted in AvB	-151*	
Total A+B	1071	
Total overall (A+B+C+D)	2229	
Additional numbers needed:	277	(=2229-1952)

Recruitment numbers used in the sample size calculation with 6.5 years of recruitment are based on the numbers recruited to date and then 100 patients recruited to A, C per 6 months (and a further 50 to D).

Numbers recruited to AvC (from 4 way randomisation) up to end 2021

2018	**2018**	**2019**	**2019**	**2020**	**2020**	**2021**	**2021**
Q1-2	**Q3-4**	**Q1-2**	**Q3-4**	**Q1-2**	**Q3-4**	**Q1-2**	**Q3-4**
28	42	48	39	22	31	36	73

Stata code for sample size:

```
artsurv, method(l) nperiod(23) ngroups(2) fp(0) edf0(0.8, 10) hratio(1, 0.624) ///
alpha(0.017) power(0.8) aratios(1 1 ) recrt(13 0, 0.034  0.051  0.059  0.048  0.027  0.038
        0.044  0.089  0.122  0.122  0.122  0.122  0.122 , 0 ) ///
 distant(0) detail(0) onesided(0) ni(0) tunit(2) trend(0)
```

Note: the Stata code uses 1:1 ratio, however the actual ratio at the end will be somewhere between 2:3 (the ratio used for the 4-arm randomisation) and 1:1 (the ratio used for the 3-arm randomisation). Using 1:1 and 2:3 results in a different number of events required but the same number of patients to

reach that number of events so has no impact on the actual sample size, therefore 1:1 has been used for simplicity.

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