The PACE Trial

(Prostate Advances in Comparative Evidence)

International randomised study of prostatectomy vs stereotactic body radiotherapy (SBRT) and conventional radiotherapy vs SBRT for organ-confined prostate cancer

PROTOCOL

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2 Protocol signature page

The PACE Trial: International randomised study of prostatectomy vs stereotactic body radiotherapy (SBRT) and conventional radiotherapy vs SBRT for early stage organ-confined prostate cancer

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 PACE Trial Manager at ICR-CTSU.

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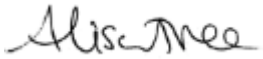
Name & Role	Signature	Date
Dr Nicholas van As (Chief Investigator)		21.12.2021
Dr Alison Tree (PACE-C Cohort Clinical Lead)		21.12.2021

This protocol describes the PACE 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.

Table of Contents

3 Study Summary

Title	The PACE trial: International Randomised Study of Prostatectomy vs Stereotactic Body Radiotherapy (SBRT) and Conventional Radiotherapy vs SBRT for Organ-Confined Prostate Cancer.
Aim	In the primary management of organ-confined prostate cancer, to assess whether hypofractionated stereotactic body radiotherapy (SBRT) offers benefit over prostatectomy or conventional radiotherapy.
Design	Multicentre, international phase 3 randomised controlled study comprising three parallel randomisations with a common experimental arm.
Objectives	Primary objective: PACE-A: To determine whether there is improved quality of life following prostate SBRT compared with prostatectomy two years from completion of trial treatment. PACE-B and PACE-C: To determine whether prostate SBRT is non inferior to conventional radiotherapy for freedom from biochemical/clinical failure in low/ intermediate risk (PACE-B) and intermediate/high risk (PACE-C) prostate cancer. Common secondary objectives (all cohorts): To determine the relative benefits of surgery (PACE-A), radiotherapy (PACE-B and PACE-C) and prostate SBRT in terms of local failure, distant failure, disease-free survival, disease-specific survival, overall survival, toxicity, quality of life in generic and organ specific domains.
Primary end-points	PACE-A: Co-primary patient reported outcomes: (1) Urinary incontinence (number of absorbent pads required per day to control leakage) measured by The Expanded Prostate Cancer Index (EPIC) questionnaire. (2) Bowel bother summary score from the EPIC questionnaire. The main time point of interest is 2 years post treatment. PACE-B and PACE-C: Freedom from biochemical (Phoenix definition) or clinical (commencement (PACE-B) or re-commencement (PACE-C) of androgen deprivation therapy, local recurrence, nodal recurrence and distant metastases) failure. The main time point of interest is 5 years from randomisation.
Secondary end-points	PACE-A: • Freedom from biochemical (Phoenix definition for SBRT arm, >0.2 ng/ml for surgical arm) or clinical (commencement of androgen deprivation therapy, local recurrence, nodal recurrence and distant metastases) failure. The main time point of interest is 5 years post treatment. Common secondary end-points (all cohorts): • Clinician reported acute toxicity using CTCAE, RTOG (SBRT and conventional radiotherapy patients only) and Clavien (surgical patients only) scales. • Clinician reported late toxicity using CTCAE and RTOG (SBRT and conventional radiotherapy patients only) scales. • Patient reported acute and late bowel, bladder and erectile dysfunction symptoms. Assessed using IIEF-5, IPSS, Vaizey score and EPIC-26 instruments. • Disease-specific and overall survival • Progression-free survival– radiographic, clinical or biochemical evidence of local or distant failure.

	• Commencement (PACE-A and PACE-B)/re-commencement (PACE-C) of androgen deprivation therapy (LHRH analogues, anti-androgens, orchidectomy).
Hypothesis	• Profound hypofractionation with SBRT has the potential to achieve equivalent tumour control rates compared to surgery and conventional radiotherapy while reducing radiation to normal tissues (bladder, rectal and penile bulb) and minimising radiation-induced side effects. • Profound hypofractionation with SBRT has the potential to improve quality of life compared with prostatectomy.
Treatment	PACE-A: Patients considered candidates for surgery, agreed by both the physician and patient, are randomised to either prostatectomy or prostate SBRT delivered with 36.25 Gy in 5 fractions. PACE-B: Nonsurgical candidates or patients who decline surgery will be randomised to either prostate SBRT (36.25 Gy in 5 fractions) or conventional radiotherapy (78 Gy in 39 fractions or 62 Gy in 20 fractions). PACE-C: Nonsurgical candidates or patients who decline surgery will be randomised to either prostate SBRT (36.25 Gy in 5 fractions) or conventional radiotherapy (60 Gy in 20 fractions). All patients will also receive 6 months of androgen deprivation therapy as part of standard care. Patients receiving extended androgen deprivation therapy to permit safe delay of radiotherapy as a result of the COVID19 pandemic will be permitted to enter.

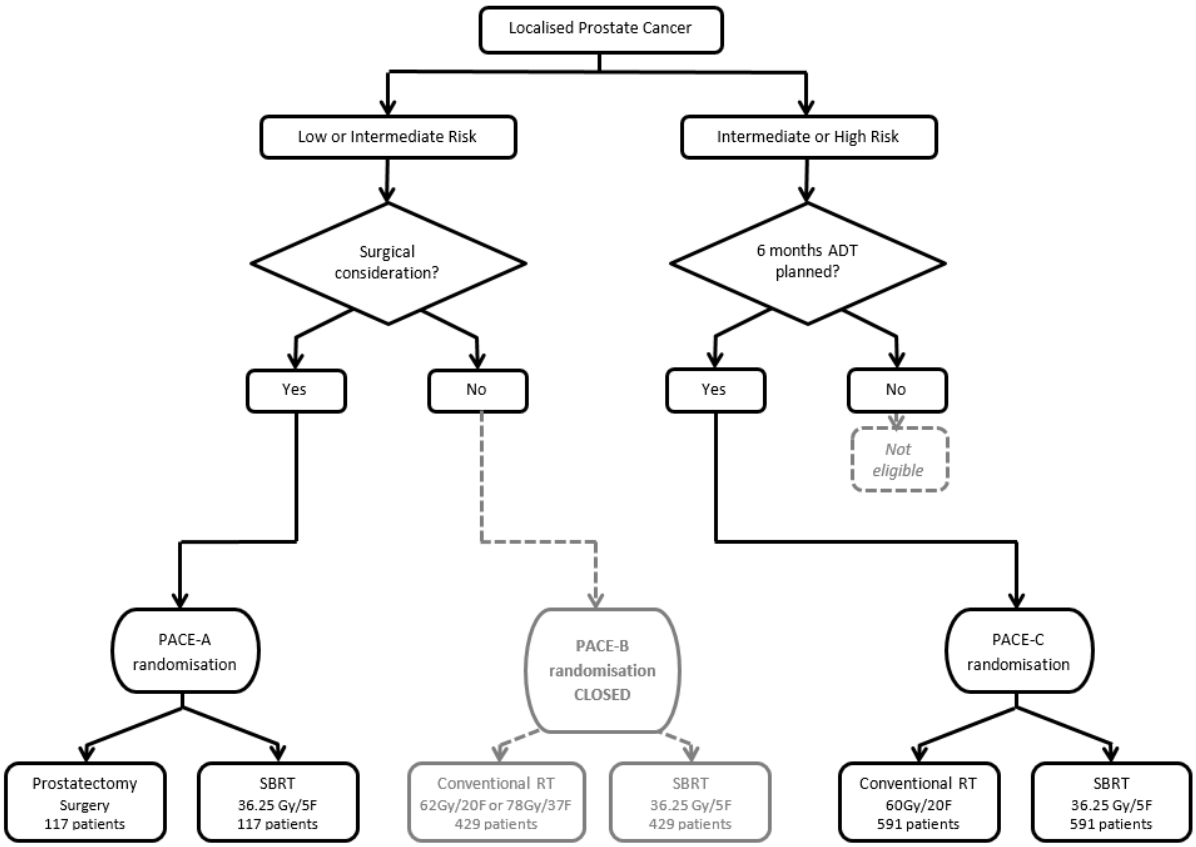
Eligibility criteria	Inclusion criteria (all cohorts):
	• Histological confirmation of prostate adenocarcinoma within the last 18 months (unless on active surveillance and not clinically indicated)
	• Men aged ≥18 years at randomisation
	• WHO performance status 0 – 2
	• Patients considered candidates for surgery are eligible for PACE-A; patients not considered candidates for surgery and patients who decline surgery or prefer to avoid surgery are eligible for PACE-B and PACE-C.
	• Ability of the research subject to understand and the willingness to sign a written informed consent document.
	
	Specific risk stratification inclusion criteria for PACE-A and PACE-B:
	• Minimum of 10 biopsy cores.
	• Gleason score ≤ 3+4
	• Clinical and/or MRI stage T1c –T2c, N0-X, M0-X
	• PSA ≤ 20 ng/ml (completed within 60 days of randomisation)
	• Patients belonging to one of the following risk groups (see Appendix 2):
	  ○ *Low risk* - patients with tumours meeting all of the following criteria:
	  ▪ Gleason ≤ 6
	  ▪ Clinical stage T1-T2a
	  ▪ PSA < 10 ng/ml (within 60 days prior to randomisation)
	  ○ *Intermediate risk* - patients with tumours meeting any one of the following criteria:
	  ▪ Gleason 3+4
	  ▪ Clinical stage T2b or T2c
	  ▪ PSA 10-20 ng/ml (within 60 days prior to randomisation)
	
	Specific risk stratification inclusion criteria for PACE-C:
	• Patients planned for a minimum of 6 months of ADT (12 months maximum). Patients receiving extended androgen deprivation therapy (18 months maximum) to permit safe delay of radiotherapy as a result of the COVID19 pandemic (only) are eligible.

	• Gleason score ≤ 4+4
	• MRI stage T1c –T3a, N0-X, M0-X
	• PSA ≤ 30 ng/ml (prior to starting ADT)
	• Patients belonging to one of the following risk groups (see Appendix 2):
	  ○ *Intermediate risk* - includes the presence of any of the following, assuming no high risk features apply:
	  ▪ Gleason 7 (3+4 or 4+3)
	  ▪ T2 (N0, M0-X)
	  ▪ PSA 10-20 ng/ml
	  ○ *High risk* - patients with tumours that meet a maximum of 2 of the following criteria:
	  ▪ Gleason 4+4 (max ≤ 50% cores)
	  ▪ T3a (N0, M0)
	  ▪ PSA >20 ng/ml
	
	<u>Exclusion criteria (all cohorts):</u>
	• Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival.
	• Prior pelvic radiotherapy.
	• Prior androgen deprivation therapy (including androgen agonists and antagonists) for PACE-A and PACE-B participants.
	• Any prior active treatment for prostate cancer (with the exception of ADT for PACE-C participants). Patients previously on active surveillance are eligible if they continue to meet all other eligibility criteria.
	• Life expectancy <5 years.
	• Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts.
	• Medical conditions likely to make radiotherapy inadvisable eg inflammatory bowel disease, significant urinary symptoms.
	• For patients having fiducials inserted: Anticoagulation with warfarin/ bleeding tendency making fiducial placement or surgery unsafe in the opinion of the clinician (see section 11, Treatment).
	• Participation in another concurrent treatment protocol for prostate cancer.
	
	<u>Specific exclusion criteria for PACE-C:</u>
	  • >14 weeks of androgen deprivation therapy prior to randomisation, patients receiving extended androgen deprivation therapy to permit safe delay of radiotherapy as a result of the COVID19 pandemic (only) are eligible. For patients affected by the COVID19 pandemic, there is no restriction on length of time patients can be on ADT prior to randomisation provided the duration of androgen deprivation therapy is less than 18 months in total and radiotherapy is completed before ADT is completed.
	• Medical conditions likely to make ADT inadvisable (e.g. significant and ongoing cardiac issues).

Target sample size	PACE-A: 234 (117 patients per arm) PACE-B: 858 (429 patients per arm) PACE-C: 1182 (591 patients per arm)

4 Study Schema

PACE is a multicentre, international phase 3 randomised controlled study comprising three parallel randomisations with a common experimental arm.



KEY: ——— Cohort pathway currently open to randomisation (PACE-A and PACE-C)
– – – – Cohort pathway currently closed to randomisation (PACE-B)

Patients are seen 4 times within the first 3 months of post-treatment follow-up with clinician reported (RTOG bladder and bowel toxicity and CTCAE) and patient reported (IPSS and/or EPIC-26, IIEF-5 and Vaizey) acute toxicity assessed. The need to continue acute toxicity assessment in PACE-C will be reviewed after 200 patients have been recruited. Thereafter patients are seen 3-12 monthly with clinician reported (RTOG bladder and bowel toxicity and CTCAE until 10 years post-treatment) and patient reported (IPSS, EPIC-26, IIEF-5 and Vaizey until 5 years post-treatment) late toxicity assessed.

Statistical design:
PACE-A: 234 patients provides 80% power to detect an 11% difference in urinary incontinence at 2 years assuming 15% in the control arm. This number of patients also provides over 90% power to detect a 5 point difference in mean bowel bother scores.

PACE-B: 858 patients provides 80% power to rule out a detriment of at most 6% (non-inferiority margin) in biochemical or clinical failure at 5 years assuming the proportion of patients biochemical or clinical failure-free is 85% in the control arm (critical hazard ratio = 1.45).

PACE-C: 1182 patients provides 80% power to rule out a detriment of at most 5% (non-inferiority margin) in biochemical or clinical failure at 5 years, allowing for 1% loss to follow-up at the time of analysis (critical hazard ratio = 1.37).

5 Background

There are several treatment options for men with early stage prostate cancer. At present these are held in a therapeutic equipoise as neither surgery nor radiotherapy has been proven to be superior. Historically, most trials that have attempted to randomise between surgical and radiation treatments have been unsuccessful and have failed due to the inherent difficulties in convincing patients to accept such different treatment modalities by chance. One study has successfully randomised between surgery and radiotherapy in prostate cancer. The ProtecT study has successfully recruited over 500 men to each of the study arms, which are external beam radiotherapy, surgery and active surveillance. This impressive feat has been made possible by conducting detailed studies of recruitment interviews and by understanding the way patients decide on their treatment. It is thought that the key to the ProTecT trial's success is funding dedicated well trained trial nurses who conduct the recruitment interviews. This robust academic approach should form the backdrop to this trial.

As physicians caring for men with prostate cancer we wish to be able to offer patients the best advice. At present we cannot tell them whether surgery, or radiotherapy or SBRT would be the more efficacious or safer treatment choice or whether there is improved quality of life with SBRT. This study is designed to help to answer these questions.

In addition, there are many radiobiological, technological, economic and practical reasons why a 5 fraction hypofractionated SBRT treatment regimen may be advantageous for patients, but before clinical practice changes we must establish conclusively if profound hypofractionation is at least as good as conventional regimens. This study is also designed to answer that question.

6 Rationale

6.1 Epidemiology and Background

Prostate cancer is the most common non-cutaneous cancer in men, and since the introduction of serum prostate specific antigen (PSA) testing, the majority of cases are diagnosed with early stage, organ confined disease, which is often asymptomatic. In Europe the incidence of prostate cancer was 400,364 new cases in 2012 [1], and the rates across Europe and in the USA are amongst the highest in the world [2]. Despite the volume of cases, the assessment and management of organ-confined prostate cancer remains challenging and controversial. Radical prostatectomy has been shown in a good quality randomised controlled trial to have an overall survival advantage compared with watchful waiting [3]. There are however several other treatment options for early prostate cancer. Fractionated external-beam radiotherapy, brachytherapy (HDR or LDR) and, for selected patients, active surveillance are all considered to be effective methods for managing prostate cancer. No superiority has yet been shown in terms of survival, and so all suitable options are discussed with men to enable treatment tailored to their circumstances and preferences.

The Prostate Testing for Cancer and Treatment (ProtecT) trial randomised over 1600 men aged 50 to 69 years with localized prostate cancer to active monitoring, prostatectomy or external beam radiotherapy (74Gy in 37 fractions) with neoadjuvant hormones. Results demonstrate a low prostate cancer specific mortality of less than 2% at 10 years median follow up, with no significant difference between the three treatment arms. The active monitoring group had a higher rate of disease progression and development of metastases in comparison to the radical treatment arms, however there was no difference in progression between surgery and radiotherapy [4].

