

The PACE Trial

(Prostate Advances in Comparative Evidence)

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

RADIOTHERAPY PLANNING AND DELIVERY GUIDELINES (PACE-A and PACE-C)

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Major Revisions since previous Version

Version No.	Major Revisions
Version 1.0	First Version
Version 1.1	Added revised rectal dose constraints as Appendix B
Version 2.0	Move of radiotherapy procedures for PACE-A and C from PACE protocol to RT Guidelines
Version 2.1	Minor correction: 40Gy rectal dose constraint
Version 2.2	Addition of procedures for PACE-B trial as Appendix B (from PACE Protocol version 9) Reduced treatment verification tolerance from 3mm to 2mm

1. INTRODUCTION

This document supplements the PACE trial protocol, and describes the radiotherapy procedures and radiotherapy quality assurance (QA) programme for the PACE-A and PACE-C trials. (The PACE-B trial is now closed and details can be found in previous versions of the PACE protocol).

All patients will receive inverse-planned prostate intensity modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT). Both are delivered with daily online image-guided radiotherapy (IGRT). Various delivery techniques are allowed (e.g. VMAT, helical tomotherapy, robotic gantry, MR-linac), and all will be referred to as IMRT/SBRT in this document unless specifically detailed.

1.1. Trial Arms

1.1.1. PACE-A

Patients meeting the eligibility criteria for PACE-A and considered as 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.

1.1.2. PACE-C

Patients meeting the eligibility criteria for PACE-C will be randomised to either prostate SBRT (36.25 Gy in 5 fractions) or conventional radiotherapy (60 Gy in 20 fractions).

2. PRE-PLANNING PROCEDURES

2.1. Fiducial Markers

It is strongly recommended that all patients randomised to radiotherapy have fiducial markers implanted for image guidance. Centres who cannot implant fiducials should speak to the RTQA team and the Chief Investigator (CI) regarding accreditation and approval. Fiducial markers are not mandatory for MR-guided radiotherapy.

Fiducial markers should be visible on CT and MRI imaging to allow image guidance and MRI/CT fusion. At least three fiducial markers will be placed under transrectal ultrasound guidance, using either transperineal or transrectal approach. Antibiotic cover with oral ciprofloxacin or equivalent and metronidazole per rectum, or equivalent, should be administered if fiducial placement is done transrectally. The operator will place seeds such that they are visible (and not superimposed) on orthogonal imaging (where used) and ideally are separated by 2 cm or more. Fiducials are usually placed as an outpatient procedure; at least three seeds must be usable for tracking translation and rotation during treatment. The use of one paired fiducial and two free fiducials (four in total) is recommended for CyberKnife SBRT treatment.

2.2. Planning CT and MRI Scans

To allow fiducial stabilisation and resolution of swelling, planning studies are recommended to be imaged at least 7 days after fiducial placement.

CT scans will be taken for treatment planning. CT slices will be 1–1.5 mm for SBRT (up to 3 mm allowed for conventional arm), with 200-300 slices taken centred approximately at the prostate. For CyberKnife SBRT scans will extend at least 15 cm above and below the level of the prostate, including the testes, so that these can be used as a blocking structure. For gantry-based SBRT and IMRT, it is suggested that scans should extend from L3/L4 intervertebral space to 2 cm below ischial tuberosities.

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.

2.3. Patient Preparation and Positioning

2.3.1. Bowel Preparation

We strongly advise bowel preparation to reduce rectal diameter for all patients receiving radiotherapy. Aim for a maximum rectal A-P diameter of 4 cm, measured at the mid-point of the prostate. We suggest daily enemas for 2 days prior to, and on the day of, CT planning. We suggest patients should restart enemas 2 days prior to starting radiotherapy. SBRT patients are suggested to have an enema on each day of treatment. Most set up inconsistencies are due to differences in bowel diameter. Conventional radiotherapy patients are suggested to have an enema daily for the first 2 weeks of treatment, unless they develop diarrhoea or proctitis.

2.3.2. Bladder Preparation

It is recommended that patients have a partially filled bladder during imaging and treatment delivery: patients should be asked to empty their bladder and then drink enough water (e.g. 325 mls) to ensure a reasonably filled bladder on the planning scan and before each fraction of radiotherapy. It is advised that the bladder should be filled to at least 150 mls to proceed with planning. However, this may not always be possible, and planning may proceed if agreed with the site Principal Investigator (PI).

2.3.3. Immobilisation

Patients will be scanned supine with arms across chest using an Alpha Cradle, vacbag or similar immobilization device, as needed. Knee and ankle supports may be used. Positioning and immobilisation should be as similar as possible during the planning MRI.

3. ORGANS AT RISK AND TARGET VOLUME DEFINITIONS

3.1. Target Volume Definition

3.1.1. The Clinical Target Volume (CTV)

When using MRI-fusion images for voluming, it is acknowledged that these tend to be less consistent more superiorly, particularly at the level of the seminal vesicles. Therefore we recommend using MRI fusion for voluming the prostate and prostate/rectum interface, but where there is a discrepancy the CT anatomy should be prioritised. All other structures should be outlined on CT.

3.1.2. CTV definition for PACE-C

Patients with upper intermediate NCCN risk disease and high NCCN risk disease in PACE-C

There are two CTVs, defined as follows:

CTVpsv = prostate plus proximal 1 cm of seminal vesicles (from insertion point in the sagittal plane, see Figure 1a)

CTVsv = prostate plus proximal 2 cm of seminal vesicles (from insertion point in the sagittal plane, see Figure 1b)

Patients with lower intermediate NCCN risk disease in PACE-C (approximates to the cohort who would have been eligible for PACE-B)

CTVpsv = prostate plus proximal 1 cm of seminal vesicles

CTVsv = identical to CTVpsv

3.1.3. CTV definition for PACE-A

Intermediate risk patients in PACE-A

CTVpsv = prostate plus proximal 1 cm of seminal vesicles (from insertion point in the sagittal plane (see Figure 1a).

Low risk patients in PACE-A

CTVp = prostate only

3.1.4. Contouring Seminal Vesicles

This is the area of the protocol that has caused the most questions/QA discrepancies. The easiest way to contour the correct amount of seminal vesicle (SV) to include into the target volumes is to contour the prostate first, expand by 1 cm and by 2 cm, and to use these 1 cm / 2 cm ring structures as a guide for SV contouring (or automatically 'clip' the SVs at these borders using the planning system). This method is illustrated in Figure 1 and described below.

Note: If the anatomy is unusual and this method does not capture the anatomy you wish to treat, then it is permitted to outline the proximal 1 cm and 2 cm of seminal vesicles for CTVpsv and CTVsv freehand using the anatomy on the planning images. This should still effectively cover the same 'length' of SV from the point of insertion of the SV into the prostate.

If including the proximal 1 or 2 cm of SVs is felt to be clinically unsafe or inappropriate due to variant anatomy, then the proportion of SV included can be amended due to clinician discretion. If this occurs, please send a screenshot to the RTQA team as a record of why the volumes deviated from the protocol.

