8.0 Technical Guidelines

8.1 Statement of treatment aim

In both treatment arms, radiotherapy will consist of a conventionally fractionated radical course of treatment that aims to deliver 64 Gy in 32 fractions over 6.5 weeks to the prostate bed (adapted from FROGG consensus guidelines45).

8.2 Treatment Schedule

Arm 1: Standard arm
Adjuvant RT commenced within 4 months of RP.

Arm 2: Experimental arm
Active surveillance with early salvage RT following a rising PSA (PSA level ≥ 0.20ng/ml prior to RT). SRT should be delivered as soon as possible (no later than 4 months) following the first PSA measurement ≥ 0.20 ng/mL.

8.3 Planning Simulation

A planning CT scan is required to define the clinical target volume (CTV), planning target volume (PTV) and the organs at risk (OAR). Intravenous contrast with delayed scanning (at least 10 minutes) and MRI may be employed to aid delineation of the anastomosis/penile bulb. If the bladder has been filled with contrast then a pixel-by-pixel density correction is inappropriate and a “bulk” correction, using typical values for normal tissue, should be applied.

Additional planning guidelines are as follows:

1. Contiguous axial slices are taken from the bottom of the SI joints to 2 cm below the ischial tuberosities.
2. The maximal CT slice thickness recommended is 2.5 - 3.0 mm and will be no more than 5.0 mm.
3. The planning CT is acquired with the patient in the supine position. The patient is simulated and treated with a full bladder. It is recommended that patients be encouraged to maintain an empty rectum at simulation and during treatment46. As a guide, it is expected that the rectal diameter shall be < 5cm. Centres shall provide details of their rectal and bladder filling protocols on the Facility Questionnaire, available from www.TROG-RAVES.org.
4. Immobilisation is as per the treating centres policy. Immobilisation and positioning will be consistent between the planning CT scan and throughout the treatment.

8.4 Daily treatment position

Daily treatment position shall be consistent between CT planning and throughout treatment. Similarly, bladder and rectal filling and use of any immobilisation devices shall be consistent between simulation and treatment.

8.5 Target volume definitions/Field Borders

Pictorial representation of target volumes may be found in Appendix VIII.

Excerpted from TROG 08.03 RAVES Final Protocol Version: 7 August, 2008
Amendment 1: 8 July 2011
8.5.1 Clinical Target Volume (adapted from FROGG consensus guidelines)

In addition to the planning CT scan and modalities outlined in section 8.3, the following information may also be utilised to assist in CTV delineation:

- Preoperative imaging
- Operation report and discussion with the operating surgeon
- Histopathology report

**Technique:**
The CTV structure will be named “CTV” at the planning computer. Delineation of the CTV surgical bed (based on CT slice thickness of 2.5-3.0 mm) shall be as defined below:

1. **Inferior border:** The inferior border of the CTV will be 5-6 mm inferior to the vesicourethral anastomosis (depending on CT slice thickness), but should be extended inferiorly if necessary to include all tumour bed clips (i.e. non-vascular).
   - i. The anastomosis can be identified on axial, coronal and sagittal reconstructions as the slice inferior to the last slice where urine is visible. To assist with the treatment plan review process, the CT slice containing the anastomosis shall contain a contour or some other identifier indicating the position of the anastomosis. This contour (or appropriate identifier) shall be labelled “anastomosis”.
   - ii. When the anastomosis is not clearly defined, the inferior border will be the first slice superior to the penile bulb.

2. **Anterior border:**
   - i. From the inferior border of the CTV to 3cm superior, the anterior border of the CTV is the posterior aspect of the symphysis pubis. In certain circumstances (e.g. positive margins at bladder neck) it may be necessary to extend this height up to the level of the superior pubic symphysis.
   - ii. More superiorly, the anterior border of the CTV should encompass at least the posterior 1.5cm of the bladder.

3. **Posterior border:** The space delineated by the levator ani and anterior rectal wall is at risk for recurrence and should be encompassed in the CTV if rectal dose constraints allow. As a minimum, the lateral posterior border must approximate the anterior rectal wall in the inferior portion. Ensure a minimum 2 cm margin from the posterior extent of the CTV to the posterior rectal wall to prevent the entire circumference of rectum receiving the full radiation dose. In creating the CTV posterior border, take into consideration that the PTV expansion and the 95% isodose must not encompass the full circumference of the rectal wall. More superiorly, the posterior border of the CTV is the anterior mesorectal fascia. This is often delineated by the posterior border of the residual seminal vesicles/seminal vesicle bed.