Radiotherapy is an extremely effective treatment for prostate cancer, but conventional treatments can be protracted over 4-8 weeks, which impact the patient's quality of life and utilisation of hospital resources. There is a compelling economic argument for treating prostate cancer using hypofractionation.

In general, increased radiation fractionation provides an increasing therapeutic advantage between tumour control and late treatment related side effects. However, studies deriving the alpha-beta ratio for prostate cancer from low dose rate brachytherapy treatments have suggested the alpha-beta ratio is possibly as low as 1.5 Gy (see Section 6.6 below). If these estimates are accurate, they would predict that hypofractionated schedules for prostate cancer should produce tumour control and late treatment related sequelae that are at least as good or better than those currently achieved with current conventional schedules using 1.8-2.0Gy daily fractions.

More recently, four large studies have reported outcomes in patients treated with moderate hypofractionation. Most importantly, the CHHiP trial randomised more than 3200 patients between 74 Gy in 37 fractions (the control arm), 60 Gy in 20 fractions, and 57 Gy in 19 fractions [5]. A short course of androgen deprivation was given to all patients. The majority of patients (88%) were NCCN intermediate or low risk. At a median follow-up of 62 months, estimated 5 year PSA progression-free survival was 88.3%, 90.6%, and 85.9% for the 74Gy, 60Gy and 57Gy groups respectively. Although the investigators found an increase in grade 2+ RTOG acute bowel toxicity in the hypofractionated groups (24.6% for 74 Gy, 38.5% for 60 Gy, and 37.9% for 57 Gy; $p < 0.001$), the differences had disappeared 18 weeks after the start of radiotherapy and late toxicity was low and less than 4% in all groups at 2 years. By five years, there was no significant difference in RTOG bowel toxcity between the three groups (1.3%, 2.3%, and 2.0%, respectively). No significant differences between the groups were found with respect to acute or late urinary toxicity. The investigators concluded that 60 Gy in 20 fractions was non-inferior to 74 Gy (HR 0.84, 90% CI 0.68, 1.03 with HR<1.0 being in favour of 60Gy group) and could be recommended as a new standard of care.

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However, 57 Gy in 19 fractions was not shown to be non-inferior (HR 1.20, 90% CI 0.99, 1.45). It is expected that the 60 Gy in 20 fraction dose (given with hormones) will be widely adopted in the UK, particularly in view of its favourable impact on radiotherapy resource use.

In the HYPRO study[6]. 820 patients were randomised between 78 Gy in 39 fractions (the control arm) and 64.6 Gy in 19 fractions over 6.5 weeks (treating three times per week). This group found that the incidence of acute G2+ RTOG rectal toxicity was significantly higher in the hypofractionated cohort (31.2% vs 42.0%; p = 0.0015). However, this difference was not maintained to 3 months and the authors themselves point out that their trial was underpowered for this comparison. It is also important to note that 64.6 Gy in 19 fractions dose is a significantly higher biologically equivalent dose than that used in the CHHiP trial. No significant differences were found in acute urinary toxicity between the groups. At 5 years median follow-up, there were no significant differences in relapse free survival (HR 0.86, 95% CI 0.63-1.16)[6, 7].

The PROFIT study recruited 1206 men with intermediate risk disease, randomising them to 78 Gy in 39 fractions daily or 60 Gy in 20 fractions over 4 weeks [8]. No patients in PROFIT received neoadjuvant or adjuvant androgen deprivation therapy. After a median follow up of 6 years, there was no difference in biochemical relapse-free survival (85% in both arms, HR 0.86, 95% CI 0.77-1.2).

Finally the RTOG Trial 0415 [9] established that hypofractionated delivery of 70.0 Gy in 28 fractions over 5.6 weeks is noninferior to conventional delivery of 73.8 Gy in 41 fractions over 8.2 weeks. 1115 patients with low-risk disease were randomly assigned to the conventional RT schedule or the hypofractionated schedule. No androgen suppression was permitted. After a median follow-up of 5.9 years, the 7-year disease-free survival (DFS) rate for hypofractionated RT was not lower than that for conventional RT by more than 7% (hazard ratio [HR] < 1.52) with the estimated 7-year DFS rate of 82% for hypofractionated RT compared with the rate of 76% for conventional RT (HR 0.85, 95% CI [0.64, 1.14]). There was also noninferiority for the biochemical recurrence endpoint (HR 0.77, 95% CI [0.51, 1.17]). Hypofractionated RT delivery produced an increase in late gastrointestinal and genitourinary toxicity however there was no statistically signifanct difference in the risk of Grade 3 or more GI events (relative risk (RR) 1.53, 95% CI [0.86, 2.83]) or GU events (RR 1.43, 95% CI [0.86, 2.37]).

The next logical question to answer is whether “profound” hypofractionation could produce non-inferior results to moderate hypofractionation. Historically, delivery of larger fraction sizes is limited by normal tissue constraints and the requirement for large planning margins. SBRT however offers the opportunity to accurately deliver larger fractions with a high degree of accuracy. Early data from the two Accuray sponsored studies of either 5 fractions with a homogenous dose distribution[10] or 4 fractions with an HDR like heterogenous dose distribution [11] show that early toxicity is low. A large series of over 1000 patients now confirm that SBRT results in 5-year biochemical control rates similar to those seen with conventional fractionation, and is associated with only transient declines in quality of life [12, 13]. Results of the multicentre single arm prospective study have recently been published [14]. With a median follow up of 61 months, 5 year biochemical relapse-free survival was 97.1%. Low toxicity rates of 2% experiencing Grade 2 or higher late GI toxicity and 12% experiencing Grade 2 or higher GU toxicity (1.3% Grade 3) were reported. Whilst this data is encouraging, without a phase III trial we cannot conclude that SBRT is equivalent to conventional therapies.

6.2 Surgical Management of Organ-Confined Prostate Cancer

Radical prostatectomy and radiotherapy are considered to be treatments of choice for early prostate cancer.

A large Spanish center has published its experience of treating 505 men with early prostate cancer (approximately half were low risk and half were intermediate risk). The 5-year biochemical relapse free survival (bRFS) for the radical prostatectomy and external beam radiation therapy (EBRT)

cohorts were 79% and 86% respectively [12]. However, many of the subjects in the EBRT cohort received what would today be considered as sub-optimal doses of radiotherapy. A total of 25% of subjects who underwent surgery reported urinary incontinence (measured using IPSS and EPIC questionnaires).

Kupelian et al. published a retrospective cohort of 1877 patients who received either prostatectomy or radical radiotherapy (median dose 70.2Gy) [15]. Both treatments resulted in a similar bRFS (70-72%), despite the radiation dose used now being considered suboptimal. In a further analysis with nearly twice as many patients, they documented a higher 5-year bRFS of 81%, which was the same for radical prostatectomy and EBRT if >72 Gy was given[16]. Biochemical relapse was defined as 0.2ng/ml for the surgical arm and three successive PSA rises (ASTRO definition) for the radiotherapy arm.

A similar retrospective study, looking at the Memorial Sloan Kettering experience revealed a 7-year bRFS rate of 79% for radical prostatectomy and 77% for EBRT [17].

For the cohort of patients eligible for this study prostate cancer specific mortality (PCSM) is likely to be low. In a large retrospective series, PCSM for patients with Gleason 7 or less was 2-5% at 15 years [18]. Another earlier study documented an 82% metastasis free survival at 15 years in patients treated at a single center [19]. The median time to metastasis from PSA elevation was 8 years (these men received no salvage therapy prior to documented metastatic disease). Once metastatic disease had been diagnosed, the median time to death was 5 years. The ProtecT trial has demonstrated no significant differnence in prostate-cancer specific survival after 10 years follow up between the three randomised groups: surgery (RP), radiotherapy (RT) and active monitoring (AM) (RT vs. AM: hazard ratio (HR): 0.51 (95%CI: 0.15 to 1.69), RT vs. RP: HR: 0.80 (0.22 to 2.99), RP vs AM: HR: 0.63 (0.21 to 1.93). Within the prostatectomy group the 10 year prostate cancer specific survival was 99% (95% CI: 97.2 to 99.6)[4].

6.3 Toxicity of Prostatectomy and Radiotherapy

The relative toxicity of the treatment options is currently an important parameter for men deciding upon treatment. The surgical literature often reports a 'Trifecta' outcome of biochemical control with continence and return of erectile function. This is the gold-standard outcome for surgery [20].

6.3.1 Urinary Toxicity

After the so-called learning curve for laparoscopic procedures, the 12-month urinary continence post prostatectomy rates vary from 75-95%, depending on age and definition of continence (leak free vs pad free) [21].

Patient reported outcomes in the ProtecT trial included urinary incontinence measured using the EPIC questionnaire at baseline, 6 and 12 months and then annually to six years. At 2 years, 20% (80/399) of patients who had radical prostatectomy reported any use of absorbent pads compared with 4% (16/394) in those who had radical radiotherapy [22]. Scores for voiding symptoms were seen to be worse in the radiotherapy group at 6 months follow up but then returned to baseline levels similar to other treatment groups. The CHHiP hypofractionation trial also collected information on urinary pad use using the EPIC questionnaire and reported 2.8% (36/1272) of patients receiving radiotherapy (across all radiotherapy regimens) using at least one absorbent pad at 2 years.

6.3.2 Erectile Function

Erectile function post-prostatectomy has also been reviewed by Ficarra and colleagues [21]. They identified two studies which used a validated questionnaire International Index of Erectile Function (IIEF) and these found rates of potency sufficient for intercourse of between 33 and 46% at 3 months post surgery. There was no significant difference between techniques.

It is important to note that radiotherapy, as well as surgery, can produce erectile dysfunction. Dose-volume parameters have not been well established for the prevention of erectile dysfunction due to radiotherapy. Traditionally the penile bulb is contoured and a dose-constraint applied to this volume, but the penile bulb itself plays a minor role in erectile function, and correlations between dose and function have not been consistently shown [23]. Data from a small cohort of the RT01 patients did show a correlation between D90 >50 Gy to the penile bulb [24].

Roach and colleagues in a recent review of the subject, agree that the data is conflicting but present their own and others data supporting a correlation between dose and function [25]. They advise that the mean dose to 95% of the penile bulb should be treated to <50 Gy with conventional fractionation.

A meta-analysis of rates of erectile dysfunction after treatment [26] compared various modalities of treatment. The chance of maintaining erectile function at 2 years post-treatment, assessed using patient questionnaires, was 25% (18 -33% confidence intervals) for nerve-sparing prostatectomy and 52% for EBRT (95% confidence intervals 48-56%). The average age of men undergoing EBRT was 69.5 years and 61 years for nerve-sparing prostatectomy.

Although some of the data included in the above meta-analysis is older, newer series of radical prostatectomies indicate similar levels of erectile dysfunction. A single institution study from Germany reports that at 1-year post surgery, only 26% of men had returned to their baseline potency rates, although the rate of nerve-sparing surgery was only 54% [27]. For the subgroup who had nerve-sparing surgery and were potent at baseline, the rate of potency at 12 months was 56%.

The relative risk of erectile dysfunction with radiotherapy compared to radical prostatectomy is still hotly contested [28] but a large prospective study of 1201 patients treated with surgery, EBRT or brachytherapy has shown that sexual function parameters for quality of life were worse for surgical patients (and their partners) compared with radiotherapy patients[29].

Within the ProtecT trial, baseline erectile function were similar across treatment groups with 67.5% of men reporting an erection firm enough in the AM group, 65.7% in the RP group and 68.4 in the RT group. At 2 years follow up, the AM group had 47.1% of men with erections firm enough for intercourse compared to 34.0% in the RT group and 18.9% in the RP group ($p<0.001$). This pattern of reduced erectile function post prostatectomy continued into longer term follow up [22].

The IIEF-5 is a validated diagnostic tool for diagnosing erectile dysfunction in men [30] and will be used to monitor men in this study.

6.3.3 Bowel Bother

Bowel function and bother scores were assessed in the ProtecT trial using the EPIC questionaire [31]. At 6 months, the bowel summary score for the AM and RP groups were unchanged from baseline (~9%), however the RT group had scores increased from 7% at baseline to 16% at 6 months ($p<0.001$). At 2 years, 7.4% of the men in the RT group reported bloody stools about half the time or more frequently compared with 0.3% in the RP group and 0.8% in the AM group ($p<0.001$). A similar pattern continued into future follow up [22].

6.4 What Should Be Our Conventional Radiotherapy Arm?

Dose escalation studies have proven that higher doses are associated with improved cure rates:

Dearnaley et al. conducted a pilot for a phase III trial randomising to 64 Gy vs 74 Gy and reported 5 year biochemical control rates of 59% (standard dose) and 71% (escalated dose) (HR 0.64, 95% CI 0.38–1.10, P=0.10) with acceptable acute and late toxicity [32]. The subsequent MRC RT01 trial randomised 862 men to the same fractionation regimens and found that at 6 months post-radiotherapy grade 2 or higher toxicity was low [33]. However almost all of this toxicity was seen in the group receiving 74 Gy. In both arms the radiotherapy was given in conjunction with androgen deprivation. This trial did also confirm an increase in biochemical progression-free survival (60% with the lower dose and 71% with the higher dose at 5 years follow-up, hazard ratio of 0.67 for clinical progression in the higher dose arm, CI 0.53-0.85, p=0.0007) and metastasis-free survival, in addition to a reduction in need for salvage androgen suppression [34]. After 10 years follow-up in the MRC RT01 trial, the higher dose continued to show a benefit over the lower dose in terms of biochemical progression free survival with estimates of 55% and 43% respectively [HR 0.69, 95%CI 0.56-0.84, p=0.0003). However, this benefit did not translate into an improvement in overall survival with 71% overall survival in both groups at 10 years[35].

Kupelian et al. pooled the data from nine institutions totalling over 4800 men. Despite the higher dose cohort (>72 Gy) having worse prognostic features, their 5-year biochemical disease-free survival (bDFS) was significantly improved compared to the cohort who received <72 Gy [36].

The MD Anderson group conducted a phase 3 trial comparing 70 Gy to 78Gy without androgen deprivation and found a significant improvement in freedom from failure (including biochemical failure) in the higher dose group (freedom from failure at 6-years 64% vs 70%, p=0.03) [37]. This included a reduction in the incidence of distant metastasis in the subgroup of patients with a PSA >10 ng/ml at 6 years of follow-up. However this trial also confirmed an increase in rectal side effects in the higher dose arm (grade 2 or higher toxicity 26% vs 12%). This trial was conducted in the era before image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT) were standard and hence higher doses are likely to be deliverable with less toxicity today.

Peeters et al also conducted a dose escalation trial randomising 664 men 68Gy or 78Gy. The higher dose was associated with a 10% increase in freedom from failure at 5 years (HR 0.74, p= 0.02) [38].

Most studies have shown that a higher dose is associated with more toxicity, but in general 78 Gy has tolerable toxicity. The EORTC 22991 trial showed 1% grade 3 gastrointestinal (GI) toxicity and 6.2% grade 3 GU toxicity, without a significantly increased rate at the higher dose levels (up to 78 Gy) [39]. The 2012 EAU guidelines on prostate cancer suggest 78 Gy is a good compromise of efficacy and tolerability [40].

These data suggest that 78 Gy in 39 fractions would be a suitable radiotherapy dose for use in the control arm for this study.

Following publication of the CHHIP trial results (described in Section 6.1), it is likely that centres will adopt a 20 fraction schedule as a new standard of care.

Given that CHHIP has shown that a dose of 60 Gy in 20 fractions is non-inferior to the control arm dose of 74 Gy in 37 fractions it is valid to include an option for investigators to use a moderately hypofractionated treatment in the PACE-B control arm, at their discretion. The control arm in PACE-B is 78 Gy in 39 fractions, 5.4% higher than that in the CHHIP control arm (discounting the two additional days of treatment time). Data from the CHHIP trial also implies that the α/β ratio for prostate cancer lies between 1.5 and 2.5 Gy. Keeping to a 20 fraction dose, and using an α/β ratio of 2, a dose 5.4% higher than 60 Gy in 20 fractions (BED = 150 Gy) is 62 Gy in 20 fractions (BED =

158.1). This calculation is relatively insensitive to α/β ratio, being 61.8 Gy for α/β = 1, and 62.1 Gy for α/β = 3.