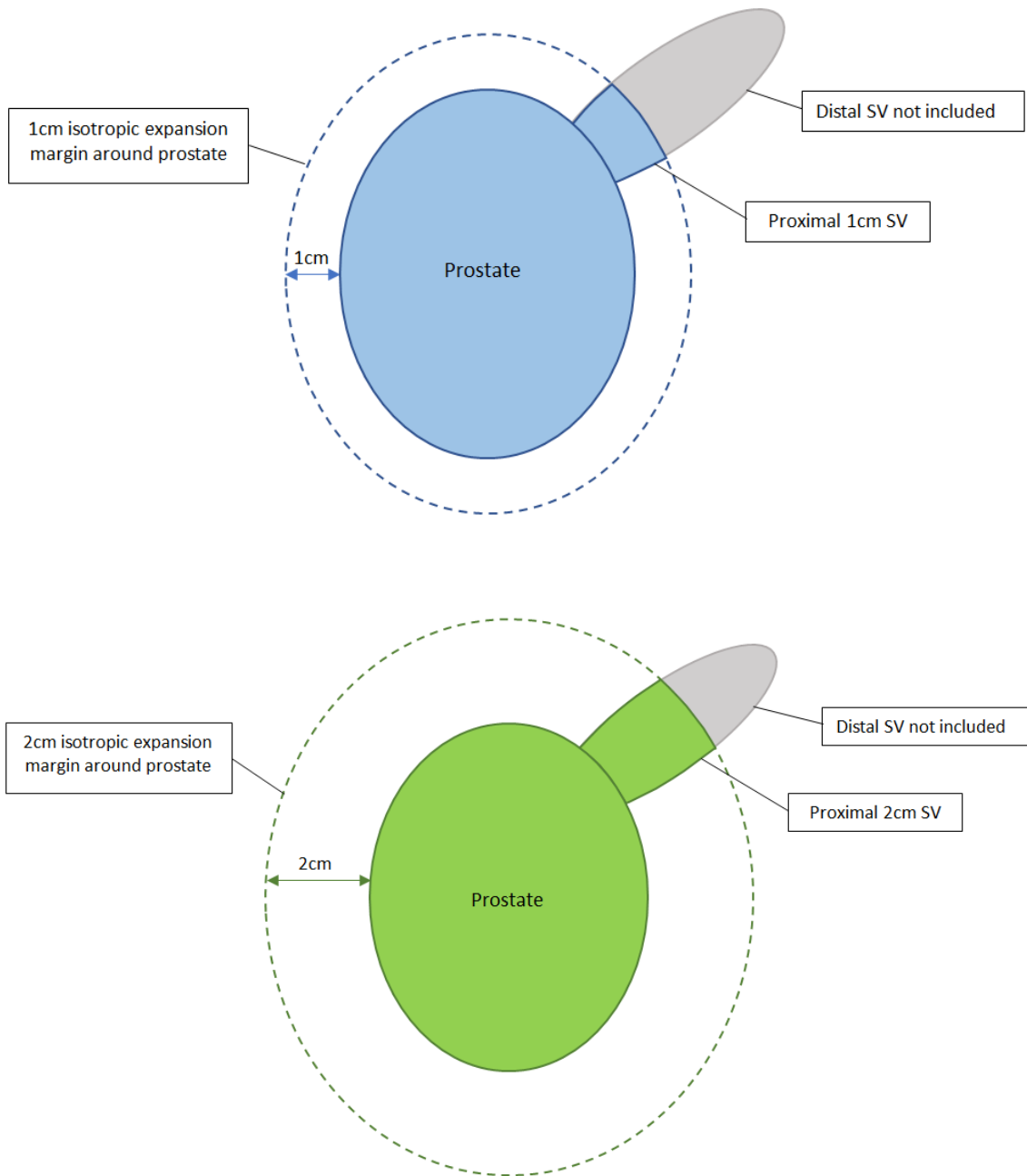


Figure 1. (a) Proximal 1 cm (for CTVpsv) and (b) Proximal 2 cm (for CTVsv) of Seminal Vesicles

First contour prostate and create 1 cm and 2 cm rings by isotropic expansion of the prostate (Figure 2).

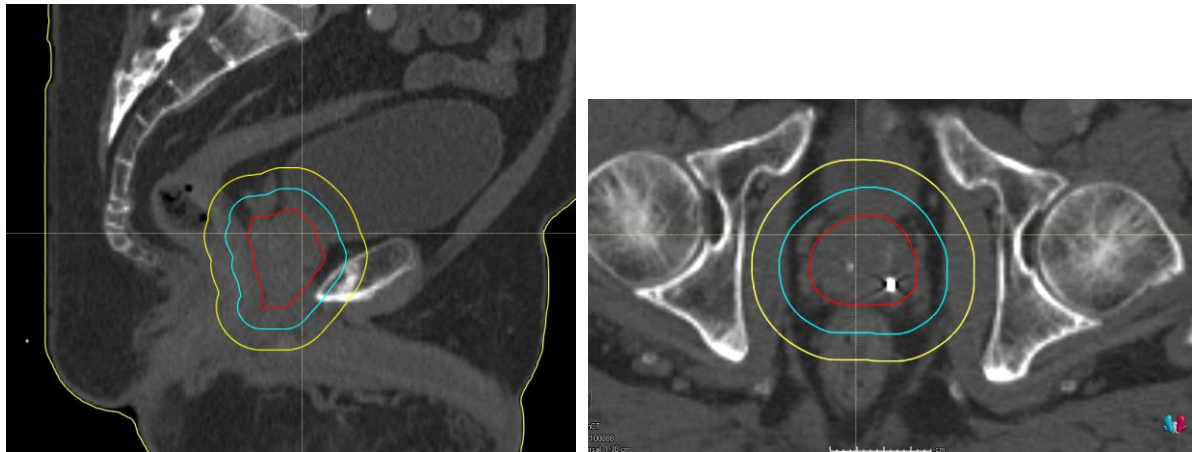


Figure 2. Sagittal (left) and axial (right) images of prostate (red) expanded by 1 cm (cyan) and 2 cm (yellow) to create isotropic rings.

After contouring the whole SV, the proximal 1 cm of SV is added to the prostate volume to form CTVpsv. The SV at 1-2 cm is coloured green, and the entire proximal 2 cm of SV will be added to the prostate volume to form CTVsv. See Figure 3.

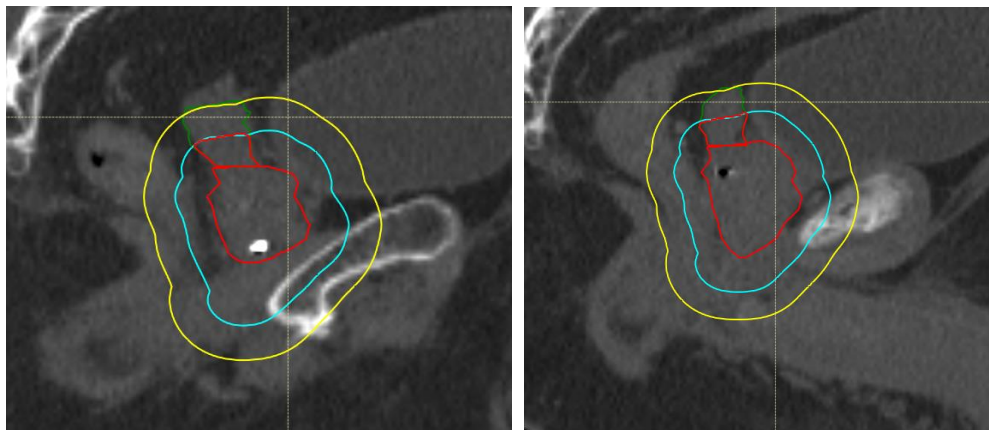


Figure 3. Sagittal images showing proximal 1 cm of SV (red) and the SV at 1-2 cm (green).

