In collaboration with the Urological Society of Australia and New Zealand (USANZ) and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

TROG 08.03

RAVES – Radiotherapy Adjuvant Versus Early Salvage

A Phase III Multi-centre Randomised Trial Comparing Adjuvant Radiotherapy (RT) with Surveillance and Early Salvage RT in Patients with Positive Margins or Extraprostatic Disease Following Radical Prostatectomy

Amendment 1: 8 July 2011
Amendment 2: 29 May 2014
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FOREWORD

This document is intended to describe a Trans Tasman Radiation Oncology Group (TROG) trial and to provide information about procedures for screening, enrolling and treating trial participants. It is not intended that the Protocol be used as a guide for the treatment of patients who are not enrolled on this trial.

TROG will not accept any data for analysis unless each Trial Site has Human Research Ethics Committee (HREC) approval for patient enrolment and participation in this trial.

Amendments to the document may be necessary; when approved by TROG, these will be circulated by the Trial Coordinating Centre, on behalf of TROG, to Trial Sites participating in the Trial.

The Protocol and all other trial related documentation including the Participant Information Sheet and Consent Form and Case Report Forms must be written in English and under no circumstances be translated into another language without prior written approval from TROG.
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<tbody>
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<td>AC</td>
<td>Anal Canal</td>
</tr>
<tr>
<td>AD</td>
<td>Androgen Deprivation</td>
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<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<tr>
<td>ART</td>
<td>Adjuvant Radiotherapy</td>
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<tr>
<td>BaCT</td>
<td>Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre</td>
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<tr>
<td>bF</td>
<td>Biochemical Failure</td>
</tr>
<tr>
<td>bFFR</td>
<td>Biochemical Failure-Free Rate</td>
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<tr>
<td>bFFS</td>
<td>Biochemical Failure-Free Survival</td>
</tr>
<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Record/Report Form</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Effects</td>
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<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
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<td>DRR</td>
<td>Digitally Reconstructed Radiographs</td>
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<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
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<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
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<tr>
<td>FROGG</td>
<td>Faculty of Radiation Oncology Genito-Urinary Group</td>
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<tr>
<td>EPE</td>
<td>Extraprostatic Extension</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>Human Research Ethics Committee</td>
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<tr>
<td>I.V.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity-Modulated Radiation Therapy</td>
</tr>
<tr>
<td>LF</td>
<td>Left Femur</td>
</tr>
<tr>
<td>MLC</td>
<td>Multileaf Collimators</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute (USA)</td>
</tr>
<tr>
<td>N-IM</td>
<td>Non-Inferiority Margin</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PSADT</td>
<td>Prostate Specific Antigen Doubling Time</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>RP</td>
<td>Radical Prostatectomy</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SRT</td>
<td>Salvage Radiotherapy</td>
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<tr>
<td>SVI</td>
<td>Seminal Vesicle Involvement</td>
</tr>
<tr>
<td>TMC</td>
<td>Trial Management Committee</td>
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<tr>
<td>TROG</td>
<td>Trans Tasman Radiation Oncology Group</td>
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1.0 Executive Summary

Background
Radical Prostatectomy (RP) is the most frequently employed treatment modality for clinically localised prostate cancer. Twenty to 50% of patients with clinically localised disease will have positive margins, extraprostatic (extracapsular) extension or seminal vesicle involvement with a subsequent high risk of relapse. Three recent randomised trials have demonstrated a significant benefit of adjuvant post prostatectomy radiotherapy (RT) in such high-risk patients, and many now regard this approach as the new standard of care. However, adopting this approach will expose nearly half of such patients to unnecessary radiotherapy and hence additional inconvenience and potential treatment morbidity. Salvage radiotherapy, given early, is recognised to be effective. There is, therefore, a need to compare these two approaches to determine the utility of adjuvant versus early salvage timing of therapy.

Aim

Primary Aim
To test the hypothesis that active surveillance with early salvage radiotherapy can be considered non-inferior to standard treatment with adjuvant (immediate) radiotherapy with respect to risk of biochemical failure (bF) in patients with extraprostatic (pT3) disease and/or positive margins following RP.

Secondary Aims
To compare differences in quality of life (QoL), adverse event rates, survival duration and time to the initiation of androgen deprivation between the two arms. A secondary aim is to also assess the simultaneous effects of several potential prognostic factors on each outcome.

Primary endpoint
Biochemical failure (bF) rate, defined as a prostate specific antigen (PSA) level \( \geq 0.40 \) ng/mL and rising following radiotherapy.

Secondary endpoints
QoL (EORTC QLQ-C30 and QLQ-PR25), anxiety/depression (Hospital Anxiety and Depression Scale), adverse events (NCI CTCAE v3.0 and Sexual Health Inventory for Men), biochemical failure-free survival, overall survival, disease-specific survival, time to distant failure, time to local failure, cost utility analysis, quality-adjusted life years and time to androgen deprivation.

Patient Eligibility

Inclusion Criteria
- Prior Radical Prostatectomy (RP) for adenocarcinoma of the prostate.
- Histological confirmation of adenocarcinoma of the prostate with the Gleason score reported (Radical Prostatectomy specimen).
- Patients must have at least one of the following risk factors:
  - Positive margins
  - Extraprostatic extension (EPE) with or without seminal vesicle involvement (pT3a or pT3b) (Appendix I)
- Capable of starting RT within 6 months of RP (a requirement if randomised to adjuvant RT arm). Note: RT commencement within 4 months of RP is recommended, but up to 6 months is permitted.
- Most recent PSA ≤ 0.10 ng/ml following RP and prior to randomisation
- Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1 (Appendix II)
- Patient able to adhere to the specified follow-up schedule and complete the Quality of Life and anxiety/depression self-assessments
- Written informed consent obtained prior to randomisation
- Completion of all pre-treatment evaluations
- 18 years and older

Exclusion Criteria
- Previous pelvic RT
- Androgen deprivation (AD) prior to or following RP
- Evidence of nodal or distant metastases
- Co-morbidities that would interfere with the completion of treatment and/or 5 years of follow-up
- Concurrent cytotoxic medication
- Hip prosthesis

Study Schema
This is a phase III multicentre randomised controlled trial. Eligible patients are randomised to either:

Arm 1: Standard arm
- Adjuvant RT (ART) commencing within 4 months of RP is recommended, but up to 6 months is permitted.
- 64 Gy in 32 fractions to the prostate bed, or

Arm 2: Experimental arm
- Active surveillance with early salvage RT (SRT)
- 64 Gy in 32 fractions to the prostate bed
- Trigger for SRT is PSA level ≥ 0.20 ng/ml. RT should commence as soon as possible (no later than 4 months) following the first PSA measurement ≥ 0.20 ng/mL.

Stratification
Patients will be stratified by seminal vesicle invasion, Gleason Score, pre-operative PSA, margin positivity (no/yes), and radiotherapy institution.

Follow-up and evaluation
Patients will be assessed as follows. See study schedule (Appendix VII) for further detail.
- Toxicity of treatment: Clinical assessments of adverse events (urinary, bowel and sexual function).
- Disease status (PSA):
  - Surveillance phase (Arm 2): 3 monthly PSA for first 5 years and 6 monthly thereafter.
  - Following radiotherapy (both arms): 6 monthly PSA until the end of the study.
Patient completed questionnaires:
- Hospital Anxiety and Depression Score (HADS), and EORTC QoL assessment at pre-randomisation, day 1 of radiotherapy (immediate and salvage arms), at the end of RT, 6 weeks following RT, annually post randomisation.
- Sexual Health Inventory for Men (SHIM) pre-randomisation and annually post randomisation.
- Health Resource Usage Questionnaire annually until trial follow-up ceases.

Quality Assurance
A quality assurance programme will provide timely feedback to participating clinicians and improve quality of post-prostatectomy radiotherapy.

Treatment of biochemical failure following radiotherapy
A patient will be deemed as having a biochemical failure if the PSA is $\geq 0.40$ ng/ml and rising following adjuvant or salvage radiotherapy. It is recommended that the initiation of androgen deprivation should not occur before 2 years unless one or more of the following clinical criteria are met or exceeded. It is not mandatory to start treatment if a criterion is exceeded:
   a) A PSA doubling time (PSADT) of less than 12 months with a PSA level of 10.00 ng/ml or more. Investigators are free to delay intervention to higher PSA levels.
   b) A PSADT $\leq 6$ months
   c) Development of metastases

Statistical considerations
Patients will be randomised with a 1:1 allocation ratio. In order to determine non-inferiority of SRT with respect to ART with 80% power, using a 10% non-inferiority margin in the 5-year biochemical failure-free rate (assumed 74% versus 64%), 160 events are required to be observed. It is estimated that this will require a sample size of 470 patients expected to be accrued over 4.7 years and followed for a further 5 years.
2.0 RAVES Schema

**Patient Selection**
Radical prostatectomy
Histopathologically confirmed adenocarcinoma
pT3 or positive margins
Post-operative PSA ≤ 0.10 ng/mL

**Stratification**
Pre-operative PSA
Gleason score
Margin positivity
Seminal vesicle involvement
Radiotherapy institution

**RANDOMISATION**

**Arm 1 - ART**
(Immediate) Adjuvant RT
64 Gy in 32 fractions

**Arm 2 - SRT**
Surveillance with early RT following rising PSA (≥ 0.20 ng/mL)
64 Gy in 32 fractions

**Primary endpoint: biochemical failure**
Defined as ≥ 0.40 ng/mL following ART or SRT
(Also includes clinical failure or initiation of androgen deprivation therapy)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>ART</th>
<th>SRT</th>
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<tbody>
<tr>
<td>PSA – pre-randomisation</td>
<td>Pre-operative and post-operative</td>
<td>3 monthly for 5 years then 6 monthly, until rising PSA (≥ 0.20 ng/mL), then day 1 of RT</td>
</tr>
<tr>
<td>PSA – prior to RT</td>
<td>n/a</td>
<td></td>
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<tr>
<td>PSA – following RT</td>
<td>6 weeks following completion of RT, then 6 monthly from randomisation until end of trial</td>
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</tr>
<tr>
<td>QoL, HADS, Toxicity, SHIM - routinely</td>
<td>Pre-randomisation, then annually from randomisation</td>
<td></td>
</tr>
<tr>
<td>QoL, HADS, Toxicity – around RT</td>
<td>Day 1 of RT, last day of RT, and 6 weeks after RT completion</td>
<td></td>
</tr>
<tr>
<td>Follow-up visits</td>
<td>6 monthly from randomisation for 5 years; then annually</td>
<td></td>
</tr>
<tr>
<td>Health Resource Usage</td>
<td>Annually until trial follow-up ceases</td>
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3.0 Introduction

Radical Prostatectomy (RP) is the most frequently employed treatment modality for clinically localised prostate cancer. In Australasia approximately 3,300 men undergo RP per annum. While RP is an extremely effective treatment for organ confined disease, clinical staging of prostate cancer is notoriously inaccurate and frequently underestimates the extent of disease. In up to 50% of patients with clinically localised disease prior to RP, the final pathology reveals extracapsular extension, seminal vesicle involvement or positive margins.

Factors that predict for biochemical recurrence after Radical Prostatectomy

There are a number of factors that predict for biochemical recurrence following RP. These include:

- Pre-operative PSA level
- Rapid PSADT prior to RP
- Gleason score
- Lymph node involvement
- Extracapsular extension (pT3a)
- Seminal vesicle involvement (pT3b)
- Positive margins

Risk of positive margins

Following RP the positive margin rate ranges between 13% and 40%, with multiple positive margins (≥ 2) in up to 30% of patients. The prostate apex is the most common site of positive margins. On multivariate analysis, a positive surgical margin is an adverse prognostic factor with a 5 year biochemical progression rate between 20 to 40% and a relative risk of recurrence ranging between 1.5 to 1.9.

Radiotherapy following Radical Prostatectomy

In patients with positive margins and/or pT3 disease, the 5 year biochemical disease free survival is between 37 to 74% and local control rate 60 to 80%. Adjuvant radiotherapy (ART) to the prostate bed is frequently employed in the setting of pT3 disease or positive margins (node negative and postoperative PSA undetectable). The aim of ART in these high risk patients is to eradicate local microscopic disease in the prostate bed.

The indications for salvage RT (SRT) include a persistently elevated PSA following RP, a rising PSA after an initial nadir, and a palpable or biopsy proven local recurrence. Sixty to 90% of patients will have a reduction in PSA following SRT, suggesting the prostate bed, at least in part, is a site of failure in most patients. If delivered early, (PSA < 1.0 ng/mL), salvage RT is effective in controlling local disease with up to 68% of patients free from subsequent PSA relapse. However, in many retrospective series salvage RT was not “early,” and the relapse rate was greater than 80%.