Therefore, a dose of 62 Gy in 20 fractions over 4 weeks (3.1 Gy per fraction) is a suitable alternative to the conventionally fractionated dose in the control arm of PACE-B.

However, in view of the results of the subsequent PROFIT study [8], indicating that 60 Gy in 20 fractions is equivalent to 78 Gy in 39, and with the use of ADT in PACE-C, it is more appropriate to revert to the international standard of 60 Gy in 20 fractions for PACE-C. As moderate hypofractionation is now considered standard, no 2 Gy/fraction option is allowed in PACE-C.

6.5 Dose-Volume Constraints For Conventional Radiotherapy

Late rectal toxicity increases with the dose and volume of rectum irradiated. There is a wealth of literature on the correlation between dose and rectal complications and this was thoroughly reviewed by Fiorino and colleages in 2009 [41]. It seems that keeping the V70 Gy <25% and the V75 Gy below 5% (at 2 Gy per fraction) results in a low incidence of rectal bleeding using conventional fractionation[41].

Other factors can play a role in the risk of late rectal bleeding including diabetes, previous abdomino-pelvic surgery and possibly androgen deprivation therapy [41]. Whilst rectal bleeding seems to be most closely associated with the higher doses received by the rectum, the risk of faecal incontinence, whilst low, seems related to the lower doses [41].

In order to develop constraints for the 62 Gy in 20 fractions control arm option (PACE-B), those used in the 78 Gy in 39 fraction group were scaled using the methods in the CHHiP trial.

6.6 Why Hypofractionate At All? The Radiobiological Argument

As discussed above, it is clear that increasing the dose to the prostate increases cure rates at the expense of increased side effects. However, it may be possible to simultaneously increase cure rates whilst decreasing toxicity by exploiting the unusual radiobiology of prostate cancer. For most cancers the alpha/beta ratio is high (around 10 Gy) indicating that these tissues are more sensitive to total radiation dose, rather than dose per fraction. For the late-reacting surrounding normal tissues the alpha/beta ratio is low (around 3) indicating a higher sensitivity to fraction size.

There is now growing evidence that the alpha/beta ratio for prostate cancer cells is lower than that of surrounding normal tissue, and may be as low as 1.5 Gy. This means that by increasing fraction size and reducing total dose would be expected to increase cure rates and decrease toxicity. Recent, very large (n>5000) patient datasets have been used to derive the α/β ratio of prostate cancer [42] [43] and estimates consistently fall around the 1.4 Gy mark. The results of the CHHiP trial suggest the a/b ratio is 1.8 Gy, ignoring overall treatment time [44].

As mentioned above, the α/β ratio of the late-reacting normal tissues is usually assumed to be 3 Gy. For prostate cancer patients, the dose-limiting structure is the rectum which lies in close proximity to the prostate gland.

Marzi et al. randomised patients to 80 Gy in 40- fractions or 62 Gy in 20 fractions and showed similar toxicity [45]. From their data they estimated the α/β ratio of the rectum for late toxicity to be around 3 Gy.

The rectal toxicity data from the RTOG 94-06 trial was analysed and the best fit α/β ratio for late rectal damage was 4.6 Gy although the confidence intervals were wide [46].

Taken together, the α/β ratio of prostate cancer appears to be significantly lower than that of the rectum, which means that the higher the dose per fraction, the higher the cell kill to the prostate cancer. This should be accompanied by a reduction in the incidence of rectal side effects due to the lower total dose required.

6.7 Experience With Profound Hypofractionation Using Brachytherapy

Many men, over many years, have been treated with hypofractionated radiotherapy in the form of HDR brachytherapy. Using this technique, fractionation regimens of 48 Gy in 8 fractions or 54 Gy in 9 fractions over 5 days have demonstrated 70% PSA failure-free survival at 5 years, despite the majority of these patients having high risk disease [47]. Relapse-free survival at 3 years was 100% for the low risk patients included in this study. Five percent of patients had grade 3 acute GU toxicity and 21% had grade 2 acute GU toxicity. With regard to late toxicity, one patient had a grade 3 GI toxicity, and 11% had grade 2 GU toxicity. Yoshioka et al. updated their results in 2010 and had treated 112 men with 54 Gy in 9 fractions with HDR brachytherapy [48]. The majority of these patients had high risk disease and also received androgen deprivation therapy (ADT). Overall 5-year bRFS was 83%. This was achieved with 5% acute and 3% late grade 3 toxicity.

Another cohort of 117 consecutive patients were treated with escalating doses of 6 fraction HDR from 36 Gy to 43.5 Gy, delivered in 2 insertions one week apart [49]. They report excellent 8 year bRFS of 94% for this group of low and intermediate-risk prostate cancer patients. Four (3%) patients had grade 3 late urinary toxicity.

Recently Demanes et al. have described their experience of treating 298 men with mostly low and low-intermediate risk prostate cancer [50]. Approximately half were treated to 36 Gy in 6 Gy fractions, and the others received 4 fractions of 9.5 Gy over 2 days. The 8-year bRFS was 97%. The grade 3 GU toxicity was 5% overall, 24 % grade 2, but this was scored per event, not per patient, and hence the same patient with more than one symptom would be scored multiple times. Late GI toxicity was <1%.

Mount Vernon hospital have published outcomes for a group of men, some with locally advanced prostate cancer [51]. This was a dose escalation study so the first cohort received 34 Gy in 4 fractions over 3 days, the second cohort 36 Gy, then the third cohort received 31.5 Gy in 3 fractions over 2 days. Only 25-31% patients had grade 1 or more toxicity at six months and two patients had grade 3 toxicity.

Aluwini et al, working at Erasmus Medical Centre have reported 166 patients treated with 38 Gy in 4 fractions with 35 months median follow-up [52]. Biochemical control was 97.6% and late G2+ urinary and rectal toxicity was 19.7% and 3.3%, respectively.

6.8 Experience With Profound Hypofractionation With External Beam Radiotherapy

The largest 5-year follow-up data for a cohort of men treated with SBRT has recently been published. King et al report on 1100 men treated with Cyberknife, 65% received 36.25 Gy in 5 fractions or above [53]. Median follow-up is 36 months and biochemical control at 5 years is 95%, 84% and 81% for low, intermediate and high risk patients, respectively. Fourteen percent of this cohort received androgen deprivation therapy (ADT) and no correlation between ADT use and biochemical outcome was noted.

A number of other non-randomised studies have examined SBRT using both Cyberknife and gantry-based systems. These have demonstrated medium term outcomes in keeping with conventionally fractionated treatments, both in terms of efficacy and toxicity [54].

Recently, as discussed in Section 6.1, the result of the first, multicentre, prospective phase II study have been published. The trial enrolled 309 intermediate and low risk patients and delivered 36.25 Gy in 5 fractions, delivered daily or alternate daily. The trial showed a 5-year disease-free survival

rate of 97%, with very little late toxicity (12% late Grade 2 GU toxicity and 2% late GI Grade 2+ toxicity) [14].

6.9 Extra-Capsular Extension

There is a theorectical concern that with such conformal isodoses and a sharp dose fall-off, undetected extra-capsular extension could be under-treated. Whilst a preponderance of marginal recurrences is not widely recognised with HDR techniques, which achieve similarly sharp dose fall-offs, this is worthy of further discussion. According to the algorithm proposed by Roach et al. [55] the most advanced patients in this cohort will have a 69% risk of extra-capsular extension (ECE). However, histopathological studies would suggest that the mean length of extra-capsular extension across all stages is 0.8mm with a median of 0.5mm [56]. A margin of 2.5mm would cover 96% of cancers in this cohort of 376 cases, some of which were Gleason 8 or 9 cancers. In addition, the radial extent of invasion is much smaller for the lower risk prostate cancers, with Gleason <7 cancers extending a median of 0.06mm. It appears likely, therefore that a margin of 1-2 mm would cover almost all possible extracapsular spread in the cohort of this trial.

Another more recent study found slightly more extensive ECE [57]. 371 prostatectomy specimens were analysed from patients receiving surgery between 1987 and 2001 i.e. prior to routine MRI staging. They found that PSA, Gleason score and clinical T score were all correlated with the risk of ECE. They found that low-risk patients had a 19% risk of ECE vs 42% for other groups (both of which are lower than the rates predicted by the Roach equation). The median ECE was 2.4mm but the 90% percentile for distance was 5.0 mm. In addition, for patients with a PSA>10 and a Gleason score of 7 or more, the chance of ECE extending more than 4mm was 20%. Almost all ECE occurred in the posterolateral direction, in the direction of the neurovascular bundles.

6.10 Margins For SBRT

For Cyberknife SBRT, most of the larger series have used a PTV margin of 5mm around the prostate/SVs, except for posteriorly where a 3mm margin has been used [53, 58-60]. Biochemical efficacy and side effect profiles have been acceptable in these series, suggesting that this margin is sufficient to cover disease without unacceptable dose delivery to normal tissues. The Cyberknife system monitors and corrects for intra-fraction motion every 30-60 seconds, which means that the dosimetric impact of motion is likely to be small.

For systems such as Calypso electromagnetic beacons which track intrafraction motion continuously, similar margins can be used. For systems where continuous intra-fraction motion monitoring is not possible, margins have to be considered carefully.

Several studies, largely using Calypso monitoring have demonstrated that prostate motion over several minutes is largely within 3mm of initial position. Curtis et al observed prostate motion in 31 patients over 1045 fractions. Over a mean fraction length of 7 minutes and 21 seconds, margins of 3mm would result in geometric coverage of the PTV 93.1% of the time and 5mm margins would ensure geometric coverage 99.4% of the time [61]. Within 180 seconds of set-up, the prostate remains within 3mm of starting position for 95.5% of the time. Bittner et al. examined prostate motion in the prone position, which may not be predictive of motion in the supine position, but found that over a mean tracking time of 12 minutes, the centroid of the transponders was ≥4mm for 4.5% of the time [62]. Langen et al. used Calypso to monitor prostate motion in 17 patients over 550 fractions. They found that the prostate was displaced >3mm and >5mm for 13.6% and 3.3% of the time respectively over a mean treatment time of 10 minutes. It seems likely therefore that margins between 3 and 5mm would be sufficient to cover intrafraction prostate motion for 3+ minutes.

6.11 Do Patients In This Study Need Androgen Deprivation?

Roach et al. conducted a meta-analysis of 2742 men enrolled into RTOG trials of radiotherapy vs radiotherapy plus hormonal therapy. No evidence could be found that those with early stages of disease, such as those eligible for this study, have any benefit from adjuvant hormonal therapy [63].

D'Amico et al. randomised 206 men with clinically localized prostate cancer to radiotherapy with 70 Gy with or without ADT. A significant improvement in overall and disease-specific survival was found. However, nearly half the men in this study had Gleason 4+3 or higher disease and 12-13% had a PSA of >20 ng/mL [64]. In addition, a dose of 70 Gy would now be considered inadequate.

Denham et al. report the results of the RTOG 9601 trial which again randomised to radiotherapy with or without hormonal therapy or either 3 or 6 months duration [65]. Radiation dose in this trial was 66 Gy. The trial showed a significant improvement in disease-free survival with the addition of hormonal therapy, however over 80% of patients were in the high risk group and once again the dose was low.

A large study of over 1200 men treated across three institutions with EBRT and HDR boost [66]. This showed no benefit in the addition of ADT on overall survival, cause-specific survival and bRFS. In addition the use of ADT was associated with an increase in the development of metastases and of cancer-specific death rates, although clearly this was confounded by the discretionary nature of ADT in this scenario.

Nearly two thousand men were entered into a trial which randomised to short-course hormones with radiotherapy or radiotherapy alone, given to a dose of 66 Gy to the prostate [67]. This showed an improvement in disease-specific and overall survival, but subgroup analysis showed this only to be the case for intermediate risk patients.

The studies discussed above included men with a mixture of prostate cancer stages, used doses of radiotherapy now considered suboptimal, and were largely conducted in the pre-IMRT and IGRT era. There is, therefore, no convincing evidence that men with low and intermediate prostate cancer benefit from the addition of ADT to radiotherapy. Indeed there is some evidence that the addition of ADT may increase the α/β ratio of prostate cancer cells, thereby reducing the predicted therapeutic benefit of hypofractionation [68]. The NCCN guidelines for prostate cancer state that men with low risk prostate cancer should not be given ADT (NCCN 2014).

A recently published study has analysed the RTOG 9406 trial data and found that in this cohort of men who received a mean dose of 78.5 Gy, the addition of hormonal therapy was of no benefit to those in any risk group, although there was a non-significant trend to improved bRFS in the high risk group [69]. This suggests that adjuvant hormonal therapy may not be the standard of care for low- and intermediate-risk patients.

Recent retrospective analyses have tried to delineate the subgroup of intermediate-risk patients who may benefit from hormonal therapy. Zumsteg et al. found that intermediate risk patients treated with >81 Gy and short-course hormonal therapy had superior biochemical control and prostate cancer specific mortality compared with those treated with radiation alone. This contrasts with the results of two other studies which showed no significant improvement in biochemical outcomes with androgen deprivation in intermediate risk disease [69, 70].

The EORTC 22991 trial randomised men with intermediate (64%) and high risk (36%) disease to radiotherapy +/- 6 months of ADT [71]. MRI staging was not mandatory. Radiotherapy was given to a dose of 70-78Gy depending on centre policy. At a median follow up of 7.2 years, there was a significant biochemical relapse-free advantage 49.1% vs 28.8%. No interaction with radiotherapy dose was noted, but PSA control rates were around half of those seen in CHHiP trial, so the relevance of this trial to the PACE population are not clear.

However, for upper intermediate risk and some high risk patients, 6 months of ADT is considered standard of care [72, 73] and is therefore a requirement for PACE -C .
During the COVID19 pandemic (starting in the UK ~March 2020) treatment recommendations based on expert opinion were to extend ADT beyond 6 months in order to permit a delayed start to radiotherapy[74, 75]. For patients recruited in 2020, and affected by the COVID-19 pandemic, there is no restriction on length of time patients can be on ADT prior to randomisation, as long as the total length of time on ADT is ≤18 months in total and radiotherapy is completed before ADT is completed.

6.12 Radiobiological Rationale For Study Doses

Table 1: Summary of BED Doses For Conventional and Hypofractionated Radiotherapy

	BED if α/β ratio = 5 Gy	BED if α/β ratio = 4 Gy	BED if α/β ratio = 3Gy	BED if α/β ratio = 2Gy	BED if α/β ratio = 1.5Gy
78 Gy in 39 fractions	109 Gy	117 Gy	130 Gy	156 Gy	182 Gy
62 Gy in 20 fractions	100 Gy	110 Gy	126 Gy	158 Gy	190 Gy
60 Gy in 20 fractions	96 Gy	105 Gy	120 Gy	150 Gy	180 Gy
36.25 Gy in 5 fractions	88 Gy	101 Gy	123Gy	168 Gy	211 Gy
40 Gy in 5 fractions	104 Gy	120 Gy	147 Gy	200 Gy	253 Gy

In summary, it is likely that the therapeutic ratio can be improved by hypofractionation and, whilst moderate hypofractionation is likely to become a new standard of care, the next question is whether more profound hypofractionation can improve outcomes for men with prostate cancer.

7 PACE-A

7.1 PACE-A Study Objectives

7.1.1 PACE-A Primary Objectives

7.1.1.1 To determine whether there is improved quality of life following prostate SBRT compared with prostatectomy two years from completion of trial treatment.

7.1.2 PACE-A Secondary Objectives

7.1.2.1 To determine whether prostate SBRT is non-inferior to surgery for freedom from biochemical/clinical failure in low/ intermediate risk prostate cancer.

7.1.2.2 To determine the relative benefits of surgery and prostate SBRT in terms of local failure, distant failure, disease-free survival, disease-specific survival, overall survival, toxicity, quality of life in generic and organ specific domains.