For those not used to contouring on MRI, the following guidelines may be helpful:



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ESTRO ACROP guideline

ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer



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3.2. Organs at Risk

The following organs at risk (OAR) will be contoured. These are given in reducing order of priority for planning constraints.

Rectum: defined as a solid structure, including the lumen and rectal wall, extending from the anus to the rectosigmoid junction. The rectosigmoid junction is usually denoted as where the rectum turns forward and laterally.

Bladder: defined as a solid structure including the bladder wall and lumen.

Urethra if visible (best seen on MR): the prostatic urethra is defined as the lumen/mucosal interface, extending from bladder neck to the membranous urethra.

Penile bulb: the portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm. The penile bulb is easily seen on the planning MRI.

Femoral heads: Femoral heads are to be outlined from their most cranial aspect to the bottom of the curvature of the femoral head (i.e. exclude the femoral neck).

Bowel: Above rectum, within 15 cm of PTV for CyberKnife SBRT and within 2 cm of PTV for gantry-based SBRT and IMRT. Bowel may be outlined as a ‘bowel bag’.

Testes: For CyberKnife SBRT, beams should not be allowed to traverse the testes, due to the effects on hormone production and subsequent confusion of biochemical outcomes [1]. The bilateral testes should therefore be used as a ‘blocking structure’.

3.3. Structure Naming Convention

As an NCRN radiotherapy trial, the PACE study uses a standardised naming convention [2]. This will avoid ambiguity and facilitate analysis of radiotherapy plan data. This convention is detailed in table 1.

Volume	Naming convention (includes target dose in cGy for target volumes)	
	PACE-A	PACE-C
Clinical target volume: prostate +/- seminal vesicles	CTVp (low risk); or CTVpsv (intermediate risk)	CTVpsv and CTVsv
Conventional treatment volumes		
	N/A	PTVpsv_6000 and PTVsv_4700
SBRT treatment volumes		
Clinical target volume: prostate +/- seminal vesicles (receives 40 Gy)	CTVp_4000; or CTVpsv_4000	CTVpsv_4000
Planning target volume (receives 36.25 Gy)	PTV_3625	PTVpsv_3625 and PTVsv_3000
Organs at risk	Approved PACE nomenclature	
Rectum	Rectum	
Bladder	Bladder	
Urethra	Urethra	
Left femoral head	FemoralHead_L	
Right femoral head	FemoralHead_R	
Penile bulb	PenileBulb	
Bowel	Bowel	

Table 1: Structure naming convention for PACE

4. MARGINS FOR PLANNING TARGET VOLUMES

Planning target volumes (PTV) will be outlined and reported in line with ICRU 83 “Prescribing, recording and reporting photon-beam intensity modulated radiotherapy (IMRT)” [3] and ICRU 91 “Prescribing, recording and reporting of stereotactic treatments with small photon beams” [4] where relevant.

The CTV to PTV margins are slightly different for prostate SBRT and conventional radiotherapy.

4.1. PTV Margins for Conventional Radiotherapy

For conventional radiotherapy (PACE-C only), margins will depend on the department’s treatment delivery accuracy. Margins align with the PIVOTALboost trial for conventional fractionation, assuming fiducials are used.

Preferred margins for conventional RT, assuming fiducials are used:

$$PTVsv_{4700} = CTVsv + 6 \text{ mm}$$

$$PTVpsv_{6000} = CTVpsv + 3 \text{ mm}$$

Permissible range for margins if above convention is not used

Margins for both PTVs should be between 4 and 8 mm:

$$\text{PTVsv}_{4700} = \text{CTVsv} + 4\text{-}8 \text{ mm}$$

$$\text{PTVpsv}_{6000} = \text{CTVpsv} + 4\text{-}8 \text{ mm}$$

4.2. PTV Margins for SBRT

It is recommended that fiducial markers are used for image-guidance. Margins may be slightly larger where fiducials are not used, and the range of permissible margins is defined below.

4.2.1. PACE-C PTV Margins for SBRT

Preferred PACE-C margins for SBRT, assuming fiducials are used:

$$\text{PTVsv}_{3000} = \text{CTVsv} + 5 \text{ mm}$$

$$\text{PTVpsv}_{3625} = \text{CTVpsv} + 5 \text{ mm} / 3 \text{ mm posteriorly}$$

(Additionally $\text{CTVpsv}_{4000} = \text{CTVpsv}$ with no margin)

Permissible range for margins if above convention is not used

$$\text{PTVsv}_{3000} = \text{CTVsv} + 6 \text{ mm}$$

$$\text{PTVpsv}_{3625} = \text{CTVpsv} + 4\text{-}5 \text{ mm}$$

4.2.2. PACE-A PTV Margins for SBRT

For prostate SBRT the PTV is defined as the CTV plus 4-5 mm, except posteriorly where the prostate abuts the rectum where a 3-5 mm margin will be applied. The PTV margin for PACE-A is not dependent on the use of fiducials.

$$\text{PTV}_{3625} = \text{CTV} + 4\text{-}5 \text{ mm} / 3\text{-}5 \text{ mm posteriorly}$$

5. EXTERNAL BEAM RADIOTHERAPY PLANNING GUIDELINES

5.1. Radiotherapy Technique

This trial simultaneously treats multiple dose-level PTV structures in a single phase. Therefore, an IMRT or VMAT planning technique must be used to obtain the prescription doses for adjacent PTVs.

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

5.2. Prescribed Dose and Fractionation

Dose for the conventional arm (PACE-C only) will be 60 Gy in 20 fractions over at least 27 days, and delivered using IMRT.

The dose for the SBRT arm will be 36.25 Gy given in 5 fractions over 1-2 weeks (i.e. daily or alternate daily). The prescription dose of 36.25 Gy shall be the dose to PTV_3625 (PACE-A) or PTVpsv_3625 (PACE-C).

Table 2. Dose to PTVs in PACE-C – Conventional fractionation

Structure	Contains / derived from	Conventional dose (median, Gy)
PTVpsv_6000	Prostate+proximal 1 cm of SV (CTVpsv)	60.0
PTVsv_4700	Prostate+proximal 2 cm of SV* (CTVsv)	47.0

*except if lower intermediate risk in which case PTVsv_4700 is grown from prostate+proximal 1 cm of SV.

Table 3. Dose to PTVs in PACE-C – SBRT

Structure	Contains / derived from	Conventional dose (median, Gy)
PTVpsv_3625	Prostate+proximal 1 cm of SV (CTVpsv)	36.25 (40 to CTV)
PTVsv_3000	Prostate+proximal 2 cm of SV (CTVsv)*	30.0

Note: For SBRT there is an additional target volume CTVpsv_4000 (CTVpsv with no margin) which receives 40 Gy

*except if lower intermediate risk in which case PTVsv_3000 is grown from prostate+proximal 1 cm of SV.