In the post-prostatectomy setting the optimal timing of radiation is yet to be defined, although there is increasing evidence supporting the use of ART in patients with pT3 disease and/or positive margins. Three recent randomised controlled trials (RCTs)
have shown improved biochemical progression free survival and local control in patients treated with ART compared with observation.

In the landmark EORTC study, 1005 patients were randomised to ART (60Gy within 16 weeks of RP) or wait-and-see. Patients were eligible if they had at least one of the following risk factors: positive margins, extracapsular extension or seminal vesicle invasion. At a median follow-up of 5 years, the biochemical progression free survival was 74.0% in the ART arm and 52% in the wait-and-see arm (p <0.0001, HR 0.48).

Collette et al investigated the homogeneity of this benefit across all subgroups. The benefit of ART was substantial in all subgroups (including both those with seminal vesicle involvement and extracapsular extension). However, the authors noted that patients with negative margins may benefit to a lesser extent than the other subgroups (heterogeneity P = 0.0568).

There was no significant difference in grade 3 or 4 late toxicity (4.2% versus 2.6%, p = 0.07), but continence and potency were not formally assessed. Quality of Life (QoL) was analysed in a subgroup of 100 patients. Patients completed the EORTC QLQ-C30 and the prostate specific PR25 questionnaires. There was no difference in global QoL, although, there was a significant detriment in the genitourinary, gastrointestinal and sexual quality of life in the patients receiving adjuvant RT.

Wiegel et al also randomly assigned patients with positive margins and/or pT3 disease to ART (60Gy) or wait-and-see (ARO 96-02 AP09/95). At a median follow-up of 40 months there was a 20% improvement in biochemical control at 4 years in the ART arm (80% versus 60%, p < 0.0001, HR = 0.4). In this study 32 patients (21%) randomised to ART were told by their Urologist not to have RT and did not receive RT. An intention to treat analysis was used.

In a third trial (SWOG 8794), 473 patients with pT3 disease and/or positive margins were randomised to ART (60 to 64 Gy) or observation. At a median follow-up of 9.7 years, the 10 year biochemical disease free survival (bDFS) was 45% for the ART arm and 20% for the observation arm. In addition, patients in the ART arm had a reduced need for androgen deprivation (30% versus 40%) and a delayed time to androgen deprivation (12.5 versus 10 years). There was a trend to both a reduction in the rate of distant metastases and an improvement in overall survival, but these were not significant. At 2 years there was no difference in QoL. Key results from these studies are shown in figures 1-3 and table 1.

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**Figure 1:**
Biochemical disease free survival with adjuvant radiotherapy (2005)

Bolla et al

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**Figure 2:**
Biochemical progression-free survival

TROG 08.03 RAVES Final Protocol Version: 7 August, 2008
Amendment 2: dated 29 May 2014
Table 1: Endpoints of 2005 SWOG study. Swanson et al.36

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Obs</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA relapse</td>
<td>77%</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(&lt;0.4ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>48%</td>
<td>0.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Mets-free</td>
<td>61%</td>
<td>0.8</td>
<td>0.17</td>
</tr>
<tr>
<td>O/S</td>
<td>63%</td>
<td>0.76</td>
<td>0.11</td>
</tr>
</tbody>
</table>
A major criticism of the three randomised trials is that there was no standard management for patients on observation that developed relapse. Relapsing patients were managed with observation, SRT, or androgen deprivation. Only 35% to 55% of patients in the observation group that relapsed received SRT. In addition, the pre-RT PSA and PSA doubling time prior to SRT were not reported. Salvage RT was often delivered too late as a number of patients had documented locoregional recurrence at the time of SRT\textsuperscript{35-37}.

Although these three RCTs show that compared with observation, ART improves the 5 year biochemical control by approximately 20%, active surveillance and delaying RT until the salvage setting has a number of advantages. Between 45% and 60% of the patients in the observation arm do not develop a biochemical relapse. This suggests that approximately 50% of patients treated with ART receive unnecessary treatment and are exposed to the potential toxicities of RT. Therefore, delaying RT until the salvage setting allows a better selection of patients that are more likely to benefit from RT. Furthermore, if SRT is required, there is a longer interval between RP and RT, allowing more time for potential recovery of urinary function and potency.

Radiotherapy is most effective when the tumour burden is at its lowest. With the availability of serum PSA tests, a reliable tumour marker following RP, delaying RT until early biochemical recurrence is probably as effective as ART. However, there are a number of series in the literature reporting the inefficacy of SRT. In these series many patients received SRT for gross disease (a palpable or biopsy proven local recurrence) or a high PSA. As the SRT was delivered too late, the results were suboptimal. There is increasing evidence supporting SRT, provided the RT is delivered at early biochemical recurrence. A number of authors have reported improved biochemical control if SRT is delivered when the PSA \( \leq 1.0 \) ng/mL compared with a PSA \( > 1.0 \) ng/mL\textsuperscript{14,40,41}. Furthermore, Stephenson et al noted better results in patients with a pre-RT PSA of \( \leq 0.6 \) ng/mL, compared with those with a PSA between 0.61 and 2.0 ng/mL. Based on this evidence, it is critical SRT is delivered early, preferably when the PSA is \( \leq 0.6 \) ng/mL\textsuperscript{42}. 

*Figure 3: Biochemical progression free survival with 2005 ARO 96-02 study. T. Wiegel et al*\textsuperscript{37}.
Quality of Life

Quality of life (QoL), the assessment of the subjective perception of social, psychological and somatic well-being and function, becomes a very important outcome measure when evaluating different treatment approaches that may have similar survival outcomes. Understanding the implications of toxicities can be central to the utility analysis that follows a finding of lack of inferiority in the salvage program. There are a number of series comparing the QoL in patients following RP, external beam radiotherapy (EBRT) and brachytherapy, showing that urinary, erectile and bowel dysfunction do impact negatively on QoL. Pearce et al examined the effect of salvage RT plus 2 years of androgen suppression on QoL. The authors reported bowel and bladder function deteriorated markedly at the end of RT but recovered after, and showed only a minor persistent disturbance in the 2 year post RT period which was of minimal clinical significance. Although it appears salvage RT has minimal impact on QoL, to date a direct comparison between the QoL in men treated with adjuvant RT and those with salvage RT has not been evaluated in a randomised trial.

Co-morbidity index

A significant covariate potentially affecting survival are co-morbidities. An index of risk of death from non-cancer causes has been devised by Post et al, using a modification of the Charlson co-morbidity index (Appendix IV). Using a simple cumulative scoring of major disease categories, a highly significant impact was found in men aged less than 70 years with prostate cancer.

Summary

In the setting of extraprostatic (pT3) disease and/or positive margins following RP, there is retrospective evidence and three RCTs showing an improvement in biochemical and local control in patients treated with ART compared with observation. What has not been addressed in a RCT is whether surveillance with early SRT is as effective as ART.

4.0 Objectives and Endpoints

4.1 Primary Objective

The principal objective of the trial is to test the hypothesis that active surveillance with early salvage radiotherapy can be considered non-inferior to standard treatment with adjuvant (immediate) radiotherapy with respect to risk of biochemical failure (bF) in patients with pT3 disease and/or positive margins following RP.

4.2 Secondary Objectives

Secondary objectives will include a comparison of the two treatment arms with respect to each of the secondary endpoints outlined in section 4.3.2.

In addition, a prognostic factors analysis will be performed for each time-to-event endpoint (sections 4.3.1 and 4.3.2).
4.3 Endpoints

4.3.1 Primary Endpoint

- Biochemical failure (bF): PSA ≥ 0.40 ng/ml and rising following RT

4.3.2 Secondary endpoints

- Quality of life (QoL)
- Adverse events
- Anxiety/depression
- Biochemical failure-free survival
- Overall survival
- Disease-specific survival
- Time to distant failure
- Time to local failure
- Time to the initiation of androgen deprivation
- Quality-adjusted life years
- Cost-utility

5.0 Trial Design

5.1 Trial Description
The research design is a two-arm, randomised, phase III, multicentre, non-inferiority trial.

5.2 Study Arms
Eligible patients will be randomised to either:

- **Arm 1** (standard arm): Adjuvant RT commenced within 6 months of RP. Note: RT commencement within 4 months is recommended, but up to 6 months is permitted.

- **Arm 2** (experimental arm): Active surveillance with early salvage RT following a rising PSA (PSA level ≥ 0.20 ng/mL prior to radiotherapy).

For both arms, RT consists of 64 Gy in 32 fractions delivered over 6.5 weeks to the prostate bed.

5.2.1 Stratification
Randomised patients will be stratified (using the minimisation technique) according to the following criteria:

- Preoperative PSA (as a continuous variable)
- Gleason Score (from RP specimen; as a continuous variable)
- Surgical margins (positive/negative)
- Seminal vesicle involvement (pT3b) (Yes/No)
- Radiotherapy institution
6.0 Patient Selection

6.1 Inclusion Criteria
All of the following must apply:

- Prior Radical Prostatectomy (RP) for adenocarcinoma of the prostate.
- Histological confirmation of adenocarcinoma of the prostate with the Gleason score reported (Radical Prostatectomy specimen).
- Patients must have at least one of the following risk factors:
  - Positive margins
  - Extraprostatic extension (EPE) with or without seminal vesicle involvement (pT3a or pT3b) (Appendix I)
- Capable of starting RT within 6 months of RP (a requirement if randomised to adjuvant RT arm). Note: RT commencement within 4 months is recommended, but up to 6 months is permitted.
- Most recent PSA ≤ 0.10 ng/ml following RP and prior to randomisation
- Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1 (Appendix II)
- Patient able to adhere to the specified follow-up schedule and complete the Quality of Life and anxiety/depression self-assessments
- Written informed consent obtained prior to randomisation
- Completion of all pre-treatment evaluations
- 18 years or older

6.2 Exclusion Criteria
None of the following must apply:

- Previous pelvic RT
- Androgen deprivation (AD) prior to or following RP
- Evidence of nodal or distant metastases
- Co-morbidities that would interfere with the completion of treatment and/or 5 years of follow-up
- Concurrent cytotoxic medication
- Hip prosthesis

6.3 Patient Withdrawal
A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Deterioration whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Withdrawal of consent by patient
- Any alterations in the patient’s condition which justifies the discontinuation of treatment in the investigator’s opinion

If the patient discontinues the study treatment due to an adverse event potentially related to study treatment, they must be followed weekly for 4 weeks or until resolution or stabilisation of the event, whichever occurs first. Patients who discontinue study treatment but have neither died nor withdrawn consent should be encouraged to complete the scheduled evaluations and continue to be followed up according to the protocol.
7.0 Patient Consent and Randomisation

7.1 Screening and Randomisation
Patients will be randomised via an internet-based randomisation system. The Trial Centre will provide each participating site with user accounts to access the web-based system. Sites will be notified of treatment arm allocation at the time of randomisation.

To randomise a patient, sites must complete electronic case report forms (CRFs) to document eligibility and stratification factors. Prior to patient randomisation, the investigator should ensure that all of the following requirements are met:

- Informed consent has been obtained prior to performing any study specific procedures.
- The patient meets all inclusion criteria and none of the exclusion criteria must apply.
- All pre-randomisation assessments and investigations have been performed.
- The eligibility checklist has been completed, signed and dated.

Patients must not start treatment before the site has received confirmation of randomisation results. Patients will not be randomised if treatment has started.

7.2 Consent for optional biological sub-studies
Patients will be approached about the optional biological sub-studies six months after randomisation. If patients wish to participate, they must sign a separate consent form for the sub-studies. If for any reason consent to the sub-studies is delayed, patients may choose to join the sub-studies at any point up until 6 months after recruitment has closed.

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 6 months of RP. Note: RT commencement within 4 months of RP is recommended, but up to 6 months is permitted.

Arm 2: Experimental arm
Active surveillance with early salvage RT following a rising PSA (PSA level ≥ 0.20 ng/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 treatment\(^6\). 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 [http://www.trog.com.au/TROG-0803-trial-documents](http://www.trog.com.au/TROG-0803-trial-documents).
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.

8.5.1 Clinical Target Volume (adapted from FROGG consensus guidelines\(^45\))

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 (eg 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. In some clinical scenarios, it may be appropriate to manually alter the posterior margin, if sound clinical justification is provided and daily imaging is done. For advice or additional information, contact the RAVES QA team via the web site: [http://www.trog.com.au/TROG-0803-trial-documents](http://www.trog.com.au/TROG-0803-trial-documents).

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 – 65.3 Gy). 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:

- 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 ≥ 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 [http://www.trog.com.au/TROG-0803-trial-documents](http://www.trog.com.au/TROG-0803-trial-documents). 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. The mean and median doses will be within -1% and +2% of 64 Gy (63.4 – 65.3 Gy).

3. 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.

4. For treatment plans created with an inverse IMRT technique (RAVES IMRT credentialled sites only):
   a. The maximum dose should be contained within the CTV, and must be contained within the volume bounded by the PTV.
   b. The minimum dose (defined as the D98) of the CTV shall be 64 Gy
   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.