7.2 PACE-A Study Design

In PACE-A, patients considered candidates for surgery, agreed by both the physician and patient, are randomised to either prostatectomy (control) or prostate SBRT delivered to a dose of 36.25 Gy in 5 fractions.

Randomisation will be stratified by randomising centre and by risk group (see Appendix 2).

Low Risk includes all of the following:

- Clinical stage T1c – T2a
- PSA <10 ng/ml
- Gleason score ≤ 6

Intermediate Risk includes the presence of any of the following:

- Clinical stage T2b-T2c
- PSA 10 – 20 ng/ml
- Gleason score 3+4

7.3 PACE-A Primary Endpoints

Co-primary endpoints:

(1) Urinary incontinence (number of absorbent pads required per day to control leakage) measured by The Expanded Prostate Cancer Index (EPIC) questionnaire.

(2) Bowel bother summary score from the EPIC questionnaire.

The primary time point of interest is two years from completion of trial treatment.

7.4 PACE-A Secondary Endpoints

7.4.1 Freedom from biochemical (Phoenix definition for SBRT >0.2 ng/ml for surgical arm) or clinical (commencement of androgen deprivation therapy, local recurrence, nodal recurrence or distant metastases) failure. The primary timepoint of interest is 5 years from randomisation.

7.4.2 Clinician reported acute toxicity, assessed using CTCAE v4.03, RTOG (for SBRT) and the Clavien scale (to assess acute post surgical complications for surgical patients).

7.4.3 Clinician reported late toxicity, assessed using CTCAE v4.03 and RTOG (for SBRT).

7.4.4 Patient reported outcomes and quality of life assessment for all patients: Assessed using International Index of Erectile Function-5 (IIEF-5)[30], International Prostate Symptom Score (IPSS)[76], Vaizey score[77], Expanded Prostate Index Composite-26 (EPIC-26)[31].

7.4.5 Disease-specific and overall survival.

7.4.6 Progression-free survival (radiographic, clinical or biochemical evidence of local or distant failure).

7.4.7 Commencement of androgen deprivation therapy (LHRH analogues, anti-androgens, orchidectomy).

7.5 Definition of Biochemical Failure

All biochemical failures need to be confirmed with a second PSA meeting the criteria for failure. In addition, it is now recognised that after SBRT a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years[13, 78, 79]. 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, for patients receiving SBRT, PSA failure before 24 months will require 3 consecutive rises in PSA resulting in a clinical diagnosis of failure, or commencement of further treatment (eg androgen deprivation therapy). After 24 months, the definition of PSA failure for patients receiving radiotherapy will revert to the Phoenix definition (i.e. nadir+2 ng/ml, see section 13.2.3.1).

7.6 PACE-A Patient Selection

Patients suitable for surgery and willing to consider a surgical treatment will be invited to enter PACE A.

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

7.6.1 PACE-A Inclusion Criteria: All of the following criteria are mandatory for inclusion:

7.6.1.1 Histological confirmation of prostate adenocarcinoma with a minimum of 10 biopsy cores taken within 18 months of randomisation (unless on active surveillance and not clinically indicated*)

**This requirement for biopsy within 18 months of randomisation may be omitted (unless clinically indicated) if the patient has become a candidate for radical treatment (e.g. due to patient choice or PSA/MRI progression) while being followed up in an active surveillance programme. The patient's most recent biopsy must satisfy all other relevant PACE trial eligibility criteria. In addition the patient must have a recent MRI confirming organ confined disease, within 8 weeks of the decision to treat. Patients progressing on Active Surveillance (AS) will be considered as having intermediate risk disease, and treated accordingly.*

7.6.1.2 Gleason score ≤ 3+4

7.6.1.3 Men aged ≥18 years

7.6.1.4 Clinical and/or MRI stage T1c –T2c, N0-X, M0-X (TNM 6th Edition[80], See Appendix 1)

7.6.1.5 PSA ≤ 20 ng/ml (within 60 days prior to randomisation)

7.6.1.6 Patients belonging to one of the following risk groups (See Appendix 2)

- Low risk (includes <u>all</u> of the following):
  - Gleason ≤6
  - Clinical stage T1-T2a
  - PSA <10 ng/ml
- Intermediate risk (includes <u>any one</u> of the following):
  - Gleason 3+4
  - Clinical stage T2b or T2c
  - PSA 10-20 ng/ml

7.6.1.7 WHO performance status 0 – 2

7.6.1.8 Ability of the research subject to understand and the willingness to sign a written informed consent document

7.6.1.9 Ability/willingness to comply with the patient reported outcome questionnaires schedule throughout the study.

7.6.2 PACE-A Exclusion Criteria: One of the following criteria is sufficient for exclusion:

7.6.2.1 Clinical stage T3 or greater

7.6.2.2 Gleason score ≥ 4 + 3

7.6.2.3 High risk disease (See Appendix 2)

7.6.2.4 Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival.

7.6.2.5 Prior pelvic radiotherapy

7.6.2.6 Prior androgen deprivation therapy (including LHRH agonists and antagonists and anti-androgens).

7.6.2.7 Any prior active treatment for prostate cancer. Patients previously on active surveillance are eligible if they continue to meet all other eligibility criteria.

7.6.2.8 Life expectancy <5 years

7.6.2.9 Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts.

7.6.2.10 Medical conditions likely to make radiotherapy inadvisable e.g. inflammatory bowel disease, significant urinary symptoms.

7.6.2.11 For patients having fiducials inserted. Anticoagulation with warfarin/ bleeding tendency making fiducial placement or surgery unsafe in the opinion of the clinician (see section 11, Treatment).

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7.6.2.12 Participation in another concurrent treatment protocol for prostate cancer.

7.7 PACE-A Study Assessments

Patients will be screened for eligibility based on the inclusion/exclusion criteria.

7.7.1 PACE-A Pre-Randomisation Evaluations (required for eligibility)

The following evaluations should be performed within 6 weeks preceding randomisation unless otherwise indicated:

7.7.1.1 Complete history and physical examination (DRE if clinically indicated)

7.7.1.2 Assessment of fitness for anaesthetic by surgeon/ anaesthetist/research nurse

7.7.1.3 Assessment of performance status (recorded using WHO scale)

7.7.1.4 Pathological confirmation of adenocarcinoma of the prostate with Gleason scoring within 18 months of randomisation (unless on active surveillance and biopsy not clinically indicated, see Section 7.6.1.1).

7.7.1.5 Local staging assessments may include digital rectal exam (DRE) and transrectal ultrasound (TRUS). It is recommended that MRI of the pelvis be used for staging purposes. These assessments do not have to be done within 6 weeks preceeding randomisation.

7.7.1.6 PSA to be checked within 60 days of randomisation

7.7.1.7 Patient should be able to complete patient questionnaires:

- International Prostate Symptom Score (IPSS)
- International Index for Erectile Function-5 (IIEF-5)
- The Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire
- Vaizey Incontinence Questionnaire

7.7.2 PACE-A Pre-Treatment Evaluations

7.7.2.1 Within 6 weeks prior to the start of treatment testosterone will be measured and baseline symptoms will be assessed using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 4.03 and RTOG bladder and bowel toxicity scoring (for patients randomised to receive SBRT).

7.7.3 PACE-A Evaluations During and Following Treatment

7.7.3.1 Patients will be assessed regularly (as per Table 2 (PACE A) during treatment and after completion of radiotherapy or from the date of surgery. For SBRT, toxicities will be recorded on the day the last fraction is delivered. For surgery, toxicities will be recorded on last day of hospitalisation. Clavien toxicity score will be taken on the last day of hospitalisation, week 2 and 4 for surgery patients.

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7.7.3.2 For the first 12 weeks after treatment completion, toxicity assessments will be recorded at each clinic attendance for all patients and then 3-monthly for the first 2 years, 6-monthly to year 5 and annually to year 10. PSA will be recorded at 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter.

7.7.3.3 At all timepoints, toxicity assessment will record the maximal toxicity since the last toxicity assessment.

7.7.3.4 Evaluations at all time points may be done as a telephone consultation, at the discretion of the treating clinician.

7.7.3.5 At 4 weeks, 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter (until year 5) the following will be recorded: EPIC-26, IIEF-5 (not recorded at 4 weeks and 9 months), IPSS and Vaizey. There are two additional assessments of IPSS at week 2 and week 8 following treatment.

Quality of life booklets should be handed out in clinic at all relevant time points, and completed by the patient. Every effort should be made to ensure that the questionnaires are completed. Please aim to ensure that all questions and all pages have been completed by the patient when the booklet is handed in; see section 10.7 for full details regarding administration of the quality of life booklets.

7.7.3.6 Follow-up visit windows:

- During treatment: ± 3 days
- Week 2 and Week 4 visit: ± 3 days
- Week 8 and Week 12 visit: ± 1 week
- Month 6 and Month 9: ± 2 weeks
- Month 12 and thereafter: ± 4 weeks.

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Table 2: PACE A (Surgery vs. SBRT) Schedule of Assessments

	Pre-randomisation	Pre-treatment	Last day of hospitalisation (surgery pts) or last fraction (SBRT pts)	Follow up post completion of treatment							
Assessment				**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Month 6**	**Month 9**	**Year 1 to year 5**	**Year 6 to year 10**
Clinical history	x										
Physical Examination (DRE if clinically indicated)	x										
ASA score (surgery patients only)	x										
PSA	x						x	x	x	x	x
Testosterone		x									
MRI pelvis [a]	x										
CTCAE		x	x	x	x	x	x	x	x	x	x
RTOG: bladder and bowel (SBRT patients only)		x	x	x	x	x	x	x	x	x	x
Clavien toxicity score (surgery patients only)			x	x	x						
QOL: (EPIC-26, IPSS, IIEF-5, Vaizey)	x			x[b]	x[c]	x[b]	x	x	x[c]	x[d]	

[a] MRI is recommended for staging purposes. MRI is strongly recommended for radiotherapy planning purposes.

[b] IPSS ONLY required at week 2 and week 8.

[c] IIEF-5 should NOT be reported at week 4 and month 9.

[d] Yearly to year 5.

Additional follow-up and investigations are permitted as per usual institutional policy.

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8 PACE-B

PACE-B closed to recruitment on 5th January 2018.

8.1 PACE-B Primary Objectives

8.1.1 To determine whether prostate SBRT is non-inferior to conventional radiotherapy for freedom from biochemical/clinical failure in low/intermediate risk prostate cancer.

8.2 PACE-B Secondary Objectives

8.2.1 To determine the relative benefits of conventional radiotherapy and prostate SBRT in terms of local failure, distant failure, disease-free survival, disease-specific survival, overall survival, toxicity, quality of life in generic and organ specific domains.

8.3 PACE-B Study Design

In PACE-B, nonsurgical candidates or patients who decline surgery are randomised to either conventional radiotherapy (control) or prostate SBRT (36.25 Gy in 5 fractions). From version 7 of the protocol, centres will be asked to select a control arm of either 78 Gy in 39 fractions or 62 Gy in 20 fractions and this will be used for all PACE-B patients allocated to the control group. Centres will be permitted to change their control arm from 78 Gy in 39 fractions to 62 Gy in 20 fractions at any point after version 7 of the protocol is implemented, but this schedule must then be used for all patients subsequently entered at that centre.

Randomisation will be stratified by randomising centre (and hence by choice of control group fractionation) and by risk group (see Appendix 2).

Low Risk includes all of the following:

- Clinical stage T1c – T2a
- PSA <10 ng/ml
- Gleason score ≤6

Intermediate Risk includes the presence of any of the following:

- Clinical stage T2b-T2c
- PSA 10 – 20 ng/ml
- Gleason score 3+4

8.4 PACE-B Primary Endpoint

8.4.1 Freedom from biochemical (Phoenix definition) or clinical (commencement of androgen deprivation therapy, local recurrence, nodal recurrence or distant metastases) failure. The primary timepoint of interest is 5 years from randomisation.

8.5 PACE-B Secondary Endpoints

8.5.1 Clinician reported acute toxicity, assessed using CTCAE v4.03, and RTOG.

8.5.2 Clinician reported late toxicity, assessed using CTCAE v4.03 and RTOG.

8.5.3 Patient reported outcomes and quality of life assessment for all patients: Assessed using International Index of Erectile Function-5 (IIEF-5)[30], International Prostate Symptom Score (IPSS)[76], Vaizey score[77], Expanded Prostate Index Composite-26 (EPIC-26)[31].

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8.5.4 Disease-specific and overall survival.

8.5.5 Progression-free survival (radiographic, clinical or biochemical evidence of local or distant failure).

8.5.6 Commencement of androgen deprivation therapy (LHRH analogues, anti-androgens, orchidectomy).

8.6 Definition of Biochemical Failure

All biochemical failures need to be confirmed with a second PSA meeting the criteria for failure. In addition, it is now recognised that after SBRT a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years[53, 78, 79]. 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, for patients receiving SBRT or conventional radiotherapy, PSA failure before 24 months will require 3 consecutive rises in PSA resulting in a clinical diagnosis of failure, or commencement of further treatment (eg androgen deprivation therapy). After 24 months, the definition of PSA failure for patients receiving radiotherapy will revert to the Phoenix definition (i.e. nadir+2 ng/ml, see section 13.2.3.1).

8.7 PACE-B Patient Selection

Patients who are not suitable for surgery or are unwilling to consider an operation will be invited to enter PACE B.

8.7.1 PACE-B Inclusion Criteria: All of the following criteria are mandatory for inclusion:

8.7.1.1 Histological confirmation of prostate adenocarcinoma with a minimum of 10 biopsy cores taken within 18 months of randomisation (unless on active surveillance and not clinically indicated*).

**This requirement for biopsy within 18 months of randomisation may be omitted (unless clinically indicated) if the patient has become a candidate for radical treatment (e.g. due to patient choice or PSA/MRI progression) while being followed up in an active surveillance programme. The patient's most recent biopsy must satisfy all other relevant PACE trial eligibility criteria. In addition the patient must have a recent MRI confirming organ confined disease, within 8 weeks of the decision to treat. Patients progressing on Active Surveillance (AS) will be considered as having intermediate risk disease, and treated accordingly.*

8.7.1.2 Gleason score ≤ 3+4

8.7.1.3 Men aged ≥18 years

8.7.1.4 Clinical and/or MRI stage T1c –T2c, N0-X, M0-X (TNM 6th Edition[80], See Appendix 1)

8.7.1.5 PSA ≤ 20 ng/ml (within 60 days prior to randomisation)

8.7.1.6 Patients belonging in one of the following risk groups (See Appendix 2)

- Low risk (includes <u>all</u> of the following):
  - Gleason ≤ 6
  - Clinical stage T1-T2a
  - PSA < 10 ng/ml
- Intermediate risk (includes <u>any one</u> of the following):
  - Gleason 3+4
  - Clinical stage T2b orT2c
  - PSA 10-20 ng/ml or

8.7.2 WHO performance status 0 – 2

8.7.3 Ability of the research subject to understand and the willingness to sign a written informed consent document

8.7.4 Ability/willingness to comply with the patient reported outcome questionnaires schedule throughout the study.

8.7.5 PACE-B Exclusion Criteria: One of the following criteria is sufficient for exclusion:

8.7.5.1 Clinical stage T3 or greater

8.7.5.2 Gleason score ≥ 4 + 3

8.7.5.3 High risk disease (See Appendix 2)

8.7.5.4 Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival

8.7.5.5 Prior pelvic radiotherapy

8.7.5.6 Prior androgen deprivation therapy (including LHRH agonists and antagonists and anti-androgens)

8.7.5.7 Any prior active treatment for prostate cancer. Patients previously on active surveillance are eligible if they continue to meet all other eligibility criteria.

8.7.5.8 Life expectancy <5 years

8.7.5.9 Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artifacts

8.7.5.10 Medical conditions likely to make radiotherapy inadvisable e.g. inflammatory bowel disease, significant urinary symptoms

8.7.5.11 For patients having fiducials inserted. Anticoagulation with warfarin/ bleeding tendency making fiducial placement or surgery unsafe in the opinion of the clinician (see section 11, Treatment).