Table 4. Dose to PTVs in PACE-A – SBRT

Structure	Contains / derived from	Conventional dose (median, Gy)
PTV_3625	Prostate+/-proximal 1 cm of SV (CTVp/CTVpsv)	36.25 (40 to CTV)

Note: For SBRT there is an additional target volume CTVp_4000/CTVpsv_4000 (CTVp/CTVpsv with no margin) which receives 40 Gy

5.3. Definition of PTVs for Dose Reporting with their Dose Constraints

5.3.1. Conventional RT

Planning target volume	Dose to PTV
PTVpsv_6000	Report dose to PTVp_6000: $D_{50\%} = 60 \text{ Gy} \pm 1\%$ (median); $D_{98\%} \geq 57.0 \text{ Gy}^*$ (95% prescribed dose), $D_{2\%} \leq 64.2 \text{ Gy}$ (107% prescribed dose, aim for $D_{2\%} \leq 63.0 \text{ Gy}$ (105%))
PTVsv_4700	Dose to PTVsv_4700 will be prescribed to a ring structure excluding PTVpsv_6000, i.e. PTVsv_4700-PTVpsv_6000, for

	which the following dose objectives will be met: D50% ≥ 47 Gy and D98% ≥ 44.7 Gy
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*The minimum dose constraint (D98%) may be relaxed where necessary in order to meet the rectum high dose constraint, with limited under-coverage permitted posteriorly where PTV overlaps rectum.

5.3.2. SBRT

For SBRT planning, the prescription isodose shall be 75-85% of Dmax and aim for D98% ≥ 34.4 Gy. This may need to be relaxed to achieve the mandatory rectal constraint.

Planning target volume	Dose to PTV
PTV_3625 (PACE-A) PTVpsv_3625 (PACE-C)	V36.25 Gy ≥ 95%; D98% ≥ 34.4 Gy
CTVp/CTVpsv	A secondary dose of 40 Gy should be delivered to the CTVp/CTVpsv (i.e. the prostate/proximal 1cm SVs) such that the CTV V40Gy ≥ 95%.
PTVsv_3000 (PACE-C only)	Dose to PTVsv_3000 will be prescribed to a ring structure excluding PTVpsv_3625 (i.e. PTVsv_3000-PTVpsv_3625), for which the following dose objective will be met: V30 Gy ≥ 95%.

5.4. Normal Tissue Dose Constraints for Organs at Risk

5.4.1. Conventional RT

Following dosimetric analyses using CHHiP trial data, revised optimal rectal dose constraints have been derived for the conventional radiotherapy arm for 3Gy per fraction moderate hypofractionation [5,6]. Note: These are constraints to aim for during plan optimisation; they are not mandatory and should not be achieved at the expense of PTV dose objectives.

Table 5. OAR dose constraints for Conventional radiotherapy

Organ at risk	Dose volume constraints		
	Dose (Gy)	Maximum volume (% or cc)	
		Mandatory	Optimal
Rectum	24	80%	70%
	32	65%	51%
	40	50%	38%
	48	35%	27%
	52	30%	-
	56	15%	-
	60	3% *	1%
Bladder	40	50%	-
	48	25%	-
	60	15%	5%

Femoral heads †	40	50%	5%
Bowel	40	70cc	17cc
	48	6cc	0.5cc
	52	0cc	-
Penile bulb	22		<50%
	48	-	10%

* May require a reduction in posterior PTV margin and/or removal of rectal overlap from PTV during plan optimisation (as for SBRT planning).

† When reporting femoral head V40Gy, report the larger calculated volume only

5.4.2. SBRT

Table 6. OAR dose constraints for SBRT

Organ at risk	Dose volume constraints		
	Dose (Gy)	Maximum volume (% or cc)	
		Mandatory	Optimal
Rectum	18.1	50%	
	29	20%	
	36	2cc	1cc
Bladder	18.1	40%	
	37	10cc	5cc
Femoral heads †	14.5	-	5%
Bowel	18.1	5cc	
	30	1cc	
Penile bulb	29.5	-	50%
Urethra (if visualised)	42	-	50%
Testicular	Blocking structure		

5.5. Dose-volume Variations for SBRT

Table 7. Minor and Major variations for SBRT dose reporting

Structure	Minor variation	Major variation
Target volumes		
CTV_4000	V40Gy = 90-94.9%	V40Gy < 90%
PTV_3625	V36.25Gy = 90-94.9%	V36.25Gy < 90%

Investigators shall attempt to keep normal tissue doses and prescription coverage as close to “per protocol” specifications as possible. If all the above “per protocol” dose-volume criteria cannot be met on a given patient, then target prescriptions may be relaxed to the “minor variation” range as follows: one minor variation in EITHER the primary or secondary dose prescription coverage (e.g. PTV

V36.25Gy = 90-95% or CTV V40Gy = 90-95%) is allowed; two minor variations or one major variation is allowed only with the consent of the site chair.

If an adequate plan cannot be achieved within these constraints, please review the contours and discuss with the RTQA team and/or the CI. All variations shall be noted.

6. RADIOTHERAPY DELIVERY

6.1. Treatment Scheduling

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).

Treatment will be given in a single phase over no more than 14 days for SBRT and 34 days for moderate hypofractionation (60 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.

6.2. Treatment Verification

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

It is recommended that all patients be set up to fiducial markers prior to treatment and if a significant shift is required (>5 mm) the patient should be re-imaged after that shift. In addition, tomographic imaging pre-treatment is encouraged to rule out any significant changes in rectal position or prostate deformation. Time from imaging review to beam on should be less than 2 minutes to reduce the risk of prostate motion.

At least three fiducials should be identified for each treatment. If fewer than three fiducials can be tracked, then additional fiducials can be placed, and the patient re-planned. Where the ability exists, rotational corrections may be made.

It is recommended that the couch is shifted for all displacements, but it is mandatory to shift for any displacement ≥ 2 mm.

For SBRT using CyberKnife, patients will have fiducial-based intra-fraction motion corrected during treatment.

For gantry-based SBRT using tomographic imaging (i.e. cone beam CT (CBCT)) without fiducials, centres must demonstrate that they are experienced in soft tissue matching to the prostate.

For centres using Calypso beacons or Elekta Clarity ultrasound monitoring, prostate motion will be monitored continually and treatment paused (and position corrected) if prostate displacement exceeds 5 mm. For Clarity a 5mm tolerance with a 5 seconds threshold is recommended.

MR-guided radiotherapy is permitted, with or without daily adaptive re-planning.

For SBRT with gantry based systems, it is anticipated that the majority of centres will use an arc-based IMRT technique, with or without flattening filter-free delivery. Flattening filter-free delivery should have a beam on time of under 3 minutes, in which case intrafraction motion control is not mandated. Where beam-on time exceeds 3 minutes, reimaging should occur between beams/arcs (or at approximately 3-4 minute intervals).

7. DOCUMENTATION ON COMPLETION OF RADIOTHERAPY

Radiotherapy plan data will be collected (in DICOM format by electronic transfer – see section 8.9) for all patients having radiotherapy within the trial. This data will be stored on a secure server by the sponsor.

8. RADIOTHERAPY QUALITY ASSURANCE

8.1. Radiotherapy Quality Assurance Overview

Radiotherapy quality assurance (RTQA) includes pre-trial and on-trial components. RTQA will be streamlined where possible when a centre has completed RTQA for another prostate trial (e.g. PACE-A/B, PIVOTALboost) – see section 8.6 for details.

RTQA documentation and data can be downloaded from the RTQA website:

<http://www.rtrialsqa.org.uk>

Please send all completed RTQA to the PACE RTQA contact at: pace.rtqa@nhs.net

Pre-trial QA includes:

- Benchmark outlining case
- Benchmark planning case for both conventional and SBRT fractionation
- Facility questionnaire

On-trial QA includes:

- Prospective and/or retrospective case reviews
- Dosimetry site visit (subject to prior RTQA dosimetry accreditation)

All plans (including MRI where feasible, CT, structures, plan and dose cube) should be exported, anonymised and sent to the RTQA team electronically (see section 8.9).