4. **Lateral border:** The medial border of the levator ani muscle or obturator internus muscle (pelvic side wall) superiorly.

5. **Superior border:**
   - i. If the seminal vesicles are not involved, the superior border should encompass all of the seminal vesicle bed as defined by post surgical changes and non vascular clips. The tips of the residual seminal vesicles do not need to be included.
ii. If the seminal vesicles are pathologically involved by tumour, ensure any residual seminal vesicles are also included in CTV.

8.5.2 Planning target volume (PTV)
The PTV is created by adding a 10 mm margin in all directions to the CTV, in order to account for day-to-day variation in patient positioning/set-up and patient and organ motion.

Planning target volume delineation:
 a) Defined as a uniform margin of 10mm from CTV to PTV for the entire dose, the PTV shall be named “PTV” at the treatment planning computer. Ensure the PTV expansion and the 95% isodose do not encompass the full circumference of the rectal wall.
 b) If the V40 rectal DVH constraints (section 8.9) cannot be met (i.e. more than 60% of the rectum is receiving > 40Gy), then we recommend reducing the posterior margin to a minimum of 0.5 cm keeping other margins to 1 cm using the auto expansion tool in the planning software. If the V40 still cannot be met, please submit case to the reviewing team who will then be in contact to discuss case.
 c) If the V60Gy constraint cannot be met despite reducing the posterior margin to 0.5cm, in some cases it may be necessary to consider a two phase technique. Any case where a two phase technique is being considered should first be discussed with a member of the RAVES QA committee.

Note that for IMRT treatments a 10 mm uniform expansion is mandatory due to the increased potential for geographic miss.

Centres should consult the QA Technical Advisory Committee if the rectal DVH constraints cannot be met.

8.6 Dose Prescription and Fractionation
The radiation dose for both arms is 64 Gy in 32 fractions over 6.5 weeks to the ICRU 50 reference point which is the centre of the planning target volume, but may be the intersection of the beam axes if this is close to the centre of the volume. When using an IMRT technique (permitted following RAVES IMRT site credentialing), the dose is typically prescribed to a volume. For IMRT plans, the dose should be prescribed as follows: the D98 (dose covering 98% of the PTV) shall be at least 95% of the total dose. The mean and median doses will be within -1% and +2% of 64 Gy (63.4 – 65.3Gy). The maximum dose (D2, dose to 2% of the PTV) shall be no more than 107% of the total dose.

Fractional dose will be 2 Gy delivered once a day, 5 days per week or 9 days per fortnight according to departmental policies. For 3DCRT techniques the prescribed dose shall be reported and normalised to the reference point and labelled as a separate point called “ICRU reference point”. The reference point must adhere to ICRU50 criteria for reference points. The 100% isodose or equivalent absolute dose in Gray (Gy) should intersect this point.

The ICRU Reference point shall be selected according to the following general criteria:

Excerpted from TROG 08.03 RAVES Final Protocol Version: 7 August, 2008
Amendment 1: 8 July 2011
• The dose at the point should be clinically relevant and representative of the
dose throughout the Planning Target Volume (PTV).
• The point should be easy to define in a clear and unambiguous way.
• The point should be selected where the dose can be accurately determined
(physical accuracy).
• The point should be selected in a region where there is no steep dose
gradient.

These recommendations will be fulfilled if the ICRU Reference point is located:
• Always at the centre, or in the central parts, of the Planning Target Volume,
and
• When possible on or near the intersection of the beam axes.

When using an IMRT technique (permitted following RAVES IMRT site
credentialing), for the purpose of plan review using the SWAN software, it will be
necessary to report the dose to a point that is representative of the traditional ICRU
50 point. For IMRT, this point may be selected after the plan has been optimised,
and can be anywhere in the centre of the volume as long as it is clinically significant.
The dose to the ICRU 50 point will be 64 Gy total dose.