CONFIDENTIAL

8.7.5.12 Participation in another concurrent treatment protocol for prostate cancer.

8.8 PACE-B Study Assessments

Patients will be screened for eligibility based on the inclusion/exclusion criteria.

8.8.1 PACE-B Pre-Randomisation Evaluations (required for eligibility)

The following evaluations should be performed within 6 weeks preceding randomisation unless otherwise indicated:

8.8.1.1 Complete history and physical examination (DRE if clinically indicated)

8.8.1.2 Assessment of performance status (recorded using WHO scale)

8.8.1.3 Pathological confirmation of adenocarcinoma of the prostate with Gleason scoring within 18 months of randomisation (unless on active surveillance and biopsy not clinically indicated, see Section 8.7.1.1).

8.8.1.4 Local staging assessments may include digital rectal exam (DRE) and transrectal ultrasound (TRUS). It is recommended that MRI of the pelvis be used for staging purposes. These assessments do not have to be done within 6 weeks preceeding randomisation.

8.8.1.5 PSA to be checked within 60 days of randomisation.

8.8.1.6 Patient should be able to complete patient questionnaires:

- International Prostate Symptom Score (IPSS)
- International Index for Erectile Function-5 (IIEF-5)
- The Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire
- Vaizey Incontinence Questionnaire

8.8.2 PACE-B Pre-Treatment Evaluations

8.8.2.1 Within 6 weeks prior to the start of treatment testosterone will be measured and baseline symptoms will be assessed using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 4.03 and RTOG bladder and bowel toxicity.

8.8.3 PACE-B Evaluation During and Following Treatment

8.8.3.1 Patients will be assessed regularly (as per Table 3 (PACE-B)) during treatment and after completion of radiotherapy. For conventional radiotherapy, toxicity assessment will be recorded at weeks 2, 4, 6 and 8 during treatment (dependent on duration of treatment – see Table 3). For SBRT, toxicities will be recorded on the day the last fraction is delivered.

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8.8.3.2 For the first 12 weeks after treatment completion, toxicity assessments will be recorded at each clinic attendance for all patients and then 3-monthly for the first 2 years, 6-monthly to year 5 and annually to year 10. PSA will be recorded at 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter.

8.8.3.3 At all timepoints, toxicity assessment will record the maximal toxicity since the last toxicity assessment.

8.8.3.4 Follow up may be done as a telephone consultation, at the discretion of the treating clinician.

8.8.3.5 At 4 weeks, 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter (until year 5) the following will be recorded: EPIC-26, IIEF-5 (not recorded at 4 weeks and 9 months), IPSS and Vaizey. There are two additional assessments of IPSS at week 2 and week 8 following treatment.

Quality of life booklets should be handed out in clinic at all relevant time points, and completed by the patient. Every effort should be made to ensure that the questionnaires are completed. Please aim to ensure that all questions and all pages have been completed by the patient when the booklet is handed in; see section 10.7 for full details regarding administration of the quality of life booklets.

8.8.3.6 Follow-up visit windows:

- During treatment: ± 3 days
- Week 2 and Week 4 visit: ± 3 days
- Week 8 and Week 12 visit: ± 1 week
- Month 6 and Month 9: ± 2 weeks
- Month 12 and thereafter: ± 4 weeks

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Table 3: PACE B (Conventional Radiotherapy vs SBRT) Schedule of Assessments

	Pre-randomisation	Pre-treatment	During treatment for conventioal radiotherapy				Last frxn for SBRT	Follow up post completion of treatment							
Assessment			**Wk 2**	**Wk 4**	**Wk 6[e]**	**Wk 8[e]**		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Month 6**	**Month 9**	**Year 1 to year 5**	**Year 6 to year 10**
Clinical history	x														
Physical Examination (DRE if clinically indicated)	x														
PSA	x										x	x	x	x	x
Testosterone		x													
MRI pelvis [a]	x														
CTCAE		x					x	x	x	x	x	x	x	x	x
RTOG: bladder and bowel		x	x	x	x	x	x	x	x	x	x	x	x	x	x
QOL: (EPIC-26, IPSS, IIEF-5, Vaizey)	x							x[b]	x[c]	x[b]	x	x	x[c]	x[d]	

[a] MRI is recommended for staging purposes. MRI imaging is strongly recommended for radiotherapy planning purposes.

[b] IPSS ONLY required at week 2 and week 8.

[c] IIEF-5 should NOT be reported at week 4 and month 9.

[d] Yearly to year 5.

[e] For conventional radiotherpay 78Gy in 39 fractions only.

Additional follow-up and investigations are permitted as per usual institutional policy.

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9 PACE-C

9.1 PACE-C Primary Objectives

9.1.1 To determine whether prostate SBRT is non-inferior to conventional radiotherapy for freedom from biochemical/clinical failure in intermediate/high risk prostate cancer.

9.2 PACE-C Secondary Objectives

9.2.1 To determine the relative benefits of surgery, conventional radiotherapy and prostate SBRT in terms of local failure, distant failure, disease-free survival, disease-specific survival, overall survival, toxicity, quality of life in generic and organ specific domains.

9.3 PACE-C Study Design

In PACE-C, nonsurgical candidates or patients who decline surgery are randomised to either conventional radiotherapy (60Gy in 20 fractions) or prostate SBRT (36.25 Gy in 5 fractions).

Randomisation will be stratified by randomising centre and by PACE-C stratification risk group (see Appendix 2).

9.3.1 PACE-C Stratification Risk Groups

Intermediate risk (includes the presence of any of the following, assuming no high risk features apply):

- Gleason 7 (3+4 OR 4+3)
- T2
- PSA 10-20 ng/ml

High risk includes the presence of any one of the following (max 2 are allowed to be PACE eligible)

- Gleason 4+4*
- T3a (M0N0)
- PSA >20-30 ng/ml

*Maximum 50% of number of cores can be Gleason 4+4

9.4 PACE-C Primary Endpoints

9.4.1 Freedom from biochemical (Phoenix definition) or clinical (recommencement of androgen deprivation therapy >3 months after completing the neoadjuvant/adjuvant course of ADT, local recurrence, nodal recurrence or distant metastases) failure. The primary timepoint of interest is 5 years from randomisation.

9.5 PACE-C Secondary Endpoints

9.5.1 Clinician reported acute toxicity, assessed using CTCAE v4.03, and RTOG.

9.5.2 Clinician reported late toxicity, assessed using CTCAE v4.03 and RTOG.

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9.5.3 Patient reported outcomes and quality of life assessment for all patients: Assessed using International Index of Erectile Function-5 (IIEF-5)[30], International Prostate Symptom Score (IPSS)[76], Vaizey score[77], Expanded Prostate Index Composite-26 (EPIC-26)[31].

9.5.4 Disease-specific and overall survival.

9.5.5 Progression-free survival (radiographic, clinical or biochemical evidence of local or distant failure).

9.5.6 Recommencement of androgen deprivation therapy (defined as restarting ADT >3 months after completing the neoadjuvant/adjuvant course of ADT).

9.6 Definition of Biochemical Failure

All biochemical failures need to be confirmed with a second PSA meeting the criteria for failure. In addition, it is now recognised that after SBRT a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years[53, 78, 79]. 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, for patients receiving SBRT or conventional radiotherapy, PSA failure before 24 months will require 3 consecutive rises in PSA and a PSA >2 ng/ml, resulting in a clinical diagnosis of failure, or recommencement of further treatment (eg androgen deprivation therapy). In this scenario, the date of failure will be the first time the PSA exceeds nadir+2. After 24 months, the definition of PSA failure for patients receiving radiotherapy will revert to the Phoenix definition (i.e. nadir+2 ng/ml, see section 13.2.3.1).

9.7 PACE-C Patient Selection

Patients who are not suitable for surgery or who do not wish to consider an operation, and who are planned to receive 6 months of ADT (or, for those diagnosed or due to start radiotherapy during the COVID19 pandemic, planned to receive extended ADT to allow delayed radiation), will be invited to enter PACE-C.

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

9.7.1 PACE-C Inclusion Criteria: All of the following criteria are mandatory for inclusion

9.7.1.1 Histological confirmation of prostate adenocarcinoma within 18 months of randomisation (unless on active surveillance and not clinically indicated*).

**This requirement for biopsy within 18 months of randomisation may be omitted (unless clinically indicated) if the patient has become a candidate for radical treatment (e.g. due to patient choice or PSA/MRI progression) while being followed up in an active surveillance programme. The patient's most recent biopsy must satisfy all other relevant PACE trial eligibility criteria. In addition, the patient must have a recent MRI confirming organ confined disease. Patients progressing on Active Surveillance (AS) will be stratified into the risk group which is most*

appropriate considering their T stage, PSA and last known biopsy, and treated accordingly.

9.7.1.2 Gleason score ≤ 4+4

9.7.1.3 Men aged ≥18 years

9.7.1.4 MRI stage T1c –T3a, N0-X, M0-X (TNM 6th Edition[80], See Appendix 1)

9.7.1.5 PSA≤ 30 ng/ml (prior to starting ADT). PSA ≤ 15 ng/ml for patients on 5-alpha reductase inhibitors.

9.7.1.6 NCCN intermediate risk or high risk disease (within the limits of the other PACE-C eligibility criteria) (See Appendix 2) i.e.:

- **Intermediate risk** includes <u>any one</u> of the following:
  - MRI stage T2 (N0, M0-X)
  - PSA 10-20 ng/ml (prior to starting ADT)
  - Gleason 3+4 or Gleason 4+3
- **High risk** includes <u>1-2</u> of the following:
  - MRI stage T3a (N0, M0)
  - PSA >20-30 ng/ml (prior to starting ADT)
  - Gleason 4+4 (and ≤50% cores positive)

* Patients will be ineligible for PACE-C if MRI stage T3a <u>AND</u> PSA >20-30ng/ml <u>AND</u> 4+4

9.7.1.7 Patients with Gleason ≥4+3 or patients with PSA ≥20 ng/ml: No evidence of nodal or distant metastases, confirmed by bone scan or PET or WBDWMRI or MRI of the axial marrow.

9.7.1.8 Patient planned for a minimum of 6 months ADT (maximum of 12 months). Patients receiving extended androgen deprivation therapy (18 months maximum) to permit safe delay of radiotherapy as a result of the COVID19 pandemic (only) are eligible.

9.7.1.9 WHO performance status 0 – 2

9.7.1.10 Ability of the research subject to understand and the willingness to sign a written informed consent document

9.7.1.11 Ability/willingness to comply with the patient reported outcome questionnaires schedule throughout the study.

9.7.2 PACE-C Exclusion criteria: One of the following criteria is sufficient for exclusion

9.7.2.1 MRI stage ≥T3b

9.7.2.2 Gleason score ≥ 3 + 5, 4+5, 5+4, 5+3 or 5+5

9.7.2.3 Low risk disease (See Appendix 2) or intermediate risk disease suitable for Active surveillance

9.7.2.4 Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival

9.7.2.5 Prior pelvic radiotherapy

9.7.2.6 Received >14 weeks of ADT prior to randomisation, except that patients receiving extended androgen deprivation therapy to permit safe delay of radiotherapy as a result of the COVID19 pandemic (only) are eligible. For these patients there is no restriction on

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duration of ADT prior to randomisation, as long as the total length of time on ADT is ≤18 months and radiotherapy is completed before ADT is completed.

9.7.2.7 Medical conditions likely to make ADT inadvisable (e.g. significant and ongoing cardiac issues).

9.7.2.8 Any prior active treatment for prostate cancer. Patients previously on active surveillance are eligible if they continue to meet all other eligibility criteria.

9.7.2.9 Life expectancy <5 years

9.7.2.10 Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artifacts

9.7.2.11 Medical conditions likely to make radiotherapy inadvisable eg inflammatory bowel disease, significant urinary symptoms

9.7.2.12 For patients having fiducials inserted: Anticoagulation with warfarin/ bleeding tendency making fiducial placement or surgery unsafe in the opinion of the clinician (see section 11, Treatment).

9.7.2.13 Participation in another concurrent treatment protocol for prostate cancer

9.8 PACE-C Study Assessments

Patients will be screened for eligibility based on the inclusion/exclusion criteria.

9.8.1 Pre-Randomisation Evaluations (required for eligibility).

The following evaluations should be performed:

9.8.1.1 Complete history and physical examination (if clinically indicated) (within 6 weeks preceding randomisation).

9.8.1.2 Assessment of performance status (recorded using WHO scale) (within 6 weeks preceding randomisation).

9.8.1.3 Pathological confirmation of adenocarcinoma of the prostate with Gleason scoring within 18 months of randomisation (unless on active surveillance and biopsy not clinically indicated (see Section 9.7.1.1)).

9.8.1.4 MRI of the pelvis prior to biopsy to be used for staging purposes. This is mandatory.

9.8.1.5 For patients with Gleason ≥4+3 or patients with PSA ≥20 ng/ml, a bone scan/other systemic imaging must be done to confirm the absence of metastases. A bone scan is reccommended but imaging (PET or WBDWMRI or MRI of the axial marrow) may be substituted where this is standard of care.

9.8.1.6 PSA for eligibiliy to be checked prior to starting ADT (must be ≤30ng/ml, or ≤15ng/ml for patients on 5-alpha reductase inhibitors).

9.8.1.7 Patient should be able to complete patient questionnaires:

- International Prostate Symptom Score (IPSS)
- International Index for Erectile Function-5 (IIEF-5)
- The Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire

  Vaizey Incontinence Questionnaire

9.8.2 Pre-treatment evaluations

9.8.2.1 PSA within 45 days prior to starting radiotherapy (on ADT). For patients with multiple PSAs taken for clinical reasons, the PSA closest to starting radiotherapy will be recorded.

9.8.2.2 Baseline symptoms, assessed using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 4.03 and RTOG bladder and bowel toxicity scoring. This should be done after consent and **before fiducial insertion** (if being used) whilst the patient is on ADT.

9.8.3 Evaluation during and following treatment.

9.8.3.1 Patients will be assessed regularly (as per Table 4 (PACE-C)) during treatment and after completion of radiotherapy. For conventional radiotherapy, RTOG assessment will be recorded at weeks 2 and 4 during treatment. For SBRT, RTOG will be recorded on the day the last fraction is delivered.

9.8.3.2 For the first 12 weeks after treatment completion, toxicity assessments will be recorded at each clinic attendance for all patients* and then 3-monthly for the first year, 6-monthly to year 5 and annually to year 10. PSA will be recorded at 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter.

** For PACE-C, the frequency of toxicity assessments will be reviewed once the first 200 patients have been recruited and data reviewed by the IDMC.*

9.8.3.3 At all timepoints, toxicity assessment will record the maximal toxicity since the last toxicity assessment.

9.8.3.4 Evaluations at all time points may be done as a telephone consultation, at the discretion of the treating clinician.

9.8.3.5 At 4 weeks, 12 weeks, 6, 9, and 12 months following treatment and yearly thereafter (until year 5) the following will be recorded: EPIC-26, IIEF-5 (not recorded at 4 weeks and 9 months), IPSS and Vaizey. There are two additional assessments of IPSS at week 2 and week 8 following treatment.

Quality of life booklets should be handed out in clinic up to week 12, and completed by the patient. Every effort should be made to ensure that the questionnaires are completed. Please aim to ensure that all questions and all pages have been completed by the patient when the booklet is handed in. From 6-months follow-up booklets will be sent by the ICR-CTSU to the patients' homes for completion. See section 10.7 for full details regarding administration of the quality of life booklets.

Where participating sites are taking part in the SPRUCE study (REC Ref: 21/WM/0223) PACE-C participants should be asked to join SPRUCE following completion of the PACE-C

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baseline booklet and randomisation into PACE-C. All PACE-C follow up quality of life booklets will be administered directly to participants by ICR-CTSU for patients participating in SPRUCE.