8.2. General principles of QA for PACE

All outlining should be either performed by, or reviewed and approved by, the PI at the centre who has been through the pre-trial outlining QA. Since this is a clinical trial and the patient numbers may not be excessive we hope this approach will be acceptable. However, where this is not feasible we recommend the following:

- The PI should review and approve clinical outlines for the first 3 PACE patients recruited by each additional clinician at that centre, after which (assuming these are satisfactory) they are also approved for PACE. Please notify the QA team of any additional clinicians who have been locally approved in this way.
- Should the PI leave and be replaced, the replacement should perform the PACE benchmark outlining QA, to be reviewed by the RTQA team.

8.3. Pre-Trial Questionnaires

8.3.1. Facility Questionnaire

The Prostate Facility Questionnaire (FQ) collects information about the RT equipment, techniques and procedures used by a centre for the trial. The questionnaire will be provided by the RTQA team as it may be pre-filled with information provided from previous trials.

If the FQ has been completed previously for another prostate trial, please update where necessary to reflect procedures and equipment for PACE trial and re-submit.

8.3.2. CBCT Questionnaire

Required for centres not using fiducials.

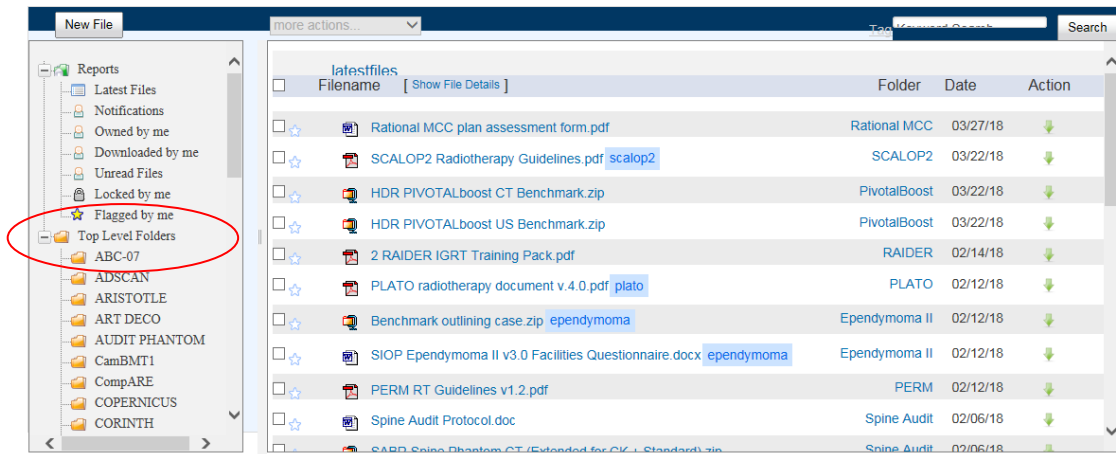
8.4. Benchmark Cases

8.4.1. Downloading data from RTTQA website

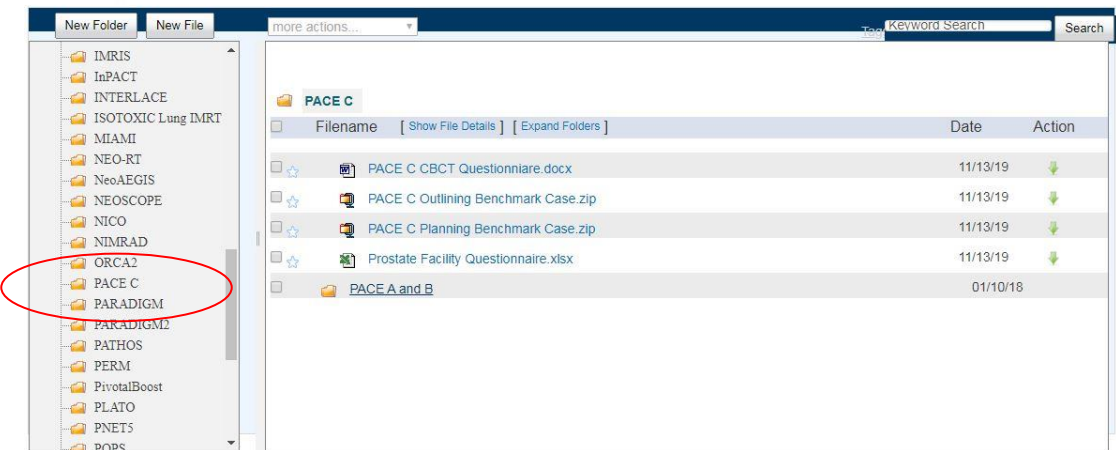
Download the benchmark case DICOM datasets from the RTTQA website <http://www.rtrialsqa.org.uk>

- Log in
- Select 'Downloads' from the menu bar
- Open 'Top Level Folders' (see below) and select the PACE folder
- Select 'Download' from the Action column

Filedepot



Filedepot



8.4.2. Outlining Benchmark Case

All centres wishing to participate in the PACE trial will need to complete a contouring exercise for a high risk patient. The planning CT and planning MRI should be downloaded from the RTTQA website; a written case summary is in APPENDIX A: Case History for pre-trial QA for PACE-C. Please import the DICOM data for Patient ID="PACE_C_2" and Name="PACE_C_outlining_benchmark" into your own outlining or treatment planning system (TPS).

It is not mandatory to use the planning MR if you do not have access to planning MR for trial patients, but if you wish to do so you will need to register it to the planning CT.

Refer to outlining instructions in section 3. Please contour the following structures on his CT, with the aid of the planning MRI scan for the target structures - please use the trial structure naming convention:

- CTVpsv (for PACE-C)
- CTVsv (for PACE-C)
- Rectum
- Bladder

- Bowel
- FemoralHead_L and _R
- PenileBulb
- Urethra (optional)

Once outlines have been created, reviewed and accepted by the local PI, please export and return the DICOM CT and Structure data, together with planning MRI and DICOM image registration object (if used), to the RTQA team (see section 8.9)

8.4.3. Planning Benchmark Case

All new PACE centres must complete and submit the PACE pre-trial planning benchmark case. One plan will be prepared for each arm of the trial – conventional radiotherapy and SBRT. The CT images and pre-outlined structure set are available for download from the RTTQA website.

Radiotherapy contouring/planning:

Please import the CT images and structure set for Patient ID="PACE_C_1" and Name="PACE_C_benchmark_plan" into your own TPS. The CT has been delineated by the CI with the following structures, which should not be edited. No additional structures, e.g. for PTV/OAR overlaps, have been created. The individual centre should create these as needed.

Target volumes: CTVp, CTVpsv

OARs: Rectum, Bladder, Bowel, FemoralHead_L and _R, PenileBulb

Two treatment plans should be prepared for this patient: a conventional plan and an SBRT plan. Create PTVs according to the margins which will be used by your centre for PACE-C.

Please complete the PACE Treatment Planning Data Capture Form (DCF), and provide a copy of the treatment planning report from your TPS.

Data Export: Once the benchmark plan has been created and reviewed and accepted by the local PI, the export of the CT images, dose matrix, RT plan and structure set in DICOM format should be returned to the RTTQA team (see section 8.9). Avoid re-anonymising as this causes problems and may delay your review.