8.7 Treatment Planning and Dosimetry
Treatment planning will be carried out with a 3D planning system which shall have,
as a minimum, the following capabilities:
• Able to handle at least 40 axial CT slices at 256 x 256 pixel resolution.
• Allows definition of multiple structures in 3D from CT data.
• Provides a 3D dose calculation algorithm (e.g. convolution / superposition
algorithm) capable of performing calculations which account for variations in
scatter in the presence of 3D-(CT) defined heterogeneities.
• Can provide permanent record of each treatment plan, both in electronic
form (data backup) and hard copy.
• Can provide hardcopy of superimposed isodose distributions on axial CT
images (sagittal and coronal planes desirable).
• Can provide digitally reconstructed radiographs (DRRs) with superimposed
target volume, critical structure contours and treatment aperture.
• Provide planning data in DICOM RT or RTOG format that can be uploaded
to CQMS. See Section 8.8, number 4 for further details.

Sites that have completed the RAVES IMRT credentialing program (see Section
8.12.2) may use an inverse planned IMRT technique. All IMRT plans must be
independently verified by the local physics department. The treatment planning
computer must therefore be capable of exporting the treatment plan to the local dose
measurement/verification software for direct measurement/verification by the
physicist.

Treatment planning guidelines include:

1. During treatment planning, if the bladder has been filled with contrast then a pixel-
by-pixel density correction is inappropriate and a “bulk” correction, using typical
values for normal tissue, should be applied.
2. An isocentric technique will be used.

3. All fields are delivered each day.

4. Treatment is delivered with a linear accelerator with $\geq 6$ megavoltage photons.

5. A minimum of 3 fields shall be used.

6. Shielding using blocks or multileaf collimators (MLC) is required to conform the high dose region to the PTV using at least 5 half-value-layers of attenuating material thereby minimising dose to normal structures. Real or virtual wedges may be employed if necessary to achieve the required target volume homogeneity.

7. IMRT techniques are permitted in this trial ONLY when the site has completed the RAVES-specific IMRT credentialing process. Centres wishing to use IMRT techniques should contact the Technical Advisory Committee for details of the credentialing process at www.TROG-RAVES.org. The IMRT credentialing process is described in Section 8.12.2 and treatment planning guidelines in Section 8.8.

8.8 Dose Distribution/Reporting
The following guidelines shall be followed for dose distribution and reporting:

1. The absorbed dose at the ICRU reference point shall be reported (see Section 8.6 for details).

2. PTV homogeneity shall be constrained as follows:
   a. The maximum dose (D2, dose to 2% of the PTV) shall be no more than 107% of the total dose.
   b. Minimum isodose covering the PTV (D98, dose covering 98% of the PTV) shall be at least 95% of the total dose.

3. For treatment plans created with an inverse IMRT technique (RAVES IMRT credentialed sites only):
   a. It is expected that the mean dose to the PTV will be within -1% and +2% of the prescribed dose.
   b. The maximum dose should be contained within the CTV, and must be contained within the volume bounded by the PTV.
   c. The dose outside the PTV will be minimised.
   d. It is recognised that treatment plans created with an IMRT technique demand extra precision in treatment delivery due to the presence of high dose gradients. Therefore planning techniques shall be robust in the presence of inter (and intra-) fraction organ motion.

4. Treatment planning data will be submitted for review in electronic format.
Instructions for exporting treatment planning data from each of the commercial treatment planning systems are available at the website: www.trog.com.au.

All centres must provide radiotherapy treatment planning (RTP) electronic data file/s exported from the treatment planning system in **DICOM RT** or **RTOG** format, including all relevant data relating to planned dose, planned treatment fields, DVH data, reference images and regions of interest. This data will be used for the purposes of QA review.

The x,y,z co-ordinates of the PTV ICRU Reference Point (relative to the DICOM origin) are required to be submitted with the RTP electronic data file. Data will be submitted for review via the Central Quality Management System (CQMS) as a zipped file. Information on CQMS user accounts and training are available on the TROG website: www.trog.com.au.