9.8.3.6 Follow-up visit windows:

- During treatment: ± 3 days
- Week 2 and Week 4 visit: ± 3 days
- Week 8 and Week 12 visit: ± 1 week
- Month 6 and Month 9: ± 2 weeks
- Month 12 and thereafter: ± 4 weeks

Table 4: PACE-C (Conventional Radiotherapy vs SBRT) Schedule of Assessments

	Pre-randomisation	Pre-treatment	During treatment for conventional radiotherapy		Last frxn for SBRT	Follow up post completion of treatment							
Assessment			**Week 2**	**Week 4**		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Month 6**	**Month 9**	**Year 1 to year 5**	**Year 6 to year 10**
Clinical history	X												
Physical Examination (if clinically indicated)	X												
PSA	X	x							x	x	x	x	x
MRI pelvis [a]	X												
Bone scan/other imaging [f]	X												
CTCAE		x				x	x	x	x	x	x	x	x
RTOG: bladder and bowel		x	x	X	x	x	x	x	x	x	x	x	x
QOL: (EPIC-26, IPSS, IIEF-5, Vaizey)	X					x[b]	x[c]	x[b]	x	x[e]	x[c, e]	x[d, e]	

[a] MRI is mandatory pre-biopsy for staging purposes. MRI imaging is strongly recommended for radiotherapy planning purposes.

[b] IPSS ONLY required at week 2 and week 8.

[c] IIEF-5 should NOT be reported at week 4 and month 9.

[d] Yearly to year 5.

[e] Questionnaires will be sent directly to the patient from ICR-CTSU from 6 months onwards, unless the participant is also taking part in SPRUCE – if so all questionnaires will be administered by ICR-CTSU after baseline.

[f] Bone scan/other systemic imaging required for all high risk patients and all intermediate risk patients with Gleason 4+3.

Additional follow-up and investigations are permitted as per usual institutional policy.

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10 Informed Consent, Randomisation and Other Procedures

10.1 Informed Consent Process

10.1.1 The protocol and the informed consent must have local ethics committee/IRB approval prior to research activity. The site Principal Investigator (PI) is responsible for ensuring that only a current ethics committee/IRB approved consent form designed specifically for the study is appropriately signed.

10.1.2 The written consent document should embody, in language understandable to the participant, all the elements necessary for legally informed consent. The trial will be conducted in English.

10.1.3 The site PI is responsible for ensuring that proper informed consent has been obtained from the research subject before any study/research activity is conducted. The site PI can designate authorised members of the research team to obtain the informed consent.

10.1.4 The site PI is ultimately responsible for determining whether a subject has the capacity to consent. As part of the consent process, the subject's questions must be answered prior to consent being given and throughout the study. The subject should be asked if there are any questions prior to consent being obtained.

10.1.5 When giving the consent, the subject needs to verbalize understanding, and sign and date the last page of the Consent Form along with the investigator or designee obtaining consent.

10.1.6 The signed consent will be filed in the patient's research study chart or record and the investigator site file. In addition, the subject will receive a copy of the consent form.

10.1.7 The sponsor or their delegate may need to review all consent documents if deemed necessary.

10.2 Randomisation Procedures

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

During the COVID-19 pandemic, in periods when the ICR-CTSU are working remotely, randomisations may be managed via email, randomisation-icrctsu@icr.ac.uk. Please refer to the most recent guidance provided by the trials team.

ALL UK & IRISH PATIENTS ARE RANDOMISED BY PHONE OR EMAIL
Complete the randomisation form and call **020 8643 7150** **or email randomisation-icrctsu@icr.ac.uk to request a call back** The randomisation service will be open from 09:00 to 17:00 (UK time) Monday – Friday

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Randomisation of other non-UK patients outside of UK office hours, should be requested by email at pace-icrctsu@icr.ac.uk. This will be processed on the next working day.

Further details of randomisation procedures for non-UK patients will be provided within the international site agreements.

An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of treating and recruiting 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.
- Patients initials, partial date of birth (month/year) and risk group.
- Patient's full name, hospital number, full date of birth, patient's postcode and NHS/CHI number (for UK patients only).

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

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

Treatment allocation will be 1:1 for surgery vs prostate SBRT (PACE-A) and 1:1 for conventional radiotherapy vs prostate SBRT (PACE-B and PACE-C). Treatment allocation will use computer generated random permuted blocks. Randomisation will be stratified by randomising centre and risk group.

PACE-B closed to recruitment on 5th January 2018.

10.3 Participation In Other Clinical Trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in PACE even if they have participated in other clinical trials prior to recruitment. Participation in non-interventional studies (eg UKGCPS study www.icr.ac.uk/ukgpcs or RAPPER study), is permitted. Participation in the ICR-CTSU study within a trial investigating electronic collection of patient reported outcomes, SPRUCE, is permitted. Participation in other clinical trials whilst participating in PACE will be considered on a trial by trial basis by the PACE Trial Management Group.

10.4 Tissue Donation For Translational Studies

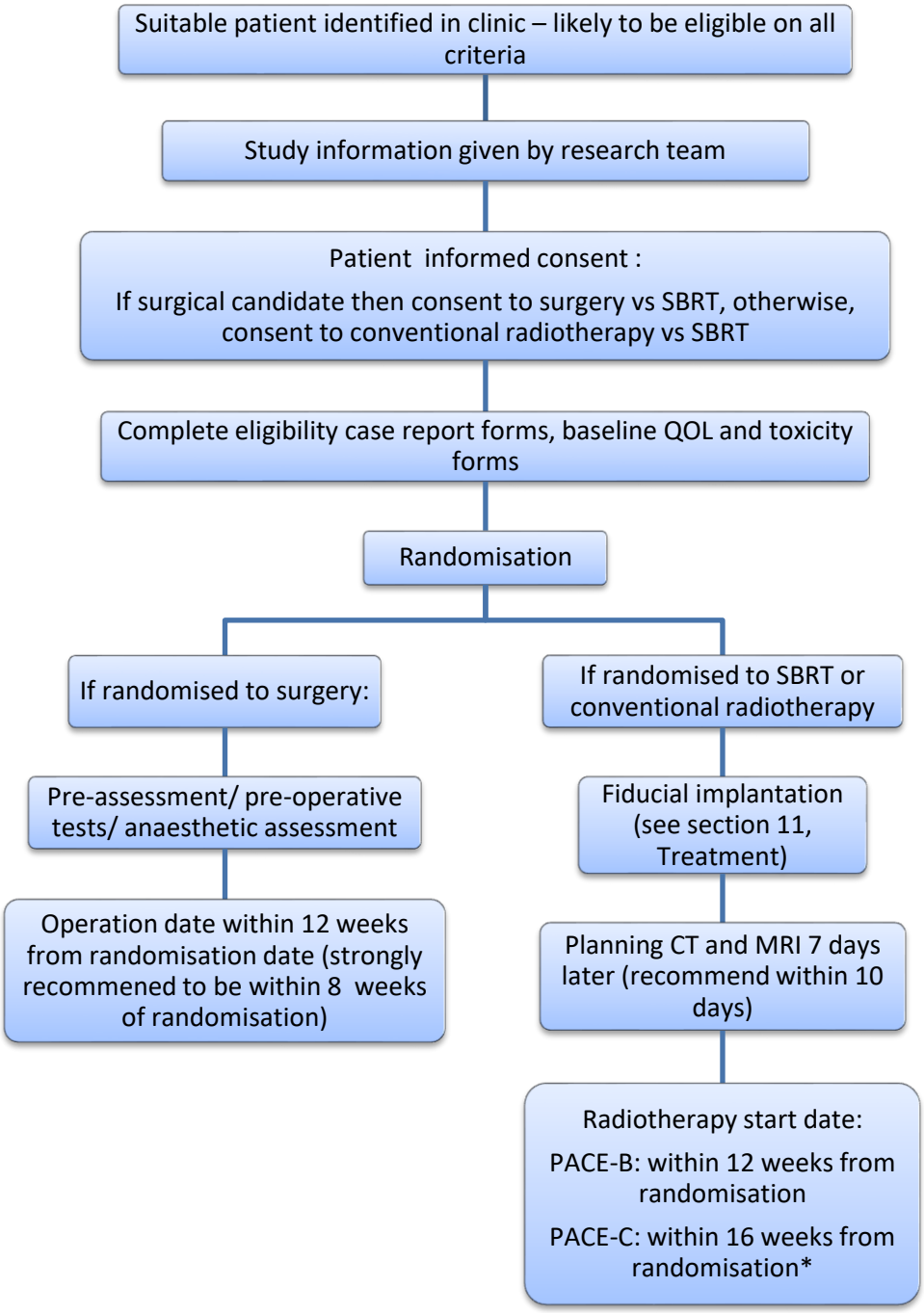
Patients will be asked at the time of consent whether they will agree to donate their biomaterials from diagnostic tissue samples for future translational research. This will be optional. The pathology number and storing hospital of donated samples will be recorded to facilitate retrospective collection of tissue for future translational studies. Patients provided with earlier versions of the patient information sheet (i.e. prior to v5 dated 5th August 2014) recruited prior to the tissue donation amendment may be invited to provide further consent for tissue donation retrospectively.

Translational research will not form part of the PACE study itself, but it is anticipated that data from PACE outcomes, along with tissues samples donated, may be used in future research studies.

10.5 Data Sharing

Combining data from many clinical trials, or using clinical trial data for secondary analyses, may help to further our knowledge of cancer and its treatment. In view of this, patients will be asked to consent to the sharing of their anonymised data with other legitimate researchers/third parties, in order to facilitate this. This will be optional. Patients provided with earlier versions of the patient information sheet (i.e. recruited prior to amendment 6) will be invited to provide further consent for sharing of anonymised data (this will only affect patients recruited at the Royal Marsden Hospital and Mount Vernon Hospital).

10.6 Patient Pathway



** In PACE-C delays to radiotherapy (with extended ADT) due to COVID19 clinical management strategies are permitted*

10.7 Instructions Regarding Administration of Patient Reported Study Questionnaires

These instructions are for the study coordinator or research nurse administering the questionnaires:

- All QL booklets will be administered by the centre, unless otherwise specified, in accordance with Tables 2, 3 and 4 of the PACE study protocol. The target timeframe for completion of follow up questionnaires will be +/- two weeks of the scheduled follow-up assessment.
- If possible the patient should be taken to a quiet area where he can complete the questionnaires prior to the clinic visit.
- Enough time should be allowed for the patient to complete the questionnaires.
- The patient should be encouraged to complete every item in order without skipping any. If the patient feels that a given question does not apply to him he should circle the response that is most applicable: no problem, not at all, none at the time, rarely or never.
- The questionnaires must be completed by the patient alone without coaching or suggestions by health care personnel or anyone else. The study staff might provide clarification without suggesting answers or discussing answers.
- The study staff will collect the questionnaires, checking for completeness. If a question or questionnaire has not been completed and the patient states he does not wish to answer the question or complete the questionnaire this can be documented on the questionnaire by the study coordinator/research nurse.
- If the patient does not come to the clinic the questionnaires can be posted to the patient by the site study staff, including a self addressed envelope so that the questionnaires can be returned to clinic. The patient will be reminded to complete and return the questionnaires in a timely manner during the phone follow-up.
- Completed patient questionnaires should be returned to the PACE Trial Manager at the ICR-CTSU.

Where participating sites are taking part in the SPRUCE study (REC Ref: 21/WM/0223) PACE-C participants should be asked to join SPRUCE following completion of the PACE-C baseline booklet and randomisation into PACE-C. All PACE-C follow up quality of life booklets will be administered directly to participants by ICR-CTSU for patients participating in SPRUCE.

10.8 Withdrawal of Patients From Study

During the course of the study, it is possible that patients will be withdrawn from the study. Factors leading to patient withdrawal may include, but are not limited to, the following:

- Patient withdrawal: A patient may voluntarily withdraw their consent from the study at any time without affecting their future medical treatment or benefits.

- Investigator termination: the investigator may terminate the patient's participation without regard to the patient's consent if the investigator believes it is medically necessary (e.g. if the patient becomes cognitively or physically incapacitated), the patient is not following the protocol, the Sponsor has stopped the study or other administrative reasons.

- Sponsor discontinuation: The sponsor may discontinue the study upon ethics committee request, or for safety issues. The sponsor shall promptly notify all investigators, and the applicable authorities in all relevant countries should the study be discontinued or

terminated prematurely. Should the study be terminated prematurely, all treatment related records and all due CRFs would be collected by the sponsor.

- Patient lost to follow-up: A patient will be considered lost to follow-up with documentation of three unsuccessful attempts by the Investigator or his/her designee to contact a patient or next of kin. For UK patients, if necessary, NHS and national health registration data will be used to obtain survival outcomes.

Patients who do not receive any or all of their allocated treatment for any reason should be treated at the discretion of their clinician. Unless the patient requests otherwise, all eCRFs, including long term follow-up, should be completed regardless of treatment actually received. A protocol deviation form should be completed to record details of deviation from treatment allocation.

Patients are asked prior to randomisation to consent to basic follow up information being provided from routine clinic visits should they withdraw from the study (see patient information sheet and consent form). Patients are however free to reverse their decision at any time without giving a reason. A study deviation form should be completed for any patient who withdraws consent for information to be provided on eCRFs or for attending study follow up visits.

Should a patient become cognitively or physically incapacitated at any point during the study they will be withdrawn for their own protection. If this were to happen during the course of the patient's radiotherapy their treatment should be reviewed as a clinical decision by the Principal Investigator at their centre. No further study procedures will be carried out and no further data will be collected on behalf of the study. Any data already collected about such patients will be fully anonymised. A study deviation form should be completed for any patient withdrawn from the study for this reason.

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. If this request is received after results have been published the course of action will be agreed between the Sponsor and independent Trial Steering Committee/Independent Data Monitoring and Steering Committee.

10.9 Compensation

Patients will not be paid. Patients, their health authorities and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol.

11 Treatment

11.1 Conventional Radiotherapy and SBRT Treatment Planning

11.1.1 Conventional Radiotherapy Treatment: In PACE B patients randomised to conventional radiotherapy received either 78Gy in 39 fractions daily over 8 weeks OR 62Gy in 20 fractions daily over at least 27 days, and delivered using IMRT, dependant on local practice. In PACE C patients randomised conventional radiotherapy will receive 60 Gy in 20 fractions over at least 27 days and delivered using IMRT. All specified doses are given over the entire course of treatment.

11.1.2 SBRT Treatment: In all cohorts patients randomised to SBRT, will recive 36.25 Gy given in 5 fractions over 1-2 weeks (i.e. daily or alternate daily).

11.1.3 Fiducial Placement: it is **strongly recommended** that all patients randomised to radiotherapy have fiducial markers implanted for image guidance. Fiducial markers are not mandatory for MR-guided radiotherapy.

11.1.4 All radiotherapy planning and outlining must be carried out in accordance with the current version of the radiotherapy planning and delivery guidelines. This document includes details of patient preparation, target and OAR definition, dose constraints and objectives and delivery guidance, and is available on request from ICR-CTSU (PACE-icrctsu@icr.ac.uk).

11.1.5 It is strongly recommended that all patients undergo MRI imaging for radiotherapy planning purposes to determine the anatomical borders of the prostate, and if possible, the urethra. The MRI will be fused to the treatment planning CT. It is recommended that MRI/CT fusion be done on implanted fiducials. No endorectal coil is allowed.

11.1.6 Radiotherapy plan data collection: Radiotherapy plan data will be collected (in DICOM format by electronic transfer) for all patients having radiotherapy within the trial. This data will be stored on a secure server by the sponsor.

11.2 *Radiotherapy Treatment Delivery and Tracking*

11.2.1 All radiotherapy techniques are to be approved in advance by the Chief Investigator and the PACE trial radiotherapy QA team.

11.2.2 It is highly recommended that radiotherapy start within 8 weeks of randomisation, but it must start within 12 weeks (PACE-A and PACE-B) or within 16 weeks (PACE-C). In PACE-C delays to radiotherapy (with extended ADT) due to COVID19 clinical management strategies are permitted and should be documented. Treatment will be given in a single phase over no more than 14 days for SBRT, no more than 61 days for conventional radiotherapy (78 Gy in 39 fractions), and 34 days for moderate hypofractionation (60/62 Gy in 20 fractions); longer planned treatment durations are to be discussed with the Chief Investigator for approval. In addition, for the 20 fraction treatment schedule overall time of treatment should be at least 27 days (as per CHHiP trial) and, in practice, means that these patients should start treatment on a Wednesday to Friday. Overall treatment duration will be recorded.