Treatment plan dosimetry check: QA dosimetry check measurements are only needed for centres where it is the method of checking the dosimetry of all IMRT plans (PDIP, phantom etc.). Please do a measurement and return the result. For other centres, please do a dosimetry check by your usual method and return the result (e.g. Mobius and RadCalc users).

8.5. Patient Case Reviews

The outlining and treatment planning for the first patient recruited to each of the two trial arms by each trial centre will be subject to review by the RTQA team. This may be a prospective (i.e. pre-treatment) or timely retrospective review, to be advised by the RTQA team on a case-by-case basis. Patient specific QA measurements should also be provided if applicable. Additional reviews may be requested by the RTQA team.

To ensure a short response time for prospective reviews please notify the RTQA team when a patient has been identified, and please allow 2 weeks between submitting data and the RT treatment start date to allow time for amendments. Please send outlining for review in advance of RT treatment planning where possible to expedite the review. Failure to give the QA team sufficient notice of a case may result in delays in the case being reviewed. Should it not be possible to complete a review prior to the planned treatment start date, it is the PI's responsibility to decide whether to start treatment as planned (prepared to re-plan for remaining treatment fractions if necessary) or to delay treatment start until review is complete.

For outlining reviews please send:

- Planning MR images and DICOM registration object(s) (if used)
- Planning CT images
- DICOM structure set

For planning reviews please send:

- Planning CT images
- DICOM structure set
- DICOM dose matrix
- DICOM plan file
- Completed Treatment Planning DCF

See section 8.9 for data export instructions.

Note the following:

1. All retrospective reviews are "timely": data to be submitted within a week of treatment start and review to be completed before another trial patient is treated.
2. The RTQA team will be in touch if a patient is recruited who needs a prospective review.

8.6. Streamlining of RTQA

Streamlining of RTQA is based on prior completion of RTQA for another NIHR-portfolio prostate trial (PACE-A/B, PIVOTALboost).

8.6.1. Facility Questionnaire

If the prostate FQ has been completed previously, please check and amend any details which have changed or are different for the PACE trial. The RTQA team will provide a copy of your FQ.

PACE-B centres: The RTQA team will provide a copy of the FQ, pre-filled with data from your PACE-B process document. Please update and re-submit if any details have changed.

PACE-A centres now recruiting to PACE-C: Please complete the FQ for the conventional RT arm only.

8.6.2. Benchmark Outlining Case

This is not a requirement if a centre and the PI have been approved for a NIHR-portfolio prostate trial (PACE-A/B, PIVOTALboost).

If the centre has been approved as above but the PI is different, then there are 2 options:

- PI completes benchmark outlining case
- The clinician with RTQA-approval for another prostate trial is responsible for reviewing and approving outlines for the first 3 patients recruited to the trial

All other centres should complete the benchmark outlining case.

8.6.3. Benchmark Planning Case

Conventional Plan

This is not required if the centre has been approved for a NIHR-portfolio prostate trial (e.g. PACE-B, PIVOTALboost) using the same planning technique (e.g. VMAT).

PACE-A only centres (who are not in PIVOTALboost) will need to complete the conventional benchmark case.

SBRT Plan

This is not required if the centre has been approved for PACE-A/B.

All other centres should complete the SBRT benchmark case.

8.6.4. Patient Case Reviews

All patients will have a prospective case review for the 1st patient recruited to each of the conventional and SBRT arms, except in the following circumstances when the review will be retrospective:

- PACE-A/B centres: The first PACE-C SBRT patient shall have a retrospective case review completed before subsequent patients are treated. If this is a lower-intermediate risk case with only 1 cm of SV, a further retrospective review of a higher risk patient (i.e. one requiring 2 cm of SVs in CTVsv) is required retrospectively. The first PACE-C conventional RT patient shall have a retrospective case review.
- PIVOTALboost centres (not in PACE-A/B): The first PACE-C conventional RT patient shall have a retrospective case review, and the first SBRT patient will have a prospective case review.

The RTQA team may request additional prospective or retrospective reviews as required.

8.7. Dosimetry Audit

All sites are required to have a recent dosimetry site visit by the RTTQA group. Sites which do not have this will be contacted individually by the RTTQA team to arrange an audit.

8.8. Ongoing Data Collection

Radiotherapy plan data will be collected (in DICOM format by electronic transfer) for all patients having radiotherapy within the trial. These data will be stored on a secure server by the sponsor. All patient data must be anonymised before transfer, and should be re-identified with the trial number.

Plans should ideally be submitted once they have been approved by the PI and had an independent check. Data associated with any re-plans during radiotherapy treatment should also be submitted.

Please send the following data:

- Planning MR images and DICOM registration object(s) (if used)
- Planning CT images
- DICOM structure set (ensure trial naming convention has been followed)
- DICOM dose matrix
- DICOM plan file

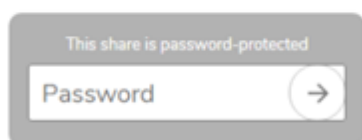
8.9. DICOM Data Export

DICOM data should be transferred to the RTTQA group via their central secure transfer service. Anonymised and encrypted data will pass through a firewall to a host server located in a secure NHS environment to which access is restricted to authorised users.

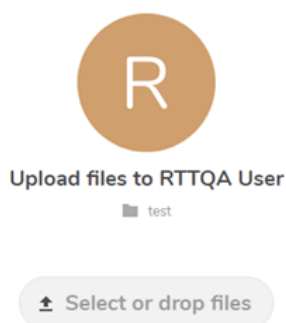
All NHS radiotherapy centres have a centre specific link and unique password to access the service – contact the RTQA team if you do not have this.

Instructions for use:

1. Data must be anonymised at source and should be encrypted using 7zip/WinZip or equivalent
2. All files for a single patient must be zipped into one file
3. Files must be labelled with the Trial Name and Trial ID, e.g. UKC022001
4. Follow unique centre link to the service



5. Insert unique centre password



6. Upload files
7. Email RTTQA contact at pace.rtqa@nhs.net to confirm data uploaded and share password to unzip data

9. REFERENCES

1. King, C.R., A. Lo, and D.S. Kapp, Testicular dose from prostate cyberknife: a cautionary note. *Int J Radiat Oncol Biol Phys*, 2009. 73(2): p. 636-7; author reply 637.
2. Santanam, L., et al., Standardizing naming conventions in radiation oncology. *Int J Radiat Oncol Biol Phys*, 2012. 83(4): p. 1344-9.
3. ICRU (International Commission on Radiation Units and Measurements), Prescribing, recording, and reporting photon-beam IMRT. Report No. 83, *Journal of the ICRU Vol. 10*, Oxford University Press, Oxford, U. K., 2010.
4. ICRU, Prescribing, recording and reporting of stereotactic treatments with small photon beams. Report No. 91.
5. Wilkins A, Naismith O et al, Derivation of Dose/Volume Constraints for the Anorectum from Clinician- and Patient-Reported Outcomes in the CHHiP Trial of Radiation Therapy Fractionation. *Int J Radiat Oncol Biol Phys*, 2020.
6. Murray J, Gulliford S et al, Evaluation of erectile potency and radiation dose to the penile bulb using image guided radiotherapy in the CHHiP trial. *Clin Transl Radiat Oncol*. 2019.