5. Centres should provide the below data for all participants for QA review. This data should be DE-IDENTIFIED (and submitted for review via the Central Quality Management System (CQMS) as zipped files). Information on CQMS user accounts and training are available on the TROG website ([www.trog.com.au](http://www.trog.com.au)).

The radiotherapy treatment plan export will be automatically de-identified at the point of upload to CQMS. The participant name and ID will be replaced with the trial identifier and the participant reference, eg 13.02 ABC123.

*Digital Export of Radiotherapy Treatment Plan*
An electronic export of the radiotherapy treatment planning data file from the treatment planning system is required. The preferred file format is DICOM-RT; however RTOG can be accepted if no other format is available. The use of RTOG is discouraged as this format is not widely accepted by plan review software.

This electronic export must be in absolute dose (Gy) and include the:

- **CT dataset** or other imaging dataset used for plan calculation, ensuring all files are included.
- **Planning files.** Please ensure the plan is calculated to the correct specifications and approved. There will be one plan file, generally prefixed RP.
- **Structure files,** Please ensure all structures including CTV/PTVs are exported and named according to protocol specifications. There will only be one file, generally prefixed RS. The exported plan should contain only those structures required for the QA review. All other structures (e.g. those created for the purpose of IMRT optimisation) shall be removed prior to export.
- **Dose files.** Please ensure the dose matrix is inclusive of all structures. There will be one dose, generally prefixed RD.
- **DVH data.** The sampling resolution for DVH data shall be 0.1 cm for contoured structures, 0.2 cm for all other tissue. The bin width shall be 0.010 Gy. Data shall be presented in absolute dose.

All these exported files need to be uploaded as a single zipped file into CQMS.

**Screen Captures of ICRU reference point and isodose distribution**

In addition to the electronic data file, a screen capture from the planning system (JPEG image) is required. It is essential the screen capture follows the format below; as it will be used to verify the accuracy of the electronic plan imported into the plan review software.

**Format**

- The screen capture should be taken at the intersection of the ICRU reference point, and demonstrate the absolute dose (Gy) at this point.
- The image should display the location of ICRU reference point (x, y, z co-ordinates) in three (3) viewing planes (sagittal, transverse and coronal).
- Relevant isodose lines should be displayed in absolute dose (Gy), colour and clearly labelled. As a minimum the max, 100%, 98%, 95%, 90%, 70%, 50%, 20%, 2% isodose lines should be included.
- CT imaging needs to be clearly visible.
Screen Capture (JPEG image) of the DVH, clearly showing the 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 plan review software and must be in colour.

7. 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: 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.

8. 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 15mm inferior to the inferior border of the CTV. The rectal contours should extend at least 15mm 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 <5cm.

**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:
- 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: http://www.trog.com.au/TROG-0803-trial-documents

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 http://www.trog.com.au/TROG-0803-trial-documents. 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 including VMAT 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: http://www.trog.com.au/TROG-0803-trial-documents.
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 discuss options 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.


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 http://www.trog.com.au/TROG-0803-trial-documents, 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. This report shall include details of absolute dose verification and the relative dose fluence check. The in-house QA protocol forms part of the
credentialing requirements, and therefore the RAVES QA committee must be alerted to any changes to the in-house QA processes prior to submitting patient reports. Refer to http://www.trog.com.au/TROG-0803-trial-documents for contact details.

8.12.5 Data required following RT completion

Form QA3 Checklist RT Treatment Data, available from http://www.trog.com.au/TROG-0803-trial-documents 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).

9.0 Treatment of relapse after radiotherapy

9.1 Indications for androgen deprivation treatment

The initiation of androgen deprivation (AD) is independent of the nature of the failure (biochemical, local or distant). It is recommended that PSA doubling time (PSADT) be based on at least 3 consecutive measurements, at least 2 months apart between each pair. It is also recommended that the initiation of AD should not occur before 2 years from the diagnosis of biochemical failure unless one or more of the following minimum clinical criteria are met. However, it is not mandatory to start treatment if a criterion is met:

a) A PSA doubling time (PSADT) of less than 12 months with a PSA of 10.00 ng/ml or more. Investigators are free to delay intervention to higher PSA levels.

b) A PSADT ≤ 6 months

c) Development of metastases

9.2 Androgen Deprivation Treatment

AD treatment may include either a luteinising hormone releasing hormone (LHRH) agonist or bilateral orchidectomy, with or without antiandrogen treatment, or monotherapy with an antiandrogen.
9.3 Continuous or Intermittent Androgen Deprivation
Androgen deprivation (AD) treatment may be continuous or intermittent. If intermittent, AD is recommended to be for a 9 month period, and to employ monotherapy or combined therapy at the clinician’s discretion. If the PSA is < 4.00 ng/ml after 9 months of AD, the patient may stop AD and be monitored with 3 monthly PSAs. When the PSA is > 5 ng/ml, or at a level greater than that at initiation of AD (whichever is lower), the patient is to be recommenced on AD.

10.0 Patient Assessment
Refer to Appendix VII for the table of assessment and follow-up visits.

10.1 Pre-randomisation assessment

10.1.1 Disease Status, Medical History and Co-Morbidities

- Medical History and Adverse events assessed using CTCAE v 3.0.
- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix II)
- Co-morbidity Index (Appendix III), including the number of prescription medications, number of co-morbid conditions, and smoking history

10.1.2 Imaging
The most recent PSA at entry into the study is ≤ 0.10 ng/ml and therefore no pre-randomisation imaging is mandated. Bone scan, CT scan and MRI scan are performed only if clinically indicated and at the discretion of the investigator.

10.1.3 Laboratory Studies

a) Histopathological confirmation of adenocarcinoma of the prostate with at least one of the following factors: positive margins, extraprostatic extension (pT3) with (pT3b) or without (pT3a) seminal vesicle involvement.

b) Pre-operative PSA level.

c) Confirmation of the most recent post-operative serum total PSA ≤ 0.10 ng/ml following RP and prior to randomisation. An acceptable serum total PSA assay is required with a lower limit of detection (LLD) ≤ 0.10 ng/ml.

10.1.4 Patient-completed questionnaires

a) Quality of Life: Pre-randomisation Quality of Life (QoL) questionnaires: EORTC global (QLQ-C30) and EORTC QLQ-PR25 (Appendix IV)

b) Anxiety: Pre-randomisation anxiety and depression: Hospital Anxiety and Depression Scale (HADS)\textsuperscript{52} (Appendix V).

c) Adverse Events: Sexual Health Inventory for Men (SHIM)\textsuperscript{53}, (Appendix XI)
10.2 Assessment during treatment phase
For both ART and SRT, clinical assessments, quality of life, anxiety/depression and adverse event assessments (excluding the SHIM) are required on day 1 of RT, the last day of RT and 6 weeks following completion of RT (see Appendix VII and section 10.4 for details).

10.3 Follow-up assessments

10.3.1 Clinical Assessment
For both arms, follow-up will be 6 monthly from randomisation for the first 5 years, then annually until the end of the trial. Clinical follow-up will be conducted as per the study schedule (Appendix VII), but can be more frequent if clinically indicated. For patients randomised to Arm 2 (SRT), it is recommended that patients be followed 6 monthly from randomisation for 2 years following salvage RT. However, data will be reported only for those time points specified in the trial follow-up schedule. Rectal examination is recommended if a rising PSA is detected.

10.3.2 Biochemical assessment

Arm 1 (ART): Following adjuvant radiotherapy, serum PSA is to be measured 6 weeks after RT, and then 6 monthly relative to randomisation until the end of the trial.

Arm 2 (SRT): In the surveillance phase, serum PSA evaluations are to be performed every 3 months from randomisation during the first 5 years, then 6 monthly thereafter until the occurrence of a rising PSA (≥ 0.20 ng/mL prior to radiotherapy) or the end of the trial. For patients proceeding to SRT, serum PSA is measured on day 1 of RT. If a PSA result that triggers SRT falls between two scheduled assessments, the relevant PSA result must be reported as an unscheduled PSA assessment.

Arm 2 (SRT): Following salvage radiotherapy, serum PSA is measured 6 weeks after RT, and then 6 monthly relative to randomisation until the end of the trial.

If the first PSA level following SRT is ≥ 0.40 ng/mL, then:

(a) bF is diagnosed if the PSA is rising when compared to the PSA from day 1 of RT.

(b) If the PSA is falling relative to the level measured on day 1 of RT, the patient is followed up as usual (this does not constitute bF).

Thereafter, PSA will continue to be measured 6 monthly (relative to randomisation) until the end of the trial. If a patient’s 6 monthly PSA and clinic visit are within 28 days of the 6 week post-RT assessment, then the 6 monthly PSA and 6 month clinic visit can be omitted.

Both Arms: If biochemical failure occurs (PSA level ≥ 0.40 ng/mL following radiotherapy), a confirmatory PSA may be performed if clinically indicated. The date of diagnosis of the bF will be that of the first PSA ≥ 0.40 ng/mL. Follow-up PSA evaluations can be performed as clinically indicated for patients on either arm, but only PSA results from the time points specified in the study schedule (Appendix VII)
will be reported. Any other laboratory investigations are to be conducted as clinically indicated. If a PSA result that meets the criteria for bF falls between two scheduled assessments, the relevant PSA result must be reported as an unscheduled PSA assessment.

10.3.3 Imaging

When clinically indicated, appropriate imaging will be arranged at the discretion of the investigator.

10.4 Quality of life, anxiety/depression and adverse event assessments
All questionnaires are to be completed prior to the patient’s receiving the serum PSA result.

10.4.1 Quality of Life

QoL patient self-assessment questionnaires are assessed prior to randomisation, day 1 of radiotherapy (ART and SRT), at the end of RT, and 6 weeks following RT. QoL assessments are then completed annually from randomisation.

10.4.2 Anxiety and Depression

Hospital Anxiety and Depression Scale (HADS) data will be collected at the same time points as QoL data (Section 10.4.1), with the aim of comparing the prevalence of anxiety and depression in both treatment arms.

10.4.3 Adverse Events

Clinician assessed adverse events are assessed prior to randomisation, day 1 of radiotherapy (ART and SRT), at the end of RT, and 6 weeks following RT, and then annually until the end of the trial. Patient assessed adverse events (erectile function) are assess prior to randomisation and then annually from randomisation.

10.4.4 Purpose of Quality of life, anxiety/depression and adverse event assessments

The purposes of these assessments are:

1. Prior to randomisation: To provide a cross-sectional description of early postoperative QoL, anxiety/depression, and adverse events.
2. Day 1 of RT: To record QoL anxiety/depression, and clinician assessed adverse events as a reference level for the effect of RT.
3. End of RT: To record impact of peak RT-related adverse events
4. Six weeks following RT: To record QoL anxiety/depression, and clinician assessed adverse events if the acute effects of RT are settling.
5. Annual assessments:
a. Year 1: To assess recovery from surgery (and recovery from RT, if applicable)

b. All years: To determine chronic and late developing toxicities and compare the two RT approaches with respect to QoL, anxiety/depression and adverse events. To additionally characterise toxicities arising from salvage radiotherapy. To identify if the interval from RP to RT influences the pattern and intensity of toxicities.

10.4.5 Health Economics Analysis

A within trial and an extrapolated health economic analysis will be conducted to evaluate differences in costs and Quality Adjusted Life Years (QALYs) between the two arms. Economic data collected during the trial will include resource use data on the use of radiotherapy and experience of inpatient admissions. Patients will self report hospitalisations annually for the duration of the trial, using the Health Resource Usage Questionnaire (Appendix 12).

11.0 Pathology Review

It is well established there is significant variability in the reporting of prostate pathology specimens. The purpose of a central pathology review is to standardise the evaluation of the Gleason grade and score, positive margins, extraprostatic extent and seminal vesicle involvement. This also provides the opportunity to evaluate inter-observer variation between the local and central pathologists.

Central pathology review will be conducted by Dr Warick Delprado MBBS FRCPA FIAC and Dr Ronnie Cohen MBBS FRCPA.

For all patients entered into RAVES in Western Australia, all slides from the Prostatectomy specimen will be sent from the patient’s local pathology laboratory with the local pathology report to the following address:

Dr Ronnie Cohen  
PO Box 1337  
West Leederville  
Western Australia 6901

For patients from the remainder of Australia and New Zealand, slides will be sent from the patient’s local pathology laboratory with the local pathology report to the following address:

Dr Warick Delprado  
Director – Histopathology,  
Douglass Hanly Moir Pathology,  
14 Giffnock Avenue  
Macquarie Park NSW 2113  
Australia.
Slides must be de-identified and labelled with the patient initials and trial registration number. Once reviewed, the slides will be returned to the patient’s local pathology laboratory with a copy of the review performed. Dr Cohen or Dr Delprado will then send the data and report to the Trial Coordinating Centre. The report template is included as Appendix X.