5. In addition to the electronic data file, planning system screen shots / screen dumps (JPEG images) for each phase of treatment are required in the following format:
   - A single image from the planning system screen showing all 3 orthogonal viewing planes at the intersection of the PTV – ICRU reference point and demonstrating dose to the PTV at the ICRU reference point (this image will be used to verify the accuracy of the plan import into the 3D review software). As a minimum requirement this must show clearly the ICRU 50 doses for reporting:
     - The clinically meaningful maximum dose (i.e. to an area of 1.5cm²)
     - Isodose plots shall be provided of the axial, coronal and sagittal planes containing the ICRU 50 reference point with isodoses; max, 100%, 95%, 90%, 70%, 50%, 20%. All isodose plots must be in colour with CT imaging visible, clearly labelled isodose values and non-colour wash on regions of interest.
     - The minimum isodose (or equivalent absolute dose in Gray) received
   - to the PTV should be displayed.
   - A screen dump of the DVH of the following structures shall be provided: CTV, PTV, (seminal vesicles if delineated as a separate structure), rectum, left femur and bladder. This image will be used to verify accuracy of DVH display in the 3D review software and must be in colour. In addition the DVH must be exported with the treatment plan, or if the treatment planning system does not support electronic DVH export, a scanned copy must be uploaded.

6. Each treatment plan shall be computed with the following specifications:
   - Dose matrix maximum grid spacing will be no greater than 2.5mm x 2.5mm x 2.5mm.
   - Data shall be presented in “absolute dose” as export in relative dose mode is not fully supported by some commercial systems.
• All exported data shall be contained in a single directory for each patient.

• The sampling resolution for the dose volume histogram data shall be 0.1 cm for contoured structures, 0.2 cm for all other tissue. The bin width shall be 0.1 Gy or 10 cGy.

• Exported data shall include the DRR for each field.

• The target and organs at risk will be named as defined in section 8.5.1, i.e. CTV, PTV, Rectum, LF (for the left femur), Bladder, Anastomosis and AC (for the anal canal if contoured).

• Contouring shall be included on all relevant CT slices for all structures. The interpolation algorithm on the treatment planning computer may be used if it is not normal clinical practice to contour on all slices.

• Size restrictions for files uploaded to CQMS: Exported data files should not exceed 50 Mb.

7. DRRs may be provided in jpeg image format

Prior to submission for QA case reviews, all RT material must be DE-IDENTIFIED in terms of patient names, medical record numbers and other personal identifying information, and re-labelled according to the registration numbers allocated to the patient for the trial.

8.9 Normal tissue contouring and dose constraints

Rectum: The external surface of the rectum shall be named “Rectum” at the treatment planning computer and should be contoured as a solid organ superiorly from the recto-sigmoid junction (where the rectum turns horizontally into the sigmoid, usually at the inferior border of the sacro-iliac joint) to 15 mm inferior to the inferior border of the CTV. The rectal contours should extend at least 15 mm superior and inferior to the CTV. It is recommended that patients be encouraged to maintain an empty rectum at simulation and during treatment. As a guide, it is expected that the rectal diameter shall be <5 cm.

Left femur: Shall be named “LF” at the treatment planning computer and will be contoured from the acetabulum to the inferior edge of the treatment field.

Bladder: The whole external wall of the bladder shall be named “Bladder” at the treatment planning computer and should be contoured to the slice superior to the anastomosis. Note: During treatment planning, if the bladder has been filled with contrast then a pixel-by-pixel density correction is inappropriate and a “bulk” correction, using typical values for normal tissue, should be applied.

Anal canal: Whilst it is not a protocol requirement to delineate the anal canal, if it is delineated, it shall be named “AC.”
8.9.1 Dose constraints

**Rectum:** The rectal dose shall be constrained as follows\textsuperscript{49-51}:
- volume of rectum receiving 60Gy shall be < 40%
- volume of rectum receiving 40Gy shall be < 60%

**Femoral heads:** The tolerance doses for femoral heads (FH) are poorly defined but the recommended volume irradiated should not exceed these constraints:
- volume of left femur (LF) receiving 35Gy shall be < 100%
- volume of LF receiving 45Gy shall be < 60%
- volume of LF receiving 60Gy shall be < 30%

8.10 Treatment Equipment Specifications/Physical Factors
Patients will be treated on a megavoltage linear accelerator with the following facilities:
- Capable of delivering at least 6 MV photons
- The minimum source-to-axis distance is 100cm
- Beam modification (i.e. real or virtual wedges; blocks and/or MLC);
- A treatment couch with vertical movement < 3 mm for patients up to 150 kg;
- Facilities for taking routine images, with electronic portal imaging devices (EPID), radiographic film, kV imaging or cone beam CT (CBCT) which can be used to verify orientation and position of the radiation fields relative to anatomical structures to within 1 mm.