10. APPENDIX A: Case History for pre-trial QA for PACE-C

Case history for pre-trial QA for PACE-C

72 year old man presents with prostate cancer – his cancer parameters are:

- PSA 14
- Gleason 4+4 in 2/15 cores, up to 80% core involvement
- T3a (MRI staging)

Please contour all target structures (including PTV) and all OARs listed in the radiotherapy planning guidelines.

For upload information please see data export instructions in section 8.9.

11. APPENDIX B. RADIOTHERAPY TREATMENT FOR PACE-B TRIAL

This Appendix specifies the radiotherapy treatment procedures that are specific to the PACE-B trial (copied from PACE protocol version 9 (14 June 2017)).

11 Treatment

11.2 Evaluated Structures

11.2.1 The Clinical Target Volume (CTV):

For the purposes of this study, the CTV shall be defined as follows:

All patients:

Low risk: CTV = prostate only (as defined on MRI planning scan where available)

Intermediate risk: CTV = prostate plus proximal 1 cm of seminal vesicles from insertion point in the superior-inferior plane. This should include the middle $\frac{1}{2}$ to $\frac{2}{3}$ of seminal vesicle width (i.e. not the tips). Please contact the QA team for example contours.

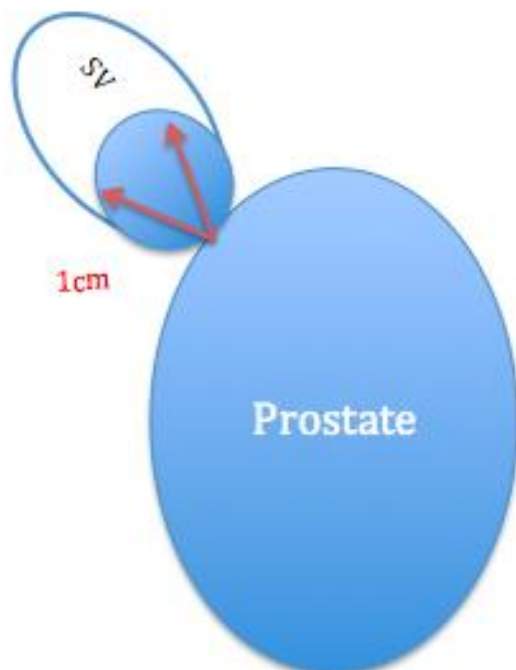


Figure 1: Schematic illustration of the seminal vesicle inclusion for PACE (“CTV” shown in blue)

11.2.2 The Planning Treatment Volume (PTV):

The CTV to PTV margins are different for prostate SBRT and conventional radiotherapy.

11.2.2.1 For conventional radiotherapy, margins will depend on the department's treatment delivery accuracy.

PTV margin for conventional radiotherapy:
PTV= CTV+ 5-9 mm, except 3-7 mm posteriorly

11.2.2.2 For prostate SBRT the PTV is defined as the CTV plus 4-5 mm, except posteriorly where the prostate abuts the rectum, where a 3-5 mm margin will be applied.

PTV margins for SBRT (36.25 Gy in 5 fractions)
PTV= CTV+ 4-5mm/ 3-5mm posteriorly

11.2.2.3 Planning volumes will be outlined and reported in line with ICRU 83 "Prescribing, recording and reporting photon-beam intensity modulated radiotherapy (IMRT)" where relevant.

11.2.3 Organs at Risk (OAR)

The following OAR will be contoured: these are given in reducing order of priority for planning constraints.

11.2.3.1 Rectum: defined as a solid structure, including the lumen and rectal wall, extending from the anus to the rectosigmoid junction.

11.2.3.2 Bladder: defined as a solid structure including the bladder wall and lumen.

11.2.3.3 Urethra if visible (prostate SBRT only): the prostatic urethra is defined as the lumen-mucosal interface, extending from bladder neck to the membranous urethra.

11.2.3.4 Penile bulb: the portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm.

11.2.3.5 Femoral heads: Femoral heads are to be outlined from their most cranial aspect to the bottom of the curvature of the femoral head (i.e. exclude the femoral neck)

11.2.3.6 Bowel: Above rectum, within 15 cm of PTV for Cyberknife SBRT and within 4 cm PTV for gantry-based SBRT and IMRT. Bowel may be outlined as a 'bowel bag'.

11.2.3.7 Testes: For CyberKnife SBRT, beams should not be allowed to traverse the testes, due to the effects on hormone production and subsequent confusion of biochemical outcomes. The bilateral testes should therefore be used as a 'blocking structure'.

11.2.4 Structured naming convention for volumes

As an NCRN radiotherapy trial, the PACE study uses a standardised naming convention. This will avoid ambiguity and facilitate analysis of radiotherapy plan data. This convention is detailed in table 3.5.

Table 3.5: Structure naming convention for PACE

Volume	Naming convention
<i>Conventional treatment volumes</i>	
Clinical target volume: prostate +/- seminal vesicles	CTVp or CTVpsv
Planning target volume (receives 78 Gy or 62 Gy)	PTV_7800 or PTV_6200
<i>SBRT treatment volumes</i>	
Clinical target volume: prostate +/- seminal vesicles (receives 40 Gy)	CTVp_4000 or CTVpsv_4000
Planning target volume (receives 36.25Gy)	PTV_3625
<i>Organs at risk</i>	
Rectum	Rectum
Bladder	Bladder
Urethra	Urethra
Left femoral head	FemoralHead_L
Right femoral head	FemoralHead_R
Penile bulb	PenileBulb
Bowel	Bowel

11.3 Dose Specifications: (all specified doses are given over the entire course of treatment).

11.3.1 Conventional radiotherapy Dose Specifications:

11.3.1.1 Dose for the conventional arm will be either 78 Gy in 39 fractions daily over 8 weeks OR 62 Gy in 20 fractions daily over at least 27 days, and delivered using IMRT. The prescription dose shall be the dose to the PTV and the following dose objectives will be met: for 78 Gy: D98%≥74.1 Gy, D50%=78 Gy ± 1%, D2%≤83.5 Gy (aim for D2%<81.9 Gy): for 62 Gy: D98%≥58.9 Gy, D50%=62 Gy ± 1%, D2%≤66.3 Gy (aim for D2%<65.1 Gy). The minimum dose constraint (D98%) may be relaxed where necessary in order to meet the rectum high dose constraint, with limited undercoverage permitted posteriorly where PTV overlaps rectum.

11.3.1.2 Dose specifications for OAR are shown in Table 4.

Table 4: Dose Specifications for Conventional radiotherapy arm

Organ at risk	Dose volume constraints			
	Dose (Gy) for 78Gy/39 fractions	Dose (Gy) for 62Gy/20 fractions	Maximum Volume (% or cc)	
			Mandatory	Optimal
Rectum	30	24	-	80%
	40	32	-	65%
	50	40	60%	50%
	60	48	50%	35%
	65	52	30%	-
	70	56	25%	15%
	75	60	5%*	3%
Bladder	50	40	50%	-
	60	48	25%	-
	74	59	15%	5%
Femoral Heads	50	40	50%	5%
Bowel	50	40	17cc	-
Penile bulb	50	40	-	50%
	60	48	-	10%

* May require a reduction in posterior PTV margin and/or removal of rectal overlap from PTV during plan optimisation (as for SBRT planning).