For the purposes of the Pathology Review the following definitions will be used:

**Seminal Vesicle Invasion (SVI)**
Tumour infiltrating the muscular coat of the seminal vesicle. Cases with invasion of the “intraprostatic portion” of the seminal vesicle should be regarded as invasion of the ejaculatory duct.

**Extra-prostatic Extension**
Tumour that has extended out of the prostate into periprostatic soft tissue (because the prostate lacks a discrete capsule, the term “extraprostatic extension” (EPE) will be used instead of “extracapsular extension” to describe tumour that has extended out of the prostate into periprostatic soft tissue).

- **Focal extraprostatic extension**: 1 field identified with EPE replacing a total volume <1 High powered field (HPF) (0.5mm) or 2 fields with EPE totalling <1HPF (0.5mm)
- **Established**: 1 field identified with EPE replacing >1 HPF (0.5mm) or 2 or more fields with EPE totalling >1HPF (0.5mm).

The location of EPE will be recorded.

**Positive Margins**
Tumour extending to the inked surface of the prostatectomy specimen which the surgeon has cut across. At many sites the radical prostatectomy specimen is surrounded by < 1 mm of periprostatic soft tissue. As tumour is not actually cut across at the ink, close margins (< 0.1 mm) should not be designated as positive margins, as they are not associated with tumour that would be left in the patient or with an increased risk of postoperative progression.

- **Focal Involved margin** will be defined as involvement of the surgical resection margin in one or two foci, each less than or equal to 1 mm.
- **Extensive Involved margin** will be defined as involvement of the surgical resection margin by greater than 1 mm in one or more regions.

The location and Gleason score at margin will be recorded.

**Gleason Score**
The sum of the predominant Gleason grade (primary pattern) and second commonest Gleason grade (secondary pattern) forms the Gleason Score (ISUP 2005 Modification). This will be based at the index tumour site. The tertiary pattern should be recorded in a comment if higher than the primary and secondary patterns. The percent grade 4/5 will be recorded.
12.0 Biological Sub-studies

12.1 RAVES Genetic Studies
Rapid advances in genotyping technology, concomitant with a more detailed understanding of human sequence variation, have recently made high-density genome-wide association (GWA) studies in adequately-powered sample sets a real prospect and technically feasible for many conditions.\textsuperscript{54,55}

These developments enable translational genetic research to be an important component of this study. There are two optional biological sub-studies in which patients who have consented to the trial may participate:

1. RAVES Genetic Study: Saliva or blood collection for DNA extraction
2. RAVES Tissue Banking Study: Tissue banking of tumour blocks

Patients will be approached at their 6 month post-randomisation follow-up visit about consenting to these optional biological sub-studies. If patients are unable to consent at 6 months post-randomisation, they can join the biological sub-studies at any time up until 6 months after recruitment closes.

12.2. RAVES Genetic Study Aims

The power of modern genetic epidemiology arises from not assuming a priori mechanisms and the ability to define novel pathogenic causes. Recent GWA studies have provided proof of principle that dense screening across the human genome in well-designed studies can discover novel pathogenic mechanisms.\textsuperscript{56,57} For instance, the Wellcome Trust Case Control Consortium has demonstrated that GWA studies represent a powerful approach to the identification of 27 new genes causally involved across 8 different common human diseases.\textsuperscript{58} Results from this Consortium detected association between common diseases and genetic variants outside genetic regions previously thought to be involved in disease progression. In addition Zheng et al demonstrated that genetic variants in five chromosomal regions plus a family history of prostate cancer have a cumulative association with prostate cancer diagnosis.\textsuperscript{59}

It remains to be seen if a similar cumulative effect is evident in disease progression. There is, however, consensus that even the current large GWA studies are underpowered to detect small effects attributable to individual genetic variants.\textsuperscript{50} The RAVES Genetic Study will provide linked clinical and genetic data that can be combined with similar international studies for final genetic analysis.

12.2.1 RAVES Genetic Study Logistics

For the RAVES Genetic Study, DNA will be extracted from saliva or blood samples and stored for future analyses to improve understanding of how biological processes are altered in prostate cancer. Molecular, protein and genetic factors will be evaluated. This research aims to discover how to predict which patients are more likely to relapse and require radiotherapy, and also which patients are more likely to respond to radiotherapy.
Sites will be provided with collection materials and instructions for collecting saliva specimens. In addition to providing the saliva sample, patients will complete one questionnaire (Appendix IX). Details regarding saliva or blood collection, sample collection protocols, processing, storage and submission are available from the Centre for Genetic Epidemiology and Biostatistics (CGEB) at the University of Western Australia. Contact details are below:

Tegan McNab  
Manager Western Australian DNA Bank  
Tel: (08) 6488 6738  
Fax: (08) 6488 6750  
Email: tegan.mcnab@uwa.edu.au  
www.wadb.org.au

12.3. RAVES Tissue Banking Study Aims
The aim of this sub-study is to develop a comprehensive annotated tissue bioresource to enable exemplary future molecular research into prostate cancer. By matching tissue to a prospective clinical outcomes dataset, molecular research capabilities will be optimised.

12.3.1 RAVES Tissue Banking Study Logistics
The tissue banking sub-study will not require any additional testing or specimen collection for the patient. All tissue will be gathered from formalin-fixed paraffin embedded (FFPE) blocks previously used for histopathological diagnosis of prostate cancer. During Central Pathology Review (Section 11) index cancer blocks will be identified. The local site will request the index cancer tissue blocks from the relevant pathology laboratory for each patient who consents to the sub-study. The blocks plus a de-identified copy of the pathology report will be sent to the Australian Prostate Cancer BioResource (APCBR) national manager. Standard operating procedures of the APCBR will be used to determine the whether each potential sample is suitable for tissue banking. If unsuitable, the tissue block will be returned to the local site. If the tissue is banked, it will be assigned a unique sample identifier, which will be relayed to the RAVES study coordinator to enable future linkage with clinical outcome information.

12.3.2. Australian Prostate Cancer BioResource
The Australian Prostate Cancer BioResource (APCBR) is a multi-state “virtual tissue bank” comprising four physically separate tissue repositories, each with its own database for collection of tissue-associated clinical and pathological data. Each database is linked by a web-based central database, containing minimum clinical and pathological datasets downloaded by the individual repositories and which can be queried to assemble specific research cohorts. A BioResource Management Committee to oversee operation is drawn from key stakeholders and experts in tissue bank collections and clinical databases across Australia.
12.3.3. Tissue management policy

All tissues will be subject to the APCBR’s standard Materials Transfer Agreements. Tissue gathered in connection with the RAVES study will be quarantined within the APCBR and cannot be accessed without meeting the following criteria:

a. RAVES trial management committee approval of the suitability of the proposed tissue research.

b. A Human Research Ethics Committee approved study protocol.

c. APCBR Tissue Management Committee approval.

If permission is granted to access tissue, it can be released along with de-identified (coded) clinical data. For all applications, cost recovery fees may be applicable.

12.3.4 Potential tissue usage

It is likely that the tissue extracted from FFPE specimens will be predominately limited to tissue microarray (TMA) production and DNA extraction, and in some cases, RNA extraction. Future requests to use the tissue are, therefore, likely to be for studies including but not limited to biomarker validation, DNA sequencing/mutation analysis, microarray analysis and DNA methylation detection.

13.0 Criteria for Assessing Treatment Outcomes

All time-to-event outcomes are measured from randomisation unless otherwise stated.

13.1 Biochemical failure (bF)

For both arms, biochemical failure (bF) will be diagnosed on the first occasion following radiotherapy that the serum PSA is $\geq 0.40$ ng/mL and rising (from the previous value). A confirmatory PSA test may be performed if clinically indicated. The date of bF will be the date of the first PSA level $> 0.40$ ng/mL. For Arm 2 (SRT), a PSA result that is $> 0.40$ ng/mL but less than the PSA result from day 1 of RT does not constitute biochemical failure. See section 13.2 for additional information on time to biochemical failure.

For patients randomised to ART who, for one reason or another, do not receive ART, bF will be diagnosed if the serum PSA is $\geq 0.40$ ng/mL on an occasion beyond one year from randomisation. The date of bF will be the date of the first PSA level ($\geq 0.40$ ng/mL beyond one year from randomisation).

For patients randomised to SRT who, for one reason or another, do not receive SRT following a rising PSA level ($\geq 0.20$ ng/mL), bF will be diagnosed if the serum PSA is $\geq 0.40$ ng/mL on any occasion beyond one year from the date the PSA was $\geq 0.20$ ng/mL. The date of bF will be the date of the first PSA level ($\geq 0.40$ ng/mL beyond one year from the date of PSA $\geq 0.20$ ng/mL).

For the purposes of this trial, the definition of ‘biochemical failure’ will also include either or both of the following:

(i) Clinically diagnosed local, regional or distant failure;

(ii) Commencement of Androgen Deprivation (AD) for failure.
The date of such failure will be the date of diagnosis of the clinical failure or commencement of AD.

13.2 Time to biochemical failure (TTbF)
Time to biochemical failure will be measured from the date of randomisation to the date of bF. It will be censored by death (without previous bF), the closeout date and loss to follow-up. Analyses of TTbF, using logrank, Cox regression and Kaplan-Meier methods, will address the primary objective of assessing the risk of bF between the two arms.

13.3 Biochemical failure-free survival (bFFS)
Biochemical failure-free survival will be measured from the date of randomisation to the date of bF or death from any cause. bFFS will be censored by the closeout date and loss to follow-up.

13.4 Quality of Life (QoL) and Anxiety/Depression
QoL and anxiety/depression will be evaluated pre-randomisation and at regular intervals, and at the start, end, and following RT. QoL and anxiety/depression will be analysed using the difference in scores from pre-randomisation. Average scores, adjusted for pre-randomisation levels, will be plotted against time. If the data permit, a repeated measures analysis of QoL and anxiety/depression will be performed as a global comparison of the arms, but this will be supplemented by comparisons of arms at fixed time points, especially since the pattern of QoL over time is likely to be quite different between the two arms, and by comparisons around RT.

13.5 Adverse events

13.5.1. NCI Common Terminology Criteria for Adverse Effects (CTCAE) v 3.0
NCI Common Terminology Criteria for Adverse Effects (CTCAE) v 3.0 is the tool used by clinicians to assess toxicities (Appendix VI). Time to late toxicity (of a given maximum grade and type) will be used to summarise and compare late toxicities. Time to late toxicity is defined as the time from treatment start to the given late toxicity and is censored by death, loss to follow-up and the closeout date for the trial. The frequency and grade of adverse events (genitourinary, gastrointestinal and sexual) will be assessed and compared between the two arms. (Appendix XI)

13.5.2. The Sexual Health Inventory for Men (SHIM)
The Sexual Health Inventory for Men (SHIM) is a 5-item patient questionnaire developed to diagnose the presence and severity of erectile dysfunction (Appendix XI). This questionnaire is psychometrically sound, and has been linguistically validated in 8 languages. It is readily self-administered in research or clinical settings. The SHIM demonstrates sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction. Sexual function scores will be compared between the two arms.

13.6 Overall survival
Overall survival will be measured from the date of randomisation to the date of death from any cause.
13.7 Disease-specific survival
Disease-specific survival is defined as the time from the date of randomisation to the date of death due to prostate cancer. Death 'due to prostate cancer' will include any death following hormone-resistant prostate cancer and any treatment-related death. Disease-specific survival will be censored by death due to other or unknown causes, loss to follow-up, and the closeout date of the trial.

13.8 Time to distant failure
Time to distant failure is defined as the time from the date of randomisation to the date of documented regional, nodal or distant failure. Time to distant failure will be censored by death without prior distant failure, loss to follow-up and the closeout date of the trial. In particular, time to distant failure will not be censored by local failure or bF without evidence of distant failure.

a) Nodal failure
The diagnosis of nodal failure must be confirmed by CT scan or MRI scan of the abdomen and pelvis.

The date of nodal failure will be the date of the CT scan or MRI scan confirming the first nodal failure.

b) Bone Metastasis
The diagnosis of bone metastasis must be confirmed on imaging: plain X-ray, bone scan, CT scan or MRI scan.

The date of bone metastasis will be the date of the first radiological investigation that documented bone metastasis.

13.9 Time to local failure
Time to local failure is defined as the time from the date of randomisation to the date of documented palpable or biopsy-proven local failure.

13.10 Time to the initiation of Androgen Deprivation (AD)
Time to the initiation of androgen deprivation will be measured from the date of randomisation to the date of initiation of androgen deprivation.