All patients will have image-guided radiotherapy to the prostate, and it is strongly recommended that this is done with fiducial guidance. Centres who cannot implant fiducials must be experienced in cone beam soft tissue match and use cone beam for daily match to prostate.

11.2.3 MR-guided radiotherapy is permitted, with or without daily adaptive replanning.

11.3 *Surgery Treatment Arm*

It is highly recommended that surgery occur within 8 weeks of randomisation, but it must occur within 12 weeks. Radical prostatectomies must be either performed open, laparoscopically or using a robotically assisted laparoscopic approach. Participating surgeons should be performing at least 20 prostatectomies per year[81]. The number of procedures performed per year should be collected on each participating surgeon, as should the positive margin rate. Lymphadenectomy should be performed only when it is the standard practice of the surgeon for that case.

Data will be prospectively recorded on: the Clavien scale of post-operative complications[82], ASA Physical Status Classification System score, and WHO performance status of patients, whether the anastomosis is closed with a continuous or interrupted suture, the number of lymph nodes nodes removed (formal lymphadenectomy is not required in all cases) and 30-day mortality.

Patients will all have deep vein thrombosis/pulmonary embolism (DVT/PE) and antibiotic prophylaxis as per local guidelines. It is anticipated that all abdominal drains will be removed by day 3, and the urinary cathether will be removed before day 14 post-operatively.

CONFIDENTIAL

12 Adverse Event Reporting

12.1 Definition of an Adverse Event (AE)

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

12.2 Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that occurs after the commencement of study treatment (fiducial placement or the first fraction of radiotherapy) and within 30 days of the last day of study treatment and:

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

In addition, any RTOG grade 4 events occurring up to 5 years after completion of radiotherapy should be reported according to serious adverse event reporting timelines.

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

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

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

Serious Adverse Reaction (SAR)

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

Definitions of Causality

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

Related Unexpected Serious Adverse Event

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

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see Appendix 3)

12.3 UK Reporting Adverse Events to ICR-CTSU

For non-UK reporting requirements please see Appendix 4.

Any toxicity, sign or symptom that occurs after commencement 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 CRF.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and the RTOG scoring system (See Appendix 5) will be used for toxicity assessment. A copy of the CTCAE Criteria can be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). The Clavien scale for post-operative complications will be used for surgical patients.

For each AE, 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.

12.4 UK Reporting Serious Adverse Events to ICR-CTSU

Any SAE that occurs from the start of study treatment (fiducial placement or the first fraction of radiotherapy) and up to 30 days following the last day of study treatment, or any RTOG grade 4 events occurring up to 5 years after completion of radiotherapy, must be reported.

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 PACE 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.

12.5 Adverse Events Exempt From Expedited Reporting

The expected adverse events listed in Appendix 3 (≤ CTCAE Grade 3) are considered expected and are exempt from expedited reporting to ICR-CTSU but should be reported using the appropriate CRF.

12.6 UK 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.

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.

12.7 UK Expedited Reporting of Related Unexpected SAEs

If an SAE (occuring within the specified reporting timeframe) 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 being notified of the event.

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

12.8 UK 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 or designee becomes aware of the outcome.

12.9 UK Annual Safety Reporting

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor and 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.

13 Statistical Considerations

All statistical analysis will be conducted by the ICR-CTSU at The Institute of Cancer Research (or in collaboration with the statistical team at ICR-CTSU).

13.1 Study Design

This umbrella study consists of three randomised parallel phase III trials with a common experimental arm. PACE-A compares prostatectomy with prostate SBRT and PACE-B & PACE-C compare conventional radiotherapy with prostate SBRT. The primary objective of PACE-A is to demonstrate superiority of SBRT in terms of patient reported outcomes compared to prostatectomy and PACE-B & PACE-C is to demonstrate non-inferiority of SBRT compared to conventional radiotherapy. PACE-A, PACE-B and PACE-C will be randomised independently and analysed separately.

13.2 PACE-A: Surgery vs Prostate SBRT Randomisation

13.2.1 Sample Size

Following advice from the independent Trial Steering Committee, the primary endpoint and sample size for PACE-A was revised due to slower than anticipated recruitment meaning that the original objective of demonstrating non-inferiority of SBRT compared to prostatectomy was not feasible. PACE-A now has co-primary endpoints based on patient reported outcomes of urinary incontinence (number of absorbent pads used daily from the EPIC questionnaire) and bowel bother (summary score from the EPIC questionnaire). The aim of the study is to demonstrate superiority of SBRT compared to surgery in terms of both of these important patient reported outcomes. The sample size is driven by the comparison of urinary incontinence (any use of urinary pads).

It is estimated that at 2 years from completion of treatment, 15% of surgical patients will be using urinary pads[22]. It is anticipated that 4% of SBRT patients will use urinary pads. Assuming a 5% two-sided alpha and 80% power, 111 patients are required in each treatment group to detect an 11% difference between groups. To allow for 5% drop-out by the time of analysis, the target sample size is 234 patients.

With this number of patients, there is over 90% power to detect a 5 point difference in mean bowel bother scores between the randomised groups. Assuming a mean bowel bother summary score of 95.0 in surgical patients with a standard deviation of 9.4[22], a difference in mean score of 5.0 will be able to be detected with 152 patients in total (assuming 90% power and a two-sided 5% alpha).

Unless otherwise advised by the IDMC, principal analyses will take place after all PACE-A patients have completed a minimum of two years follow-up.

13.2.2 Co-primary endpoints: Patient Reported Urinary Incontinence and Bowel Bother

Urinary incontinence will be assessed using the 'number of absorbent pads required per day to control leakage' question on the EPIC questionnaire. The proportion of patients at two years from the completion of treatment reporting any use of daily pads is of primary interest.

Bowel bother will be assessed using the bowel bother summary score from the EPIC questionnaire. The mean score at two years from the completion treatment is of primary interest. A low bowel bother score indicates more bother.

13.2.3 Secondary Endpoints

13.2.3.1 Freedom From Biochemical/Clinical Failure

The definition of biochemical progression is different for the two treatment groups. For patients receiving surgery, biochemical failure will be defined as PSA>0.2ng/ml. For patients receiving prostate SBRT, PSA failure will be defined as nadir +2ng/ml (nadir is the lowest value recorded after the commencement of radiotherapy). The commencement of androgen deprivation also counts as biochemical failure. Clinical failure is defined as local recurrence, nodal recurrence or distant metastases. Time will be measured from randomisation in both groups. The primary time point of interest is 5 years.

In all cases, PSA failure will be confirmed with a second measurement (>4 weeks from the index measurement) also meeting the criteria for PSA failure.

In addition it is now recognised that after SBRT a benign PSA bounce is seen in up to 20% of patients, usually within the first 2 years[53, 78, 79]. 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, for patients receiving SBRT or conventional radiotherapy, PSA failure before 24 months will require 3 consecutive rises in PSA resulting in a clinical diagnosis of failure, or commencement of further treatment (eg androgen deprivation therapy). After 24 months, the definition of PSA failure will revert to the Phoenix definition described above (ie nadir+2 ng/ml).

It is recognised that whilst freedom from biochemical/clinical failure is a key secondary outcome measure there is limited power to make conclusions regarding the non-inferiority of SBRT compared to surgery on this endpoint. For example, if the 5 year freedom from biochemical/clinical failure rate is 85% with surgery non-inferiority margins of 12% (HR 1.95) and 11% (HR 1.84) could be ruled out with 80% or 70% power respectively (1-sided 5% alpha). Relaxing the type 1 error rate to 10% would permit margins of 10% or less (HR 1.76; 80% power) and 9% or less (HR 1.66; 70% power) to be ruled out.

13.2.3.2 Acute Toxicity

Acute toxicity will be assessed at the end of treatment and for 12 weeks post completion of treatment using CTCAEv4.03 and RTOG scales. Surgical toxicity will be also be assessed using the Clavien toxicity scale prior to discharge and at weeks 2 and 4. Direct comparisons of PACE-A and PACE-B toxicity will not be possible.

13.2.3.3 Late Toxicity

Late toxicity will be assessed using CTCAEv4.03 and RTOG scales measured from any time after the 12 week assessment post-treatment completion. Adverse events of grade 2 or greater experienced at 24 months from treatment is of primary interest.

13.2.3.4 Progression Free Survival

This will be measured as the first occurrence of biochemical failure, commencement of hormone therapy, local recurrence, pelvic/lymph node recurrence, distant disease or death from any cause. Time will be measured from randomisation. Local progression and pelvic/lymph node progression will be measured as the first occurrence of positive local biopsy following randomisation. Rectal examination is not done routinely during follow up but should be recorded on the eCRF if done. MRI/Ultrasound and biopsies are performed when indicated by rising PSA. Distant disease is defined as a positive result for any of the following: CT/MRI scan showing metastatic disease without new primary; bone scan; choline or PSMA PET, chest X-ray.

13.2.3.5 Disease Specific Survival

This will include deaths from prostate cancer only. In general, patients with death recorded as prostate cancer related with no prior progression 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 thye 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.

13.2.3.6 Overall Survival

This will include deaths from any cause. Time will be measured from randomisation.

13.2.3.7 Distant Progression

This will be measured as the first occurrence of distant disease. Distant disease is defined as a positive result for any of the following: CT/MRI scan showing metastatic disease without new primary; bone scan; choline or PSMA PET, chest X-ray. Patients who died without progression will be censored at date of death. Time will be measured from randomisation. A sensitivity analysis may be conducted assuming patients reporting a prostate cancer death without prior distant progression have distant disease at the date of death.

13.2.3.8 Commencement of Hormone Therapy

Date on which anti-androgens or LHRH analogues/antagonists are started or date on which orchidectomy occurs.

13.2.3.9 Acute and Late Patient Reported Outcomes

Bladder, bowel and sexual function will be assessed using EPIC-26. Erectile dysfunction will be assessed using IIEF-5. Urinary and bowel incontinence will also be assessed using the IPSS and Vaizey questionnaires respectively. Acute is defined as 12 weeks from the end of treatment and late from any time after the 12 week assessment

13.3 PACE-B and PACE-C: Conventional Radiotherapy vs Prostate SBRT Randomisation

13.3.1 PACE-B Sample Size

The sample size is based on a five year freedom from biochemical/clinical failure of 85% in patients receiving conventionally fractionated radiotherapy of 78 Gy in 39 fractions or 62 Gy in 20 fractions. The aim of the study is to demonstrate non-inferiority of SBRT compared to conventional radiotherapy. Table 10 gives the total number of patients required to demonstrate non-inferiority based on various minimum desirable differences to rule out. A one-sided 5% significance level has been used and an allowance for 10% drop-out at the time of analysis. It was originally anticipated that recruitment will take four years and there will be a staggered start to recruitment as centres open. However, due to the change in sponsorship opening of new centres has been delayed so anticipated recruitment is now 4.5 years. Extending the recruitment period by 6 months allows the sample size to remain unchanged. Revised recruitment predictions took in to account actual recruitment during year 1 and then expects 20% of patients to be recruited in year 2, 30% in years 3 and 4 and 15% of total recruitment in the final 6 months of recruitment.

Unless otherwise advised by the IDMC, principal analyses will take place after the required number of events have been observed or after a minimum of five years follow-up for all patients.

It can be seen that a 6% difference at 5 years (corresponding to a critical hazard ratio of 1.45) could be ruled out with 858 patients randomised in total (80% power). Sample size may be increased if accrual is faster than anticipated, in order to increase the power of the study.

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Table 10. Total sample size estimates for PACE-B (total number of events required in brackets)

Difference to rule out	Hazard ratio	80% power	90% power
5%	1.373	1224 (269)	1595 (350)
6%	**1.450**	**858 (194)**	1118 (252)
7%	1.529	641 (149)	835 (194)
8%	1.608	500 (119)	652 (155)

The target sample size is 858 patients. The decision to close the study to further recruitment on achieving the target sample size will be taken with advice from the Independent Data Monitoring Committee (IDMC).

Toxicity associated with prostate SBRT is also an important endpoint. It is anticipated that 24 months RTOG bladder and/or bowel toxicity of grade 2 or greater will be approximately 10% for patients receiving conventional radiotherapy[83]. With 429 patients in each arm there would be 80% power to rule out a 6% difference in toxicity with SBRT i.e. exclude more than 16% toxicity at 24 months with prostate SBRT (non-inferiority, 5% one-sided alpha).

13.3.2 PACE-C Sample Size

The sample size is based on an estimated 5 year biochemical/clinical failure-free rate of 85% for the conventional radiotherapy arm. This estimate is based on the subset of upper intermediate and high risk patients in the 60Gy group of the CHHiP trial [44] which has a 5 year biochemical/clinical failure free rate of 84.7% (95%CI: 79.6-88.9). The aim of the study is to demonstrate non-inferiority of SBRT compared to conventional radiotherapy. Table 11 gives the total number of patients required to demonstrate non-inferiority based on various minimum desirable differences to rule out. A one-sided 5% significance level has been used and an allowance for 1% loss to follow up (based on CHHiP data) at the time of analysis.

A total of 1182 patients will be required (591 per group) to give 80% power (5% one-sided alpha) to exclude a hazard ratio (HR) of 1.37 (i.e. 5% non-inferiority margin around 85%). Following patient and clinical input a 5% NI margin has been specified. The sample size assumes uniform recruitment over 3.5 years and five years follow-up on all patients before the target number of events (268) is expected to be reached.

Sample size may be increased if accrual is faster than anticipated, in order to increase the power of the study.

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Table 11. Total sample size estimates for PACE-C (total number of events required in brackets)

Difference to rule out	Hazard ratio	80% power	90% power
4%	1.30	1740 (385)	2268 (502)
5%	**1.37**	**1182 (269)**	1541 (350)
6%	1.45	829 (194)	1080 (252)

Based on uniform recruitment over 3.5 years and five years follow-up on all patients.

Unless otherwise advised by the IDMC, principal analyses will take place after the required number of events have been observed or after a minimum of five years follow-up for all patients.

13.3.3 PACE-B and PACE-C Primary Endpoint: Freedom From Biochemical/Clinical Failure

Biochemical progression after 24 months is defined as an increase in serum PSA of at least 2ng/ml greater than the post-radiotherapy nadir (the lowest PSA to date) confirmed by a second consecutive reading also of at least 2ng/ml greater than the post-treatment nadir. A commencement of androgen deprivation (recommencement in PACE-C) also counts as biochemical failure. Clinical failures is defined as local recurrence, nodal recurrence or distant metastases. Time will be measured from randomisation. The primary timepoint of interest is 5 years.

As described above, to prevent patients with a benign PSA bounce after radiotherapy being incorrectly classified as PSA failures, PSA failure before 24 months will require 3 consecutive rises in PSA resulting in a clinical diagnosis of failure, or commencment of further treatment (eg androgen deprivation therapy).

13.3.4 PACE-B and PACE-C Secondary Endpoints

13.3.4.1 Acute Toxicity

Acute toxicity will be assessed using RTOG during treatment and using CTCAE v4.03 and RTOG scales for 12 weeks after completing treatment. As data regarding toxicity of SBRT gathers, it may not be useful to continue to gather in depth acute toxicity data of all cohorts. For PACE-C an interim analysis will be conducted after the first 200 patients have been recruited and completed their week 12 post treatment toxicity assessment. If acute toxicity patterns seen are similar between SBRT and 20 fractions, and similar to those seen in PACE-B, then the IDMC will be asked to review whether further acute toxicity monitoring is required.

13.3.4.2 Late Toxicity

Late toxicity will be assessed using CTCAE v4.03 and RTOG scales. Any toxicity recorded after the 12 week post-treatment assessment will count as late toxicity. Toxicity at 24 months from treatment will be the time point of primary interest.

13.3.4.3 Progression Free Survival

This will be measured as the first occurence of biochemical failure, commencement/recommencement of hormone therapy, local recurrence, pelvic/lymph node recurrence, distant disease or death from any cause. Time will be measured from randomisation. Local progression and pelvic/lymph node progression will be measured as the first occurrence of positive local biopsy following randomisation. Rectal examination is not done routinely during follow up but should be recorded on the eCRF if done. MRI/Ultrasound and biopsies are performed

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when indicated by rising PSA. Distant disease is defined as a positive result for any of the following: CT/MRI scan showing metastatic disease without new primary; bone scan; PET scan, chest X-ray.