11.3.2 Dose specifications for hypofractionated radiotherapy delivered with SBRT:

11.3.2.1 The dose for the SBRT arm will be 36.25 Gy given in 5 fractions over 1-2 weeks (i.e. daily or alternate daily). The prescription dose of 36.25 Gy shall be the dose to the PTV. V36.25 Gy to the PTV shall be greater than or equal to 95%. A secondary dose of 40 Gy should be delivered to the CTV (i.e. the prostate/SVs) such that the CTV V40 Gy is greater than or equal to 95%. For CyberKnife planning, the prescription isodose shall be 65-85% of Dmax (or 75-85% if urethra not contoured). For gantry-based SBRT, the following dose objectives should be met with respect to the PTV: D98%≥34.4 Gy, Dmax<48 Gy, and aim for D2%≤42.8 Gy, where possible. (A planning guide for gantry-based SBRT is available).

11.3.2.2 Dose specifications for OAR for SBRT are shown in Table 5. Minor and major variations are shown below.

Table 5: Dose Specifications for SBRT (36.25 Gy in 5 fractions)

OAR	Dose constraint
Rectum	V18.1 Gy <50% (i.e. 50% rectum <18.1 Gy) V29 Gy <20 % (i.e. less than 20% rectum receiving 29 Gy) V36 Gy <1cc
Bladder	V18.1 Gy <40% V37 Gy <10cc (optimal V37 Gy <5cc)
Prostatic urethra (if visualised)	V42 Gy <50% (optimal, not mandatory)
Femoral head	V14.5 Gy <5%
Penile Bulb	V29.5 Gy <50%
Testicular	Blocking structure
Bowel	V18.1 Gy <5cc V30 Gy <1cc

11.3.2.3 Rectum dose variations:

11.3.2.3.1 Minor variation: V36 Gy \geq 1 cc, but < 2 cc.

11.3.2.3.2 Major variation: V36 Gy \geq 2 cc

11.3.2.4 Bladder dose variations:

11.3.2.4.1 Minor variation: V37 Gy \geq 10 cc, but < 20 cc.

11.3.2.4.2 Major variation: V37 Gy \geq 20 cc

11.3.2.5 Target volume variations:

11.3.2.5.1 Minor variation: CTV V40 Gy 90-94.9%

11.3.2.5.2 Minor variation PTV: V36.25 Gy 90-94.9%

11.3.2.5.3 Major variation CTV: V40 Gy < 90%

11.3.2.5.4 Major variation PTV: V36.25 Gy < 90%

11.3.2.6 Investigators shall attempt to keep normal tissue doses and prescription coverage as close to “per protocol” specifications as possible. If all the above “per protocol” dose-volume criteria cannot be met on a given patient, then normal tissue constraints and target prescriptions may be relaxed to the “minor variation” range as follows: one minor variation in EITHER the primary or secondary dose prescription coverage (e.g. PTV V36.25 Gy 90-95% or CTV V40 Gy 90-95%) is allowed; two minor variations or one major variation is allowed only with the consent of the site chair.

11.3.2.7 Additional minor variation is allowed for constraints on the rectum and bladder. Major variations on OAR constraints are only allowed with the permission of the site chair. All variations shall be noted.

11.4 Radiotherapy plan data collection

11.4.1 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.

11.5 Radiotherapy Treatment Delivery and Tracking

11.5.1 All radiotherapy techniques are to be approved in advance by the Chief Investigator and trials QA team.

11.5.2 It is highly recommended that radiotherapy start within 8 weeks of randomisation, but it must start within 12 weeks. 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 31 days for moderate hypofractionation (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.

11.5.3 All patients will have image-guided radiotherapy, and it is strongly recommended that this is done with fiducial guidance. It is recommended that all patients be set up to fiducial markers prior to treatment and if a significant shift is required (>3 mm) the patient should be re-imaged after that shift. In addition, tomographic imaging pre-treatment is encouraged to rule out any significant changes in rectal position or prostate deformation.

11.5.4 At least three fiducials should be identified for each treatment. If fewer than three fiducials can be tracked, then additional fiducials can be placed, and the patient replanned. Where the ability exists rotational corrections should be made.

11.5.5 For SBRT using CyberKnife, patients will have fiducial-based intra-fraction motion corrected during treatment.

11.5.6 For SBRT with gantry based systems, it is anticipated that the majority of centres will use an arc-based IMRT technique, with or without flattening filter-free delivery. Flattening filter-free delivery should have a beam on time of under 3 minutes, in which case intra-fraction motion control is not mandated. Where beam-on time significantly exceeds 3 minutes, re-imaging should occur between beams/arcs (or at approximately 3-4 minute intervals). It is recommended that the couch is shifted for all displacement but it is mandatory to shift for any displacement ≥ 3 mm.

11.5.7 For centres using Calypso beacons or Elekta clarity ultrasound monitoring, prostate motion will be monitored continually and treatment paused (and position corrected) if prostate displacement exceeds 3 mm.

11.5.8 For gantry-based SBRT using tomographic imaging (i.e. cone beam CT) without fiducials, centres must demonstrate that they can deliver treatment to the required accuracy (given the significant prostate motion which may occur during treatment). This will be discussed and agreed on an individual centre basis with the Chief Investigator and trial QA team.

14 Quality assurance (QA)

14.2 Radiotherapy QA

The following QA documents and exercises must be completed by new centres for each radiotherapy treatment arm before commencing recruitment:

- Statement of unit calibration protocol
- Independent beam output audit
- Process document
- Benchmark case (see 14.2.1 below)
- IGRT benchmark test (conventional linac delivery only)
- Prospective individual case reviews will be performed for the first patient randomised to each treatment arm (see 14.2.2 below)

14.2.1 Benchmark Study: All potential sites shall receive, prior to patient enrolment, anonymous electronic patient data sets including CT and MRI images. A treatment plan shall be developed according to the protocol for both SBRT and IMRT, and the plan reviewed by the study team; completion of satisfactory benchmark plans is required prior to patient enrolment.

14.2.2 The first patient for each treatment allocation will undergo pre-treatment review. The treatment plan of the first patient enrolled at each site for each treatment must be reviewed prior to beginning treatment. The study team shall be notified at the time of enrolment of each patient, and of the proposed first treatment date, to assure the team's availability for review. There is the option for contours to be reviewed prior to planning if the centre prefers. After planning is complete, the treating site will make the treatment plan available to the study team site for review. The study team shall complete review within 2 weeks of receipt; treatment will only begin after any necessary corrections are implemented and final plan is approved. In addition, the first intermediate risk case must also be reviewed if the cases reviewed above were both low risk and did not include the seminal vesicles.

14.2.3 Thereafter plans will be reviewed as deemed necessary by the study team.

14.2.4 All outlining should be either performed by or reviewed and approved by the PI at the centre who has been through the pre-trial outlining QA. Since this is a clinical trial and the patient numbers may not be excessive we hope this approach will be acceptable. However, where this is not feasible we recommend the following:

14.2.4.1 The PI should review and approve clinical outlines for the 1st 3 PACE patients recruited by each additional clinician at that centre, after which (assuming these are satisfactory) they are also approved for PACE. Note: Please ensure at least one is an intermediate risk group case, since many inconsistencies with proximal seminal vesicle outlining have been reported.

14.2.5 Should the PI leave and be replaced, the replacement should perform the PACE benchmark outlining QA to be reviewed by the PACE QA team.

14.2.6 Treatment plan exports

All patient treatment plans will be exported in DICOM format, anonymised, and sent to the RT QA team electronically.