13.11 Quality Adjusted Life Years and Cost-utility
Patients will self-report hospital admissions using the Health Resource Usage Questionnaire. To estimate QALY gains, utility weights will be estimated using a mapping algorithm that has been estimated for the EORTC QLQ-C30, which is being used to assess quality of life in all patients 12 monthly from randomisation. To estimate the longer term costs and benefits, a health economic decision model will be built and populated. The model will use trial data to describe the pathway of patients between prostate cancer-specific health states (e.g. disease-free, local recurrence and distant recurrence). External data will be sought to predict subsequent pathways between these states (and death) so that costs and QALYs gained over the lifetime of the trial population can be estimated.
14.0 Data Management and Documentation

14.1 Case Report Forms (CRFs)
The study site will retain a copy of the completed CRFs, with the original CRFs sent as soon as practicable to:

    RAVES Trial Coordinating Centre
    Auckland Regional Cancer and Blood Service
    Private Bag 92024
    Auckland 1142
    New Zealand

All corrections to CRFs must be made so that the original entry remains legible. Corrections should be crossed out with a single line using a black pen, and must be initialled and dated.

Data clarification queries will be sent to participating institutions as necessary. Sites must return their response to data clarification queries to the Trial Coordinating Centre, with a copy retained at site, and amend their copy of the CRF as necessary.

14.2 Recording of data and retention of documents
The investigator or suitably trained staff at each site must complete the CRFs, transmit the data as instructed, and retain a copy of the CRFs for each patient at their site in a secure place. Data on subjects collected on CRFs will be documented in an anonymous fashion, and the subject will only be identified by the subject number, and by his initials. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, TROG and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information reported on the CRFs, including laboratory data, etc. Sites must keep a copy of the signed informed consent form and completed CRFs for each patient. All information on CRFs must be traceable to these source documents kept in the patient's file.

Essential documents, as listed below, must be retained by the investigator to comply with national and international regulations. Essential documents include:

1. Human Research Ethics Committee (HREC) approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies
4. Patients' informed consent forms (with study number and title of trial)
5. Any other pertinent study documents
14.3 Database management and quality control
Data from the CRFs are to be checked by Trial Centre staff and entered into the study database. Possible errors or omissions will be alerted to the investigational site for resolution.

15.0 Adverse Event Scoring and Reporting

15.1 Definitions

15.1.1 Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product (or any other protocol specified intervention including Radiation Therapy, surgery or use of a device) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (or associated with the use of any other protocol specified intervention including radiation therapy, surgery or use of a device).

AEs include: ‘Adverse Drug Reactions’, i.e.

A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected.

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase ‘responses to a medicinal product’ means that a causal relationship between a medicinal product and an adverse event is at least reasonably possible, i.e. the relationship cannot be ruled out.

Regarding marketed medical products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

15.1.2 Unexpected Adverse Event (UAE)

An Unexpected Adverse Event is an AE for which the nature or severity of the event is not consistent with the information in the relevant source documents (or with the applicable side effect risk profile for radiation therapy, surgery or use of a device).

UAEs include: ‘Unexpected Adverse Drug Reactions’, i.e.

The nature and severity of the ADR is not consistent with the information in the Investigators Brochure for an unapproved investigational product, or the product information/package insert/summary of product characteristics for an approved product.
15.1.3 Serious Adverse Event (SAE)

Adverse events and adverse drug reactions are considered ‘serious’ if they threaten life or function.

SAEs include: ‘Serious Adverse Drug Reactions’, i.e.

During clinical investigations, adverse events may occur, which if suspected to be medicinal product related (‘adverse drug reactions’) might be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, monitoring, consent). This is particularly true for reactions, which in their most severe form threaten life or function.

Due to the significant information they provide, Serious Adverse Events (including Serious Adverse Drug Reactions) require expedited reporting. SAEs are defined as any adverse event or adverse drug reaction which:

- Results in death (i.e. fatal/grade 5 CTC AE)
- Is life-threatening (i.e. grade 4 CTC AE)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation*
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect

Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was immediately at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a serious adverse event if the only reason for the hospitalisation or prolongation was:

- administration of chemotherapy
- administration of trial procedures
- placement of a permanent intravenous catheter
- hospice placement for terminal care
- pre-trial scheduled elective surgery
- out-patient hospitalisation for procedures such as:
  - Elective day surgery
  - Convenience purposes (eg. transportation difficulties)
  - Planned admission as part of supportive care for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding (ie. did not occur following urgent admission as a result of weight loss or other patient medical events)

15.1.4 Attribution of Cause of an Adverse Event

Attribution of cause requires at least a reasonable possibility of a causal relationship between the event and the use of a pharmaceutical product (or any other protocol specified intervention including radiation therapy, surgery or use of a device), i.e. the relationship cannot be ruled out. One or more of the following categories should be attributed as the cause of an event:
- Pharmaceutical product (an SAE which is \textit{drug related} is considered a Serious Adverse Drug Reaction)
- Radiation Therapy
- Medical Device
- Surgery
- Unrelated to trial treatment (i.e. progressive disease, concurrent medication, concurrent disorder or other

All protocol specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Unrelated
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

15.2 Reporting

15.2.1 Adverse Event Reporting

15.2.1.1 Trial Sites/Investigators

All relevant adverse events (including those that are \textit{non-serious or expected}) which occur whilst the participant is enrolled on the trial must be reported in the patients’ medical records and recorded on the relevant CRF. The Common Terminology Criteria for Adverse Events (CTCAE version 3.0 – see appendices) must be used to grade the severity of an event.

15.2.1.2 Trial Coordinating Centre (TCC)

Data from the CRF will be entered onto the trial database at the Trial Coordinating Centre and accessed when required by TROG. Regular analyses of cumulative AE data should occur at the TCC. If significant safety issues are identified from analyses the TCC must inform the TSC, other investigators and responsible HRECs.

15.2.2 Serious Adverse Event Reporting

15.2.2.1 Trial Sites/Investigators

Serious Adverse Events must be reported to the Trial Coordinating Centre (TCC) and the TROG Central Operations Office (TCOO) whether or not considered related to the treatment under investigation. For Arm A (ART), all SAEs that occur from the time a participant starts radiation therapy to within 30 days of the final protocol specified treatment are required to be reported. For Arm B (SRT), all SAEs that occur from commencement of radiotherapy to...
within 30 days of the final protocol-specified treatment are required to be reported.

The Principal Investigator (PI) must:

- Determine whether an AE is ‘Serious’ (refer to criteria at 10.1.3)
- For SAEs, the PI must then ascertain the suspected cause
- The attribution to the SAE must be recorded in the patients’ medical records and reported on the SAE form.
- The PI must then determine whether the SAE (or Serious Adverse Drug Reaction) is expected or unexpected.
- Both expected and unexpected Serious Adverse Events and Serious Adverse Drug Reactions must be recorded in the patients’ medical records and reported to the TCC and TCOO

No pharmaceutical products that meet CTN criteria are used in this trial and therefore TGA reporting is not required.

**SAEs must be reported by completing the TROG SAE form and FAXING it to the following:**

<table>
<thead>
<tr>
<th>Fax To:</th>
<th>Fax Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Coordinating Centre (TCC)</td>
<td>+64 9 359 9981</td>
</tr>
<tr>
<td>TROG Central Operations Office (TCOO)</td>
<td>+61 (0)2 401 43902</td>
</tr>
</tbody>
</table>

SAE forms are required at the following points:

<table>
<thead>
<tr>
<th>Initial Report</th>
<th>Within <strong>one working day/24 hours</strong> of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided in the comments section of the SAE form.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete Reports*</td>
<td>If all details are not available at the time of the initial report a completed report must be sent within the <strong>next 10 days.</strong></td>
</tr>
<tr>
<td>Updated Report</td>
<td>If the event is not resolved (or is ‘on-going’) at the time of the initial report, the ‘UPDATE: Outcome of Event’ section’ of the SAE Form must be completed and the form submitted to the TCC and the TCOO as soon as the event is resolved (with or without sequelae) or if death has occurred.</td>
</tr>
</tbody>
</table>

*The Investigator is ultimately responsible for reporting the SAE and must sign the SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24 hour period, a comment to this effect must be written on the form and the form faxed without signature to the TCC and TCOO. The investigator must sign the SAE form as soon as possible and re-fax to the TCC and the TCOO.*
The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and subsequently notifying the HREC of SAEs as required.

All Serious ADRs (expected and unexpected) are required to be reported to the TCC and the TCOO according to section 15.2.2 above.

15.2.2.2 Trial Coordinating Centre (TCC)

The TCC will ensure all SAEs are forwarded for immediate clinical review by a qualified independent reviewer to ensure any safety issues and subsequent actions are identified as soon as possible.

The Investigator at the Trial Site is responsible for reporting Serious ADRs to the responsible HREC according to local requirements.

No pharmaceutical products that meet CTN criteria are used in this trial and therefore TGA reporting is not required.

15.2.3 Other Situations requiring expedited Reporting

15.2.3.1 Overdoses

Overdoses (drug or radiation) must be reported to the TCC and TCOO (see section 10.4.2) if the event(s) associated with the overdose meet the SAE definitions in section 10.1.4. If no serious adverse events are experienced the overdose must be reported in the patients medical record and transcribed onto the relevant trial CRF.

15.2.3.2 New Cancers

The development of new cancers at any time during the trial must be reported in the patients’ medical record and transcribed onto the relevant trial CRF. If any events associated with the new cancer meet the SAE definitions listed at section 15.1.4 above, then they should also be reported to the TCC and TCOO (see section 15.4.2).

16.0 Statistical Considerations

16.1 Trial Design

This is a two-arm, randomised, non-inferiority trial whose main aim is to determine, in patients with clinically localised prostate cancer with positive margins and/or extraprostatic (pT3) disease following radical prostatectomy, whether active surveillance with early salvage (delayed) radiotherapy (SRT) can be considered non-inferior to standard treatment with adjuvant (immediate) radiotherapy (ART) with respect to risk of biochemical failure (bF).

Secondary aims are to compare arms with respect to quality of life, treatment-related adverse events, overall survival, biochemical failure-free survival (bFFS), disease-specific survival, time to distant failure, time to local failure, and time to the initiation of androgen deprivation. A secondary aim also is to assess the simultaneous effects of several potential prognostic factors on each outcome. Simultaneous assessment of efficacy and quality of life will be undertaken using Quality Adjusted Life Years.
(QALYs) analyses. A cost-utility analysis will be undertaken to determine and compare the cost implications of the two strategies being evaluated.

16.2 Treatment Assignment
Patients will be randomised in the ratio of 1:1 between the two arms: ART and SRT. Allocation to treatment arms will be balanced by radiotherapy institution, Gleason score (continuous), preoperative PSA level (continuous), surgical margin status (positive/negative) and seminal vesicle involvement (pT3b: yes/no), using the minimisation technique.

16.3 Statistical Methods
16.3.1 Patient Subsets to be Analysed
The following defined patient subsets will be used for the different types of analyses to be used.
- **As-randomised subset**: All patients who are randomised on the trial and who have a diagnosis of prostate cancer. Analysis is performed according to the intention-to-treat (ITT) principle.
- **Per-protocol subset**: All patients who comply with entry criteria receive adequate treatment and do not otherwise deviate from the protocol in an important way. Analysis will be according to the treatment actually received.
- **As-treated subset**: All patients who begin treatment. Analysis will be according to treatment actually received. The as-treated population will be used for safety analyses.

The analysis of the primary objective will be conducted according to both ITT and per-protocol methods. The ITT principle says that patients will be analysed according to the arms to which they were randomised, regardless of compliance with entry criteria or the treatment they actually receive or whether they subsequently withdraw from treatment or deviate from the protocol. A definitive conclusion regarding non-inferiority will follow if these analyses are consistent. (See the comments on this at the end of the section, *Analysis of the Primary Objective.*) Secondary objectives will be conducted similarly, except that safety analyses will be performed using the as-treated subset of patients.

16.3.2 Pre-Randomisation Statistics and General Methods
Pre-randomisation characteristics by treatment arm will be summarised in frequency tables and by the use of descriptive statistics for quantitative variables. Summary tables will be prepared giving numbers of patients by treatment arm and by randomisation irregularities, treatment compliance, eligibility infringements, and losses to follow-up (as per CONSORT guidelines).

All times to events will be measured from the date of randomisation unless otherwise stated. A close-out date will be determined at the time of final analysis as the earliest date of last contact of all patients alive and not lost to follow-up. All follow-up beyond this date will be ignored for the purposes of analysis in order to minimise bias arising from the differential reporting of follow-up for patients who do or do not experience an event.
Ninety-five percent confidence intervals (95% CI) for differences between arms of all important endpoints will be calculated, and p-values will be two-sided. An exception is the analysis of the primary objective, as described below.

16.3.3 Analysis of the Primary Objective

The primary endpoint is bF. (Note: For the purposes of the trial, bF will include any clinically diagnosed failure and initiation of AD for failure.

Non-inferiority of SRT with respect to ART will be assessed by first nominating a non-inferiority margin (N-IM), defined as the maximum ‘difference’ between the arms consistent with the assertion that SRT is effectively non-inferior to ART. The N-IM will be specified as a hazard ratio (SRT:ART) corresponding to specified 5-year bF-free rates (bFFR). The N-IM will, therefore, be represented by a hazard ratio greater than one. (See section 16.4.2 below for rates and ratio used to define the N-IM for this trial.)