13.3.4.4 Disease-Specific Survival

This will include deaths from prostate cancer only. In general, patients with death recorded as prostate cancer related with no prior progression 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 thye 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.

13.3.4.5 Overall Survival

This will include deaths from any cause. Time will be measured from randomisation.

13.3.4.6 Distant Progression

This will be measured as the first occurrence of distant disease. Distant disease is defined as a positive result for any of the following: metastatic disease on CT/MRI; bone scan; PET scan; chest X-ray. Patients who died without progression will be censored at date of death. Time will be measured from randomisation. A sensitivity analysis may be conducted assuming patients reporting a prostate cancer death without prior distant progression have distant disease at the date of death.

13.3.4.7 Commencement of Hormone Therapy

Date on which anti-androgens, LHRH analogues or antagonists are commenced/recommenced (PACE-C) or date on which orchidectomy occurs.

13.3.4.8 Acute and Late Patient Reported Outcomes

Bladder, bowel and sexual function will be assessed using EPIC-26. Erectile dyfunction will be assessed using IIEF-5. Urinary and bowel incontinence will also be assessed using the IPSS and Vaizey questionnaires respectively. Acute is defined as 12 weeks from the end of treatment and late from any time after the 12 week assessment.

13.4 Statistical Analysis (for PACE-A, PACE-B and PACE-C)

13.4.1 Primary Analysis Population

Analyses of outcome data will be on the basis of intention to treat and therefore include all patients randomised into each study (regardless of ineligibility for study treatment, unwillingness to continue with follow-up visits, withdrawal of consent after randomisation, deviation from allocated treatment and lost to follow-up). However, randomised patients who have not received at least one fraction of radiotherapy (or did not receive surgery if allocated to that group) will not be included in toxicity analyses.

13.4.2 Analysis Methods

PACE-A: The primary comparison of patient reported outcomes between surgery and prostate SBRT will be at two years from the completion of treatment. For urinary incontinence, the proportion of patients with any use of asborbent pads will be presented by treatment group. The chi-squared or Fisher's exact test will be used to compare the two groups. For bowel bother, the summary score will be presented as mean and standard deviaton for each treatment group[31]. The t-test will be used to compare the two groups, if data are normally distributed (if not, the Mann-Whitney test will be used). A 5% significance level will be used for both comparisons.

PACE-B and PACE-C: The primary comparison will be conventional radiotherapy versus prostate SBRT. Analyses will estimate the size of the treatment effect with a 90% confidence interval for the

estimated difference between randomisation groups (equivalent to one-sided 95% confidence interval). The primary analysis of freedom from biochemical/clinical progression will be event driven unless the Independent Monitoring Committee and Trial Steering Committees agree that analysis prior to the target number of events being observed would be mature and robust to have potential to influence clinical practice. Freedom from biochemical/clinical progression will be analysed by the logrank test. Information will be provided on both the absolute and relative treatment effects. Estimates of event rates will be calculated using the Kaplan-Meier method. Primary analyses will be unadjusted. The Cox proportional hazard model will be used to adjust for risk group and important known prognostic factors. In PACE-C adjusted models will include duration of ADT (as a result of COVID19 related delays to radiotherapy). Methods to account for non-proportionality will be used if appropriate. The origin time will be taken as the date of randomisation. Patients alive and free of event at the time of analysis and patients lost to follow-up will be censored at the last available PSA assessment. The primary time-point of interest is 5 years.

PACE-A, PACE B and PACE-C: For all time-to-event endpoints (other than freedom from biochemical/clinical failure) analyses will use the logrank test. Hazard ratios will be presented with a 95% confidence interval. Estimates of event rates will be calculated using the Kaplan-Meier method. Principal analyses will be unadjusted. Methods to account for non-proportionality will be used if appropriate. The origin time will be taken as the date of randomisation for efficacy endpoints and date of treatment completion for toxicity endpoints. Patients alive and free of event at the time of analysis and patients lost to follow-up will be censored at the last available assessment. The primary time-point of interest is 5 years.

- Acute and late toxicity will be summarised by the proportions experiencing grade ≥2 side effects with comparisons made (where appropriate) using chi-squared based tests or Fisher's exact test if expected cell frequencies are less than 5. In addition, methods for ordinal data will be used. For acute toxicity, the week 12 assessment post treatment is of specific interest and a formal comparison of grade 2 or greater in each treatment arm will be conducted
- For late toxicity, the 24 month assessment is of specific interest and a formal comparison of grade 2 or greater in each treatment arm will be conducted

The number and percentage of patients with acute toxicity of each grade in each treatment group at each time point will be specified. Late toxicity will be summarised as the number and percentage of each grade in each treatment group at each time point.

Time-to-event analyses will also be conducted for time to first grade 1+, grade 2+ and grade 3+ event. Kaplan-Meier curves (by treatment group) will be presented for time to event data, point estimates (with 95% CIs) will be reported. Patients alive and free of an event at the time of analysis will be censored at last available toxicity assessment. Patients who have died will be censored at date of death.

Any quality of life data collected from PACE-C participants within the SPRUCE study will be shared with PACE-C for analysis. Standard algorithms will be used to derive scores from and handle missing data in quality of life questionnaires (IPSS, IIEF-5, Vaizey and EPIC-26). Treatment groups will be compared at individual time-points and analyses to account for the longitudinal nature of the data (generalised estimating equations) may be used. To make some adjustment for multiple testing a significance level of 1% will be used for comparisons of quality of life endpoints other than for analysis of the co-primary endpoints in PACE-A.

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.

13.5 *Stopping Rules and Interim Analyses*

It is planned that an Independent Data Monitoring Committee (IDMC) will meet at approximately 6 monthly intervals to review the accumulating safety and emerging efficacy data.

Once 30 patients have been treated with SBRT on a conventional linac (ie non-Cyberknife systems), the toxicity, acute and late, will be reviewed by the IDMC to ensure there is not an augmented rate of side effects in this cohort. After this, conventional linac SBRT vs Cyberknife SBRT toxicity and outcomes will continue to be monitored by the IDMC separately and together to ensure ongoing safety of this technique.

Timelines for maturity of data in PACE-B and PACE-C will be reviewed by the IDMC and TSC who will advise on timing of release of results and whether results from PACE-B have implications for the statistical plan for PACE-C.

After a minimum of 12 patients receiving MR-guided SBRT, a technical feasibility and toxicity analysis will be carried out to ensure outcomes consistent with non-MR-guided radiotherapy.

An acute toxicity analysis is planned in PACE-C after the first 200 patients have been recruited and completed their week 12 toxicity assessment. These data will be reviewed and compared with acute toxicity data from the SBRT arm of PACE-B (and PACE-A). Assuming the emerging acute toxicity data for PACE-C is comparable (similarly distributed) with that observed in PACE-B, then intense acute toxicity data collection for all PACE-C patients will not be required. This data will be reviewed by the IDMC who will make a recommendation on continued collection of acute toxicity data in PACE-C to the TSC.

14 Quality assurance (QA)

14.1 Surgery QA

Surgical workload is the best measure of quality of surgery, and hence a minimum number of procedures per year has been specificed (>20). Sites will be asked to complete a surgical QA form which will be reviewed by a surgical member of the PACE TMG member. In addition, data on surgical margin positivity and postoperative complications will be reviewed by the IDMC to ensure a reasonable level of consistency across all sites.

14.2 Radiotherapy QA

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

Centres participating in PACE-B or PACE-A (or other agreed prostate trials) will have their QA minimised as appropriate.

14.2.1 Pre-trial Quality Assurance Programme

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

1. Facility questionnaire / process document
2. Benchmark outlining case
3. Benchmark planning case(s)
4. CBCT QA questionnaire (for centres not using fiducials)

14.2.2 On-Trial Quality Assurance Programme

1. Prospective* and/or retrospective case reviews
2. Dosimetry site visit (subject to prior RTQA dosimetry accreditation)
3. DICOM data collection for all patients

15 Ethical and regulatory aspects

15.1 *Research Governance*

15.1.1 Sponsor responsibilities:

The sponsor of this clinical trial is the Royal Marsden NHS Trust. Responsibilities of participating sites are defined in an agreement between the individual participating site and the Sponsor.

15.2 *Trial Administration & Logistics*

15.2.1 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 in discussion with the Chief Investigator or Sponsor deems it is appropriate.

15.2.2 Investigator training:

Each centre will complete the comprehensive pre-trial section of the quality assurance programme prior to commencing recruitment, as detailed in section 14. The quality assurance programme will continue throughout the trial, with investigator training as required.

15.2.3 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.

15.2.4 Central data monitoring:

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

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

15.2.5 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. Within the PACE study source data worksheets may be used as source documentation, where the information contained within does not form part of routine care (eg RTOG and CTCAE gradings).

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

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will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

15.2.6 Completion of the study and definition of study end date:

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

15.2.7 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.

15.3 *Patient Protection And Ethical Considerations*

15.3.1 Trial approvals:

This trial has been formally assessed for risk by the Sponsor and ICR-CTSU. The trial has received ethical approval from a research ethics committee for multi-centre trials and global R&D approval via the NIHR Coordinated System for gaining NHS Permission. 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.

15.3.2 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.

15.3.3 Informed consent:

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

15.3.4 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 allow linkage with routinely collected NHS data. For non-UK patients appropriate similar data may be collected.

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, the Sponsor, the site's Research and Development Office and the regulatory authorities may require access to participants' hospital notes for quality assurance purposes. Confidentiality of participants will be maintained at all times and information by which participants could be identified will not be reproduces or disclosed.

15.3.5 Data Protection

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

15.3.6 Liability

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

15.4 *Financial Matters*

This trial is investigator designed and led and PACE-B has been endorsed by the Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK. Research grants have been given to the trial Sponsor by Accuray, Varian and the Royal Marsden Cancer Charity.

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.

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16 Study management and oversight

The study will be conducted in line with relevant regulations and will conform to the GCP principles. Three bodies will be set up to ensure the study is managed appropriately:

16.1 *Trial management group (TMG)*

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

16.2 *Independent data monitoring committee (IDMC)*

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chairman and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

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

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

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

It would be within the remit of the IDMC to monitor toxicity and freedom from biochemical/clinical failure rates and survival rates in the surgery and conventional radiotherapy arms (on which the sample sizes has been calculated) and advise whether the assumptions are valid for emerging data from the trial.

16.3 *Independent Trial Steering Committee (TSC)*

A Trial Steering Committee (TSC) comprising independent experts in oncology, surgery and statistics will provide high level oversight of the trial. The TSC will monitor progress against recruitment milestones and will advise the TMG on any major protocol amendments. It is anticipated that the TSC will meet at least annually. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

17 Study sponsorship

17.1 Study organisation

This is an academically led study sponsored by the Royal Marsden NHS Foundation Trust, London, SW3 6JJ. Statistical analyses will be conducted by ICR-CTSU (or in collaboration with the statistical team at ICR-CTSU). Trial Coordination will be performed by ICR-CTSU (a UKCRC registered NCRI cancer clinical trials unit) who will be responsible for the day to day conduct of the trial.

17.2 Contracts

Study sites will enter into a written research agreement with the Royal Marsden NHS Foundation Trust (sponsor) which sets out the responsibilities for study conduct. There is no per patient payment for entering patients into this study.

An additional research agreement between the Sponsor and ICR will define ICR-CTSU's roles and repsonsibilities including those related to central trial co-ordination, database provision, central statistical monitoring, interim analyses/reports for review by the IDMC and principal analysis for presentation/publication.

18 Publication policy

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

Separate primary publications are planned for PACE-A, PACE-B, and PACE-C. With the consent of the IDMC and TSC and where this will not compromise the ongoing integrity of the trial, results of toxicity analyses may be published ahead of the primary analysis of efficacy data.

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

No Investigator may present or attempt to publish data relating to the PACE trial without prior permission from the Trial Management Group.

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19 Appendices

19.1 Appendix 1: Staging

UICC/AJCC 2002 TNM classification[80]

T - Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumour confined within the prostate*
T2a	Tumour involves one-half of one lobe or less
T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

N - Regional lymph nodes***

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

M - Distant metastasis****

MX	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

*Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

** Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.

***The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.

Laterality does not effect the N classification.

****When more than one site of metastasis is present, the most advanced category should be used.

Reference: Greene FL, Page DL, Fleming ID et al. (eds). AJCC Cancer Staging Manual, Sixth Edition. Heidelberg Berlin New York: Springer 2002.

19.2 Appendix 2: Risk Groups

Stratification risk groups in PACE are based on National Comprehensive Cancer Network (www.nccn.org) Risk Groups within the limits of the PACE trial inclusion/exclusion criteria:

19.2.1 PACE-A and PACE-B Stratification Risk Groups

Low-risk (includes the presence of all of the following):

- T1c-T2a
- Gleason ≤6
- PSA <10 ng/ml

Intermediate risk (includes the presence of any of the following):

- T2b-T2c
- Gleason 7 (3+4)
- PSA 10-20 ng/ml

19.2.2 PACE-C Stratification Risk Groups

Intermediate risk (includes the presence of any of the following, assuming no high risk features apply):

- T2
- Gleason 7 (3+4 OR 4+3)
- PSA 10-20 ng/ml

High risk includes the presence of any one of the following (max 2 are allowed to be eligible for PACE-C)

- T3a
- Gleason 4+4*
- PSA >20-30 ng/ml

*Maximum 50% of cores Gleason 4+4

19.3 Appendix 3: Expected Adverse Events

The following are possible anticipated treatment related AEs (i.e. expected occurrences), ≤CTCAE Grade 3, which are not subject to expedited reporting to ICR-CTSU but all such events should be reported in the appropriate section of the CRF.

19.3.1 Surgery

- Bowel strictures
- Ureteric obstruction
- Immediate postoperative urinary incontinence
- Immediate postoperative erectile dysfunction
- Pulmonary embolus/ Deep vein thrombosis
- Greater than 1500 ml intraoperative blood loss
- Return to theatre for bleeding, haematoma or any other reason
- Intraoperative damage to adjacent organ
- Persisting urinary leak that prevents abdominal drain removal
- Ileus lasting greater than three days
- Urinary septicaemia
- Readmission to hospital for operation related complication
- Clinical indication that delays removal of urethral catheter

19.3.2 SBRT and Conventional Radiotherapy

- Urinary toxicities:
    - Urinary frequency/urgency/nocturia
    - Urinary retention
    - Urinary obstruction/strictures
    - Haematuria
    - Cystitis/bladder spasms
    - Urinary incontinence/leakage
    - Pain (prostate, urinary/dysuria)
- GI Toxicities:
    - Pain (rectal, pelvic, abdominal)
    - Diarrhoea
    - Constipation
    - Rectal bleeding/ulcer
    - Fistula
    - Proctitis
    - Bowel obstruction or perforation
- Sexual function
    - Erectile dysfunction
    - Decreased volume of ejaculate/absence of ejaculate
    - Decreased libido
- Dermatology/Skin
    - Rash
    - Hair loss in treatment area
- Bone fractures
- Related to fiducial marker insertion
    - Bleeding
    - Sepsis (urinary and systemic)
    - Pain

19.3.3 Additional expecetd events related to use of ADT as standard of care (PACE-C only)

- Hot flushes
- Fatigue
- Mood changes
- Weight gain
- Erectile dysfunction
- Loss of libido
- Reduction in bone mineral density
- Cardiovascular events (MI, CVA)

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19.4 Appendix 4: Non-UK Safety Reporting Requirements

The site Principal Investigator or designee is responsible for reporting SAEs to their individual Institutional Review Board (IRB) and/or Institutional Ethics Committee (EC) as per local standards.

The collaborative group in each participating country will report related unexpected SAEs as per their local requirements to IECs and local investigators.

Further Sponsor safety reporting notification requirements will be agreed in the international site agreements.

19.5 Appendix 5: 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 12 week follow up visit]:

Bladder changes – cystitis/frequency:

Grade 0: No symptoms

Grade 1: Frequency of urination or nocturia twice pretreatment 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 decompression or bowel diversion.

Grade 5: Death directly due to radiation morbidity.

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

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