All monitor unit calculations will be independently verified (i.e. independent of the normal planning system).

8.11 Treatment Verification
To verify field size and shielding, each portal shall be visually checked on at least one occasion during the first week of treatment.

To verify patient position, at least two port films or images (e.g. AP and one lateral) will be acquired in the first week of treatment and then weekly. Films or images will be compared with DRRs to detect systematic differences between the position of the radiation field and the intended (planned) field.

It is recognised that treatment plans created with an IMRT technique demand extra precision in treatment delivery due to the presence of high dose gradients. Without the use of soft tissue imaging, it may be difficult to verify accurately the target position. Soft tissue imaging is not mandatory in this trial. However, centres using IMRT techniques are expected to demonstrate that an imaging policy is in place, which is appropriate for the margins specified in this protocol. Sites will be required to describe their imaging protocol in detail on the Facility Questionnaire.

8.12 Quality Assurance Program
RT technical reviews involving audit of the planning and treatment data will be conducted. Reviewed parameters and protocol deviations will be in accordance with the TROG Policy and Procedures Manual (Quality Assurance Statement of Minimum
Requirements for Clinical Trials). Results will be reported to the TMC at least 6 monthly, and at the TROG meetings bi-annually.

The target volume specifications in this protocol are based on the recommendations of the Faculty of Radiation Oncology Genito-Urinary Group (FROGG) Consensus Guidelines on post-prostatectomy radiation therapy. To ensure consistency in contouring treatment volumes and adherence to the technical requirements of the trial protocol, centres will participate in a "dry run" and submit electronic treatment planning data in either RTOG Data Exchange or DICOM-RT format for all trial patients for timely review. Each centre shall successfully complete the dry run before they commence registering patients into the trial.

Centres that wish to use inverse IMRT planning techniques must complete the RAVES IMRT credentialing process summarised in Section 8.12.2.

Contact details for the RT QA team are listed on the RT QA website: www.TROGRAVES.org

8.12.1 Dry run

8.12.1.1 Each treating clinician will be required to contour a CT dataset. A minimum of one treatment planning exercise must be completed by each department prior to site activation, but a plan must be submitted for each clinician who plans to participate.

8.12.1.2 Contouring and treatment planning will be in accordance with the trial protocol.

8.12.1.3 The CT dataset will be provided in DICOM format and participating centres will transfer this dataset to their treatment planning computer to complete the contouring and planning exercise.

8.12.1.4 The completed exercise will be saved in electronic format (either RTOG Data Exchange or DICOM-RT format) and submitted electronically along with the Dry Run Data Submission Form, available from www.TROG-RAVES.org. Data should be uploaded to the TROG QA Centre via CQMS.

8.12.1.5 Specific instructions for saving the completed exercise in electronic format and uploading data via CQMS may be found on the TROG web site: www.trog.com.au or requested by emailing qa@trog.com.au.

8.12.1.6 Centres wishing to use IMRT techniques should refer to section 8.12.2 and to the document TROG 08.03: Quality assurance and credentialing requirements for sites using inverse planned IMRT Techniques for more detailed instructions on completing the dry run. This document may be found on the website: www.TROGRAVES.org.

The RT QA team will review the completed exercise and provide timely feedback to the participating centre. The completed exercise will contain all data specified in the instructions provided with the datasets (and may be reviewed on the RT QA website). Any missing or incorrect data will delay the review process. Successful
completion of the dry run is required (i.e. no major deviations identified by the reviewer) by each investigator prior to registering a patient on the trial. Should a major deviation be identified, it may be necessary to complete a second dry run prior to registering patients in this trial.

8.12.2 IMRT credentialing program

The QA procedures for sites using IMRT techniques are summarised below:

- **Facility Information**: All sites must first complete the Facility Questionnaire, including the section specifically related to IMRT techniques.

- **External Audit**: Sites must satisfactorily complete an external dosimetry audit (phantom study). Sites that have not yet completed a TROG approved external IMRT dosimetry audit should contact the Coordinating Trial Centre to make arrangements for a site visit.