A one-sided 95% confidence interval (CI) for the hazard ratio (SRT:ART) of the form (0 to upper-limit), (or, equivalently, a two-sided 90% CI for the hazard ratio) will be calculated and if this CI lies below the N-IM it will be concluded that SRT is, effectively, non-inferior to ART.

The primary analysis will be performed using a Cox regression model to calculate a 2-sided 90% CI for the hazard ratio which adjusts for the stratification variables (excluding institution), viz Gleason score, preoperative PSA, seminal vesicle involvement and surgical margin status. Secondary analyses will include an unadjusted analysis. The Kaplan-Meier method will be used to estimate curves for time to bF (TTbF).

The equivalent analysis in terms of hypothesis testing is to test the null hypothesis:

\[ H_0 : \text{HR}(\text{SRT:ART}) > \text{N-IM} \text{ (inferiority)}, \]

versus the one-sided alternative hypothesis:

\[ H_1 : \text{HR}(\text{SRT:ART}) \geq \text{N-IM} \text{ (non-inferiority)}, \]

where \( \text{HR}(\text{SRT:ART}) \) is the hazard ratio of SRT relative to ART. \( \text{HR} = 1 \) means exact equivalence and \( \text{HR} > 1 \) means SRT has a higher bF rate than ART.

It will be important in this trial to ensure that data quality is very high. Any noise in the data would have the effect of narrowing any difference between the groups being compared, thereby increasing the likelihood of demonstrating equivalence when it does not exist, i.e. increasing the chance of a false positive result (of non-inferiority).

Hence, analysis of the primary objective will include both: (i) an ITT analysis; and (ii) analysis using the per-protocol patient subset. A conclusion of non-inferiority will be made if these analyses are consistent in indicating non-inferiority.
16.3.4 Analyses of Secondary Objectives

Frequencies of early toxicity rates will be tabulated and compared between arms using exact contingency table methods. Late toxicity rates will be estimated using Kaplan-Meier curves and compared using logrank and Cox regression methods.

The Kaplan-Meier method will be used to estimate curves for bFFS, overall survival, disease-specific survival, and times to distant failure, local failure, and androgen deprivation. Cumulative rates of local failure and distant failure will also be estimated from cumulative incidence curves obtained from competing risks analyses (see Time-to-event Definitions for details). Cox regression will be used to compare arms for the various time-to-event endpoints, including those adjusting for prognostic factors and for prognostic factor analyses.

16.4 Sample Size and Power

16.4.1 Anticipated Accrual Rate

As a result of surveying likely participating sites, the accrual rate to the trial is expected to be 100 evaluable patients per year.

16.4.2 Sample Size Calculation

It is assumed that the 5-year bFFR of the standard arm (ART) is 74% (35). SRT will be considered to be non-inferior to ART if its 5-year bFFR is at most 10% lower than the 5-year bFFR for ART. That is, given 74% bFFR for ART, the experimental arm (SRT) will be considered non-inferior if its 5-year bFFR is 64% or higher. Assuming proportional hazards, 74% versus 64% corresponds to a hazard ratio (HR) for SRT:ART of 1.482 (1/0.675). (The N-IM is 1.482.)

A difference of 10% in 5-year bFFR was chosen because it is felt that if there is a less than 10% difference in biochemical control between arms the likelihood of any meaningful difference in clinical endpoints such as distant failure or overall survival will be very small. Also, it is expected that many patients would accept an increase in risk of bF of up to 10% at 5 years in order to obtain a better expected QoL (from the likely avoidance of the need for radiotherapy).

The sample size is based on the primary outcome variable of time to biochemical failure (time from randomisation to bF).

The following assumptions are made in the calculation of the required sample size:
- Biochemical failure-free curves follow exponential distributions;
- The biochemical failure-free rate for ART at 5 years is 74%;
- The N-IM is that corresponding to a biochemical failure-free rate for SRT at 5 years of 64%, viz a hazard ratio (SRT:ART) of 1.482;
- There are no competing risks;
- The required power of the trial to declare non-inferiority when the two arms are identical (74% bFFR at 5 years for both arms) is 80%;
- The significance level is 5% (for a one-sided test with type I error, alpha = 0.05);
- Patients will be allocated to treatment arms in the ratio of 1:1.
- The accrual rate for the trial will be 100 patients per year;
- Patients will be followed up for a further 5 years following close of accrual.

The above assumptions require that 160 biochemical failures be observed by the time of the main analysis. This number of biochemical failures can be expected if 454 patients are accrued. To allow for losses to follow-up and patients who are not fully evaluable the trial will aim to accrue 470 patients, which is expected to take 4.7 years. So, in summary:

In order to determine non-inferiority of SRT with respect to ART with 80% power, using a 10% non-inferiority margin in the 5-year biochemical failure-free rate (assumed 74% versus 64%: HR = 1.482) 160 events are required to be observed. It is estimated that this will require a sample size of 470 patients expected to be accrued over 4.7 years and followed for a further 5 years.

Sample sizes that would be required for other N-IMs and for 90% power, given the bFFR for ART = 74%, are:

<table>
<thead>
<tr>
<th>Difference in 5-year bFFR</th>
<th>N-IM (HR)</th>
<th>Events required</th>
<th>Power = 80%</th>
<th>Power = 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>1.232</td>
<td>570</td>
<td>1300</td>
<td>1600</td>
</tr>
<tr>
<td>6%</td>
<td>1.281</td>
<td>410</td>
<td>960</td>
<td>1250</td>
</tr>
<tr>
<td>7%</td>
<td>1.330</td>
<td>310</td>
<td>780</td>
<td>1000</td>
</tr>
<tr>
<td>8%</td>
<td>1.380</td>
<td>240</td>
<td>650</td>
<td>850</td>
</tr>
<tr>
<td>9%</td>
<td>1.431</td>
<td>200</td>
<td>550</td>
<td>700</td>
</tr>
<tr>
<td>10%</td>
<td>1.482</td>
<td>160</td>
<td>470</td>
<td>600</td>
</tr>
</tbody>
</table>

About one year prior to the end of accrual a confidential assessment by the IDMC, with the assistance of the trial statistician, of the assumptions underlying the estimation of sample size will be made. This assessment will examine:

- the assumptions made about the time to bF: viz exponential curve for ART, and proportional hazards;
- an assessment (based on the bF rate for ART) of whether the required number of events will be observed following 5 years of follow-up after end of accrual;
- the likely number of patients who would not be fully evaluable for a per-protocol subset analysis.

If it is judged to be necessary, an adjustment to the required number of patients to be accrued will be made to ensure the required number of bFs will be observed. No analysis of difference or non-inferiority will be made at this time.
16.5 Analysis Plan

It is planned to do interim analyses of adverse events after approximately 2, 3 and 4 years of accrual, a futility analysis after about 3 years, an interim analysis of efficacy 2 years following close of accrual, and a final (main) analysis after 160 events have been observed. The schedule for analyses may vary if the accrual rate is significantly different from that expected.

Table: Summary of main events and analyses.

Legend: SOA = start of accrual; EOA = end of accrual; EOF = end of follow-up; IAn = nth interim analysis; FA = final analysis.

<table>
<thead>
<tr>
<th>Event</th>
<th>Purpose</th>
<th>Trigger</th>
<th>Expected Date</th>
<th>Years from SOA</th>
<th>Expected accrual</th>
<th>Expected no. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA1</td>
<td>Toxicity</td>
<td>Earlier of 200 patients and 2 years after SOA</td>
<td>Aug 2008</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IA2</td>
<td>Toxicity, futility</td>
<td>Earlier of 300 patients and 3 years after SOA</td>
<td>Aug 2011</td>
<td>3</td>
<td>300</td>
<td>26</td>
</tr>
<tr>
<td>IA3</td>
<td>Toxicity, sample size assumptions</td>
<td>Earlier of 400 patients and 4 years after SOA</td>
<td>Aug 2012</td>
<td>4</td>
<td>400</td>
<td>45</td>
</tr>
<tr>
<td>EOA</td>
<td></td>
<td>470 patients</td>
<td>May 2013</td>
<td>4.7</td>
<td>470</td>
<td>64</td>
</tr>
<tr>
<td>IA4</td>
<td>Efficacy</td>
<td>2 years after EOA</td>
<td>May 2015</td>
<td>6.7</td>
<td>470</td>
<td>102</td>
</tr>
<tr>
<td>EOF</td>
<td></td>
<td>160 events</td>
<td>May 2018</td>
<td>9.7</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>FA</td>
<td>Assess all objectives</td>
<td></td>
<td>Aug 2018</td>
<td>10</td>
<td>470</td>
<td>160</td>
</tr>
</tbody>
</table>

* given 74% vs 64% bFFR at 5 years in ART and SRT arms, respectively.

16.5.1 Interim status and safety reports

Regular progress reports will be done six-monthly for the TMC and TROG meetings. These will comprise a) reports of accrual to TROG and b) accrual and data timeliness and quality to the TMC. The IDMC will receive safety reports by arm. An analysis will be conducted on the first 100 patients randomised to ART who received the protocol treatment and had at least one year of follow-up. The aim of this analysis is to document the late toxicities experienced for the purposes of a publication designed to improve accrual to the trial. The IDMC will review the analysis and plans for publication.

16.5.2 Interim analysis No. 1

This will be an analysis of toxicity two years after start of accrual or after 200 patients have accrued, whichever occurs first. An analysis of toxicity will be submitted to the IDMC for consideration. The analysis will include rates of grade 2 or worse late urinary and bowel toxicity. It is not expected that the trial will be stopped for reasons of toxicity but the IDMC may recommend modification of the treatments.

16.5.3 Interim analysis No. 2

This will be an analysis of toxicity and one for futility three years after start of accrual or after 300 patients have accrued, whichever occurs first. The futility analysis will
test at an early stage whether there is any evidence that the risk of bF for SRT is significantly inferior to that of ART at the 5% one-sided significance level.

16.5.4 Interim analysis No. 3

This will be an analysis of toxicity and to assess the sample size assumptions, four years after start of accrual or after 400 patients have accrued, whichever occurs first. The sample size reassessment will examine (i) the shapes of the bFF curves to assess whether the proportional hazards assumption is reasonable and that the curves are approximately exponential, and (ii) whether the bFF rate in the ART arm is consistent with 74% at five years. The analysis will be strictly confidential and the IDMC will advise on whether the sample size should be modified.

16.5.5 Interim analysis No. 4

This will be an analysis of efficacy two years after the end of accrual for the purposes of presentation of interim results at an international forum. The results will not influence the decision to continue to full follow-up until 160 events (bFs) are observed (expected to be five years after accrual ends) and so will not affect the alpha level used at final analysis. The final analysis will be carried out if 160 events have not occurred by seven years following end of accrual.

16.5.6 Final analysis

This will occur after 160 events have been observed, expected to be five years after the end of accrual. If, five years after the end of accrual, 160 events have not occurred, or won’t occur soon, a confidential futility analysis will be performed involving calculation of the conditional power (probability that a statistically significant outcome will be achieved by the earlier of 160 events or 7 years from end of accrual, given the alternative hypothesis of no difference and the data to hand). If this conditional power is sufficiently low (say < 0.20), the IDMC will recommend that the trial be analysed, otherwise continue to the earlier of 160 events or 7 years accrual.

16.6 Early Closure Criteria

Early stopping of the trial will be considered in the event of:

- Inadequate recruitment: once a consistent accrual rate has been established. If this is less than 50 patients per year the TMC will review the viability of the trial.

- Unacceptable toxicity. However, as the experimental arm is the administration of less intensive treatment, then it is not foreseen that there will be a need to terminate accrual based on toxicity. If the rates of toxicity are high, then treatment guidelines will be reviewed.

- Evidence becoming available, during the accrual phase of the trial, which clearly demonstrates that it is unethical to randomise patients to one or both of the trial arms.

- Evidence of inferiority of the SRT arm.

The IDMC will review confidential reports of relevant analyses of trial data and recommend whether the trial should be stopped or undergo modification or continue without change.
17.0 Responsibilities

The study will be performed in accordance with the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) in Australia and the Interim Good Clinical Research Practice Guidelines in New Zealand, issued by Medsafe.

17.1 Investigator responsibilities

The investigator is responsible for ensuring that written informed consent by the patient is obtained before study entry. The investigator is responsible for informing the ethics committee of any serious adverse events and/or major amendments to the protocol as per local requirements.

The investigator is responsible for ensuring that all regulatory requirements are followed.

The investigator is required to ensure compliance with respect to all aspects of the protocol. It is the responsibility of the investigator to maintain adequate and accurate case report forms (CRFs) as per sections 14.1 and 14.2.

18.0 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee has been established. It comprises three members, a radiation oncologist, a urologist and a statistician. The committee will meet biannually.

The role of the IDMC in general is to monitor patient safety and the scientific integrity of the trial and, more specifically, to:

a) Provide confidential and expert review of the interim analyses. The IDMC can recommend early closure of the trial.

b) Monitor AE and SAE data

c) Assess adequacy of accrual

d) Review protocol violations

e) Review the frequency of, and reasons for, patient withdrawal (includes both withdrawal of consent and loss to follow-up)

Following each IDMC meeting, the IDMC Chair will provide a progress report, including any recommendations, to the Trial Chairs.

19.0 Ethical Considerations

19.1 Ethical principles and Regulatory Compliance

The trial will be conducted according to the following regulations and guidelines:

- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Australia, July 2000)
- The Australian Code for Responsible Conduct of Research (August 2007)
• Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (last amended by the World Medical Association, 2008)
• Interim Good Clinical Research Practice Guidelines (New Zealand, August 1998),
• National Statement on Ethical Conduct in Human Research, (Australia, 2007)
• Guidelines on Ethics in Health Research (NZ, 2005), and
• Current TROG Policy Statements

This Protocol, including the Participant information Sheet and Consent Form (PIC) must be approved by the responsible HREC before enrolment of trial participants.

No pharmaceutical products that meet CTN criteria are used in this trial.

19.2 Adherence to the protocol

Except for an emergency situation in which proper care for the protection, safety and well being of the trial participant requires that an alternative treatment be used, the trial shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be recorded and explained.

19.3 Informed Consent

The Principal Investigator is responsible for ensuring that written Informed Consent is obtained from trial participants before trial entry.

A template PIC for this trial is provided in the protocol appendices. The Principal Investigator must insert site specific information into the template and have this approved by the TCC prior to submitting the PIC to the responsible HREC for final approval.

19.4 Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant. An exception is where the trial participant has provided written consent for his/her records to be included in source document verification. In this instance, the records may be inspected by (a) a representative of TROG for the purposes of source document verification or quality audit as stipulated in the ICH GCP Guidelines, or (b) a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to trial participants will be treated in strict professional confidence.
20.0 Insurance and Compensation

TROG endorses the principles of the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company Sponsored Trial and the Research Medicines Industry equivalent in New Zealand.

To provide protection for trial participants involved in TROG Clinical Trials, TROG maintains a clinical trials insurance policy.

21.0 Publication and Presentation Policy

21.1 Reporting of Results

The Trial Management Committee will be responsible for decisions regarding presentations and publications arising from this trial according to the TROG Authorship, Publication and Spokesmanship Guidelines.

Access to data during the trial will be limited to the TCC, the TCOO as required for QA reviews, the TMC, the DMC and appropriate regulatory bodies. The primary analysis of trial results for publication will be performed by the TMC statistician. The primary trial results will be published by TROG.

Acknowledgement of TROG is required in all publications, abstracts and presentations. Publications and abstracts must be presented to the TMC for review and approved prior to submission. In addition, publications must be reviewed by the TROG Publications Committee prior to submission.

21.2 Trial Registry

The TCOO is responsible for registering all TROG trials with an appropriate clinical trials registry prior to the accrual of the first participant. All TROG trials are registered at www.clinicaltrials.gov and Australian and New Zealand Clinical Trials Registry (ANZCTR) www.anzctr.org.au.
REFERENCES


47. ICRU Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). International Commission on Radiation Units and Measurement 1999


### Primary Tumor, Pathologic (pT)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2*</td>
<td>Organ confined (<em>Note: There is no pathologic T1 classification</em>)</td>
</tr>
<tr>
<td>pT2a</td>
<td>Unilateral</td>
</tr>
<tr>
<td>pT2b</td>
<td>Bilateral</td>
</tr>
<tr>
<td>pT3</td>
<td>Extraprostatic extension</td>
</tr>
<tr>
<td>pT3a</td>
<td>Extraprostatic extension (<em>i.e. without seminal vesicle invasion</em>)</td>
</tr>
<tr>
<td>pT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of bladder, rectum</td>
</tr>
</tbody>
</table>
APPENDIX II. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### APPENDIX III. Co-morbidity Index

<table>
<thead>
<tr>
<th>Does the patient have a history of, or presently have:</th>
<th>Tick if present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>☐</td>
</tr>
<tr>
<td>Heart failure</td>
<td>☐</td>
</tr>
<tr>
<td>Angina, intermittent claudication, or abdominal aortic aneurysm</td>
<td>☐</td>
</tr>
<tr>
<td>Other malignancies (except basal skin carcinoma)</td>
<td>☐</td>
</tr>
<tr>
<td>Peptic ulcer disease (medically or surgically treated, but not reflux)</td>
<td>☐</td>
</tr>
<tr>
<td>Cerebrovascular accident (stroke) or Transient Ischaemic Attacks</td>
<td>☐</td>
</tr>
<tr>
<td>Diabetes mellitus (medically treated)</td>
<td>☐</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary diseases</td>
<td>☐</td>
</tr>
<tr>
<td>Dementia</td>
<td>☐</td>
</tr>
<tr>
<td>Connective tissue / autoimmune diseases: eg. Sarcoid, SLE, Wegener's granulomatosis, Rheumatoid</td>
<td>☐</td>
</tr>
<tr>
<td>Liver disease (any LFT &gt; 1.5 times normal)</td>
<td>☐</td>
</tr>
<tr>
<td>Kidney diseases (renal function &gt;1.5 times normal)</td>
<td>☐</td>
</tr>
<tr>
<td>Bowel diseases: Crohn's disease, ulcerative colitis</td>
<td>☐</td>
</tr>
<tr>
<td>Hypertension (or on antihypertensive therapy)</td>
<td>☐</td>
</tr>
<tr>
<td>Hypercholesterolaemia (or using cholesterol lowering agents)</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Number of other medical diagnoses**

**Number of regular prescription medications taken** (including aspirin)

*Validated co-morbidity index of Post et al.*
APPENDIX IV. EORTC QLQ-C30 & QLQ-PR25

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: I I I I

Your Birth Date (Day, Month, Year): I I I I I I I I I I

Today's date (Day, Month, Year): I I I I I I I I I I

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Have you had diarrhoea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

<table>
<thead>
<tr>
<th>Rating</th>
<th>Very poor</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

30. How would you rate your overall quality of life during the past week?

<table>
<thead>
<tr>
<th>Rating</th>
<th>Very poor</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had to urinate frequently during the day</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had to urinate frequently at night?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>When you felt the urge to pass urine, did you have to hurry to get to the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had difficulty going out of the house because you needed to be close to a toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had any unintentional release (leakage) of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have pain when you urinated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Answer this question only if you wear incontinence aid. Has wearing an incontinence aid been a problem for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have your daily activities been limited by your urinary problems?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have your daily activities been limited by your bowel problems?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had any unintentional release (leakage) of stools?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had blood in your stools?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have a bloated feeling in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have hot flushes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had sore or enlarged nipples or breasts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had swelling in your legs or ankles?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the last 4 weeks:

47. Has weight **loss** been a problem for you?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

48. Has weight **gain** been a problem for you?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

49. Have you felt less masculine as a result of your illness or treatment?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

50. To what extent were you interested in sex?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

51. To what extent were you sexually active (with or without intercourse)?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

**PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS.**

52. To what extent was sex enjoyable for you?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

53. Did you have difficulty getting or maintaining an erection?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

54. Did you have ejaculation problems (eg dry ejaculation)?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

55. Have you felt uncomfortable about being sexually intimate?  
   Not at all  1  A little  2  Quite a bit  3  Very much  4

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APPENDIX V. Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked “A”, and to depression “D”. The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

<table>
<thead>
<tr>
<th>A</th>
<th>I feel tense or ‘wound up’:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most of the time</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>A lot of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>From time to time, occasionally</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I still enjoy the things I used to enjoy:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definitely as much</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not quite so much</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Only a little</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hardly at all</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I get a sort of frightened feeling as if something awful is about to happen:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very definitely and quite badly</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Yes, but not too badly</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>A little, but it doesn’t worry me</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I can laugh and see the funny side of things:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As much as I always could</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not quite so much now</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Definitely not so much now</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>Worrying thoughts go through my mind:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A great deal of the time</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>A lot of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>From time to time, but not too often</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Only occasionally</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I feel cheerful:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Not often</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Most of the time</td>
<td>0</td>
</tr>
<tr>
<td>A</td>
<td>I can sit at ease and feel relaxed:</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Usually</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Not often</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I feel as if I am slowed down:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nearly all the time</td>
</tr>
<tr>
<td></td>
<td>Very often</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I get a sort of frightened feeling like ‘butterflies’ in the stomach:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Occasionally</td>
</tr>
<tr>
<td></td>
<td>Quite often</td>
</tr>
<tr>
<td></td>
<td>Very often</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I have lost interest in my appearance:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definitely</td>
</tr>
<tr>
<td></td>
<td>I don’t take as much care as I should</td>
</tr>
<tr>
<td></td>
<td>I may not take quite as much care</td>
</tr>
<tr>
<td></td>
<td>I take just as much care as ever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I feel restless as I have to be on the move:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very much indeed</td>
</tr>
<tr>
<td></td>
<td>Quite a lot</td>
</tr>
<tr>
<td></td>
<td>Not very much</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I look forward with enjoyment to things:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As much as I ever did</td>
</tr>
<tr>
<td></td>
<td>Rather less than I used to</td>
</tr>
<tr>
<td></td>
<td>Definitely less than I used to</td>
</tr>
<tr>
<td></td>
<td>Hardly at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I get sudden feelings of panic:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very often indeed</td>
</tr>
<tr>
<td></td>
<td>Quite often</td>
</tr>
<tr>
<td></td>
<td>Not very often</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>I can enjoy a good book or radio or TV program:</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>D</td>
<td>Often</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Not often</td>
</tr>
<tr>
<td></td>
<td>Very seldom</td>
</tr>
</tbody>
</table>

Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.

0 – 7 = Normal  
8 – 10 = Borderline abnormal  
11 – 21 = Abnormal

Reference: Zigmond and Snaith (1983)\textsuperscript{52}
## APPENDIX VI. NCI CTCAE v 3.0
NCI Common Terminology Criteria for Adverse Effects (CTCAE) v 3.0 (August 9th 2006)

<table>
<thead>
<tr>
<th>Genitourinary</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Cystitis</strong></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary Incontinence</strong></td>
<td>Occasional (e.g., with</td>
</tr>
<tr>
<td></td>
<td>coughing, sneezing, etc.),</td>
</tr>
<tr>
<td></td>
<td>pads not indicated</td>
</tr>
<tr>
<td><strong>Urethral Stricture/Stenosis</strong></td>
<td>Asymptomatic, radiographic or endoscopic findings only</td>
</tr>
<tr>
<td><strong>Urinary Frequency/Urgency</strong></td>
<td>Increase in frequency or nocturia up to 2 x normal; enuresis</td>
</tr>
<tr>
<td><strong>Urinary Retention</strong></td>
<td>Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period</td>
</tr>
<tr>
<td><strong>Haemorrhage, GU</strong></td>
<td>Minimal or microscopic bleeding intervention not indicated</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>GRADE</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Diarrhoea¹</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>Proctitis</td>
<td>Rectal discomfort intervention not indicated</td>
</tr>
<tr>
<td>Haemorrhage, GI (Rectal)</td>
<td>Mild, intervention (other than iron supplements) not indicated</td>
</tr>
<tr>
<td>Incontinence (Anal)²</td>
<td>Occasional use of pads</td>
</tr>
</tbody>
</table>

¹ Diarrhoea includes diarrhoea of small bowel or colonic origin, and/or ostomy diarrhoea.
² Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention

<table>
<thead>
<tr>
<th>Sexual Function</th>
<th>GRADE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Dysfunction</td>
<td>Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated</td>
<td>Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated</td>
<td>Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th>GRADE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer to CTCAE v3.0 (<a href="http://ctep.cancer.gov/reporting/ctc.html">http://ctep.cancer.gov/reporting/ctc.html</a>) and use exact term or specify other</td>
<td>Mild Adverse Event</td>
<td>Moderate Adverse Event</td>
<td>Severe and undesirable Adverse Event</td>
<td>Life-threatening or disabling Adverse Event</td>
<td>Death related to Adverse Event</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VII. Study Schedule for patient assessments and follow-up