- **Submission of RAVES-specific case**: All clinicians must complete the contouring and planning benchmarking exercise (Dry Run, see Section 8.12.1) prior to trial recruitment. For a site to be credentialed to use IMRT in the RAVES trial, at least one site benchmarking case must use an IMRT technique AND must be verified by direct measurement using the approved in-house physics IMRT dosimetry QA protocol. The physics QA dosimetry report will be submitted with the treatment plan for the RAVES-specific case for review using CQMS.

More detailed instructions about the IMRT credentialing program may be obtained from the document *TROG 08.03: Quality assurance and credentialing requirements for sites using inverse planned IMRT Techniques*, available from the RT QA website: [www.TROG-RAVES.org](http://www.TROG-RAVES.org).

8.12.3 Radiation Therapy Technical Review

Radiation therapy technical reviews will be conducted in two stages. Planning data, outlined in Section 8.12.4, is due at least one week prior to the patient’s RT start date. Treatment data, outlined in section 8.12.5 is due within four weeks of the RT end date.

8.12.3.1 The treatment plans for all registered patients from each treating centre will undergo timely review by the designated RT QA team. The treatment plan shall be submitted at least 1 week prior to the commencement of radiotherapy. The treatment plan will be reviewed by the RT QA team and feedback provided in a timely manner. Should a major deviation be identified during the review process, the RT QA team will contact the treating centre to discuss timely modification of the treatment plan.

8.12.3.2 Should it be necessary to re-plan the patient part way through treatment, the revised plan shall be submitted for review within 1 week of the revised plan being created.

8.12.3.3 The review will be conducted using SWAN software.
8.12.3.4 Review parameters and treatment violations will be in accordance with the TROG Policy and Procedures Manual (Quality Assurance Statement of Minimum Requirements for Clinical Trials). Results will be reported to the TMC at least 6 monthly and to the TROG Trials Review Meeting biannually.

8.12.3.5 All data submitted to the RT QA team must be de-identified. The unique patient identification number assigned to each patient at registration must be used on all data and documents submitted. Details for removing patient identifiers from the digitally exported treatment planning data may be requested from the TROG QA office by email: qa@trog.com.au

8.12.3.6 All clinical documentation and RT data for registered patients should be stored and remain available for auditors for at least 15 years after completion of the trial.

8.12.4 Data required for timely review
Form QA2 Checklist RT Planning Data, available from www.TROG-RAVES.org, will be completed for each patient at least one week prior to the RT start date, and uploaded to CQMS with the electronic dataset. Data to be included with the forms include:

- Trial ID assigned at registration and patient initials
- Clinical data as appropriate (e.g. site of positive margins)
- Pathology report
- Prescription data
  - Total dose
  - Number of fractions
  - Dose per fraction
  - Total treatment time
  - Prescription point relative to the DICOM origin of the CT slices used
- Beam arrangement
  - Field sizes
  - Radiation energy for each beam
  - Gantry angle
  - Blocks/MLC margin
- Supplemental treatment plan data
  - Treatment planning computer and version of software used
- Screen dump(s)/ screen shots as described at section 8.8 number 5.
- The treatment plan for all trial patients planned using an IMRT technique (credentialed sites only) must be verified using the in-house dosimetry QA protocol. The physics dosimetry QA report must be submitted with the plan for review.

8.12.5 Data required following RT completion
Form QA3 Checklist RT Treatment Data, available from www.TROG-RAVES.org will be completed for each patient within four weeks after the RT end date. The following data are to be submitted:

- Documentation of any changes made to the treatment plan since submission of planning data for timely review. If any changes have been
made, the QA team should be contacted to determine if Form QA2 Checklist RT planning must be resubmitted.

- Radiation therapy summary
- Portal images log

8.13 Site Visits

No QA dosimetry site visits are scheduled for this trial (unless an external dosimetry audit is requested by the site for IMRT credentialing). However, the RT QA team may undertake a site visit if requested or if appropriate support could not be given remotely.

At the discretion of the TMC, site visits may be undertaken as part of the data monitoring activities of this study. The identification of variables requiring verification from the source data, and the percentage of patients to be audited, will be determined by the Independent Data Monitoring Committee (IDMC).