**Arm 1 (Adjuvant Radiotherapy – ART)**

<table>
<thead>
<tr>
<th>Assessment (relative to randomisation)</th>
<th>Pre-randomisation</th>
<th>Day 1 RT</th>
<th>End RT</th>
<th>6 wks post-RT</th>
<th>Follow up relative to randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation data (eligibility criteria, stratification factors)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>0-5 yr 5 yrs to trial end</td>
</tr>
<tr>
<td>Medical history/Physical exam</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbidity Index</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X*</td>
<td>6 monthly* 12 monthly</td>
</tr>
<tr>
<td>Adverse events (CTCAE V 3.0)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 monthly 12 monthly</td>
</tr>
<tr>
<td>Central pathology review</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>6 monthly PSA* 12 monthly PSA*</td>
</tr>
<tr>
<td>Adverse Events SHIM</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>12 monthly 12 monthly</td>
</tr>
<tr>
<td>Quality of Life EORTC GLQ-C30</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 monthly 12 monthly</td>
</tr>
<tr>
<td>Quality of Life EORTC GLQ-PR25</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 monthly 12 monthly</td>
</tr>
<tr>
<td>Anxiety/depression HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 monthly 12 monthly</td>
</tr>
<tr>
<td>Hospitalisation questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optional biological sub-study questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months post-randomisation*</td>
</tr>
<tr>
<td>Optional Biological Substudies:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour blocks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Not required prior to randomisation.
2. Quality of Life (QoL) questionnaires, SHIM and hospital anxiety and depression scale (HADS) - to be done prior to the PSA result being revealed.
3. Includes rectal examination if rising PSA till documented local failure.
4. If the first 6 monthly assessment coincides within 28 days of the 6 week post-RT assessment, the 6 monthly assessment can be omitted.
5. If it is not feasible to approach the patient about the optional biological sub-studies at 6 months post-randomisation, they can choose to participate at any time up until 6 months after recruitment closes.
6. PSA tests should be +/- 28 days from target date(s) calculated relative to randomisation. If a PSA result that triggers SRT or meets the criteria for bF falls between two scheduled assessments, the relevant PSA result must be reported as an unscheduled PSA assessment.
### Arm 2 (Salvage radiotherapy – SRT)

<table>
<thead>
<tr>
<th>Assessment (relative to randomisation)</th>
<th>PSA &lt; 0.2 ng/mL</th>
<th>During and following RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surveillance, relative to randomisation</td>
<td>Day 1 RT</td>
</tr>
<tr>
<td></td>
<td>0-5 yrs</td>
<td>5 yrs to trial end</td>
</tr>
<tr>
<td>Randomisation data (eligibility criteria, stratification factors)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical history/ Physical exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Co-morbidity index</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>6 monthly</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Adverse events (CTCAE V 3.0)</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Central pathology review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Pre-operative</td>
<td>3 monthly&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse events Post-operative</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Quality of Life&lt;sup&gt;2&lt;/sup&gt; EORTC QLQ-C30 EORTC QLQ-PR25</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Anxiety/depression&lt;sup&gt;2&lt;/sup&gt; HADS</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Hospitalisation questionnaire</td>
<td>12 monthly</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Optional Biological sub-study questionnaire</td>
<td>At 6 months post-randomisation</td>
<td></td>
</tr>
<tr>
<td>Optional Biological Substudies: Sputum collection</td>
<td>At 6 months post-randomisation</td>
<td></td>
</tr>
<tr>
<td>Tumour blocks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Not required prior to randomisation.

<sup>2</sup> Quality of Life (QoL) questionnaires, SHIM and hospital anxiety and depression scale (HADS) - to be done prior to the PSA result being revealed.

<sup>3</sup> Includes rectal examination if rising PSA till documented local failure.

<sup>4</sup> If a 6 monthly assessment coincides within 28 days of the 6 week post-RT assessment, the 6 monthly assessment can be omitted.

<sup>5</sup> If it is not feasible to approach the patient about the optional biological sub-studies at 6 months post-randomisation, they can choose to participate at any time up until 6 months after recruitment closes.

<sup>6</sup> PSA tests should be +/- 28 days from target date(s) calculated relative to randomisation. If a PSA result that triggers SRT or meets the criteria for bF falls between two scheduled assessments, the relevant PSA result must be reported as an unscheduled PSA assessment.
Appendix VIII. Pictorial Contouring Guidelines

Figure 1
**FIGURE LEGENDS**

**Figure 1:** [CTV – yellow, vesicourethral anastomosis – white, rectum – blue, bladder – green, vas deferens – red]. Serial CT slices of a sample post-prostatectomy patient demonstrating the contouring guidelines. Delayed scanning following intravenous contrast allowed contrast accumulation in the bladder so as to ascertain the most inferior slice where urine is last visible (C). The anastomosis is located one slice below this (B), and the most inferior CTV slice a further 5mm lower (A). Images D to G illustrate that the anterior border of the inferior 3cm of the CTV lies behind the symphysissymphysis pubis. More superiorly (H – J) the anterior border encompasses the posterior 1.5cm of the bladder, and posteriorly extends to the mesorectal fascia. The most superior slice of the CTV (J) encompasses the last slice where the vas deferens is visible and all non-vascular surgical clips.

**Figure 2:** [PTV – pink, other structures as per Figure 1]
A. Sagittal reconstruction illustrating the anterior margin of the CTV extending to the border of the pubic symphysis for the inferior 3cm of the CTV. The PTV is a 10mm uniform expansion upon the CTV contours.
B. More superiorly, the anterior border of the CTV should encompass the posterior 1.5cm of the bladder wall.
C. The space bounded by the levator ani and the rectum anteriorly (arrow) is a significant site of recurrence and should be encompassed if the volume of rectum being treated is not prohibitive. Ideally, the distance between the posterior margin of the CTV and the posterior rectal wall should be no less than 2cm to avoid treating the entire circumference of the rectum.
D. The vas deferens are usually identified superiorly as thin horizontal cylindrical structures which become small round structures more inferiorly.
Appendix IX: Biological Sub-study Patient Questionnaire

RAVES - Radiotherapy Adjuvant Versus Early Salvage

A Phase III Multi-Centre Randomised Trial Comparing Adjuvant Radiotherapy (RT) With Early Salvage RT in Patients With Positive Margins or Extraprostatic Disease Following Radical Prostatectomy.

RAVES GENETIC STUDY PARTICIPANT QUESTIONNAIRE

Your saliva will provide a sample of your DNA. DNA is the chemical compound that genes are made of. Genes are inherited from both biological parents.

There will be marked similarities between your genetic profile and that of your biological parents, brothers, sisters and children. Non-identical twins are no more alike than ordinary brothers and sisters. Genetically identical twins, on the other hand, look so much alike that people often mistake one for the other, especially during their childhood.

Half-brothers and half-sisters will display less similarities compared to your genetic profile. Adopted children and step-children will display only random similarities when compared to your genetic profile. This is why we only ask for cancer history information about your biological or blood relatives. For those family members who have been diagnosed with cancer, it is useful to know what type of cancer this was.

If you have any questions, please discuss these with clinic staff at your next appointment or call the RAVES Genetic Study Coordinator on 1800 783 110

COMPLETION INSTRUCTIONS

Please use a BLACK pen.

Please read each question carefully and answer all of the questions that are relevant to you. Please select ONE answer for each question, unless otherwise specified.

Please shade the circles completely.

Please write in BLOCK CAPITALS within the boxes

If you make a mistake, or want to change any of your shaded responses, please place a cross through the incorrect response and shade the correct response.

If you make a mistake, or want to change any of your written responses, please cross out the incorrect response and write your new response just above or below the one you have crossed out.
PART 1 - DEMOGRAPHY

Today's date

Date of Birth

A. MULTIPLE BIRTHS

A1. Are you a twin?
○ No ---> please go to question A2
○ Yes
○ Don't know

A1a. If yes, are you an identical twin?
○ Yes
○ No

A2. Are you a triplet or other multiple birth?
○ Yes
○ No
○ Don't know

B. EDUCATION

B1. What is the highest level of education you have completed?
○ Primary school (this includes some primary school)
○ Year 8 or 9 (some high school)
○ Year 10 or 11 (some high school)
○ Year 12 (graduation from high school)
○ Vocational training (Trade Certificate, Technical College, or Diploma)
○ University degree – did not graduate
○ University degree – graduated
○ Postgraduate degree (Master, PhD)
○ Other (please specify below)

Page 2 of 12
Participant Questionnaire
RAVES Genetic Study

Amendment 2: dated 29 May 2014
PART 1 - DEMOGRAPHY

C. ETHNICITY

C1. Please describe which group(s) best defines the ancestry/ethnicity (based on a mixture of culture, religion, skin colour and language) of you and your biological parents. You may choose more than one group for each person.

A. Caucasian - Australia/NZ (Anglo European), Europe (includes Russia Central and West Asia), North Mediterranean, America, Canada, South Africa & Zimbabwe.
B. Indigenous Australian - Aboriginal, Torres Strait Islands.
C. Pacific Islander - New Zealand Maori or Pacific Islands, Hawaii, New Guinea.
D. South-East Asian - Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar/Burma, Philippines, Singapore, Thailand, Vietnam.
E. South Asian - Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka.
F. North East Asian - China, Hong Kong, Japan, Korea, Macau, Taiwan.
H. Middle Eastern, North African, Somali Peninsular - Algeria, Bahrain, Djibouti, Eritrea, Ethiopia, Egypt, Israel, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Oman, Palestinian Territories, Turkey, Turkish Cypriots, Qatar, Saudi Arabia, Somalia, Syria, Tunisia, United Arab Emirates, Yemen.
J. Central/South American - Central/South America.
K. Other
L. Don't Know

Your Biological Father

Your Biological Mother

You

A. Caucasian
B. Indigenous Australian
C. Pacific Islander
D. South-East Asian
E. South Asian
F. North East Asian
G. North Asian
H. Middle Eastern, North Africa, Somali Peninsular
I. Sub-Saharan African
J. Central/South American
K. Other (please specify below)
L. Don't know

C1a. If other, please specify for each:

Ethnicity of your biological father:

Ethnicity of your biological mother:

Your ethnicity:

Page 3 of 12
Participant Questionnaire
RAVES Genetic Study

Amendment 2: dated 29 May 2014
PART 1 - DEMOGRAPHY

D. SMOKING HISTORY

D1. Do you currently smoke tobacco (cigarettes, cigars or a pipe)?
   - [ ] Yes, on most or all days
   - [ ] Only occasionally
   - [ ] No ---> please go to D5

D2. How many cigarettes do you usually smoke each day?
   (include hand-rolled cigarettes if smoked)
   - [ ] cigarettes
   - [ ] Don’t know

D3. How many cigars or small cigars do you usually smoke each day?
   - [ ] cigars
   - [ ] Don’t know

D4. How many pipes do you usually smoke each day?
   - [ ] pipes
   - [ ] Don’t know

D5. If you do not smoke now, have you ever smoked in the past?
   - [ ] Yes, smoked on most or all days
   - [ ] Yes, smoked occasionally
   - [ ] Just tried once or twice ---> please go to E1
   - [ ] I have never smoked ---> please go to E1

D6. During the period you smoked the most, how many cigarettes did you usually smoke each day?
   - [ ] cigarettes
   - [ ] Don’t know

D7. During the period you smoked the most, how many cigars or small cigars did you usually smoke each day?
   - [ ] cigars
   - [ ] Don’t know

D8. During the period you smoked the most, how many pipes did you usually smoke each day?
   - [ ] pipes
   - [ ] Don’t know
PART 1 - DEMOGRAPHY

D. SMOKING HISTORY continued

D9. How old were you when you first started smoking on most days?
   □ years old  □ Don’t know

D10. How old were you when you last smoked on most days?
    □ years old  □ Don’t know

D11. In your lifetime, have you smoked a total of at least 100 cigarettes or equivalent?
    □ Yes  □ No  □ Don’t know

E. HEIGHT, WEIGHT & EXERCISE

E1. How tall are you without shoes on?
   □ feet, □ inches  OR  □ □ centimetres

E2. What is your current weight?
    □ □ stones, □ pounds  OR  □ □ kilograms

E3. What was your weight one year before your cancer was diagnosed?
    □ □ stones, □ pounds  OR  □ □ kilograms

E4. What is your waist measurement?
   □ □ inches
   OR
   □ □ centimetres

   Waist measurement should be taken at the narrowest (or mid) point between the lower costal border and iliac crest.
   Waist measurement should be taken at the end of normal expiration with arms relaxed at the sides.
E5. What is your hip measurement?

- [ ] inches

- OR

- [ ] centimetres

*Hip measure should be taken at the level of greatest posterior protuberance of the buttocks. Subject is to stand with feet together and should NOT tense the gluteal muscles*

---

This section is about your usual physical activities since your cancer diagnosis.

E6. How many days each week do you usually walk for at least 10 minutes at a time?

- [ ] days each week

- [ ] No walking

E7. How much time in total do you usually spend on one of those days walking?

- [ ] hours per day

- [ ] minutes per day

E8. Think about only those physical activities that you do for at least 10 minutes at a time. How many days each week do you do moderate physical activities, like bicycling at a regular pace, swimming at a regular pace, golf, gardening, bowls or other similar activities?

- [ ] days per week

- [ ] No moderate activity for leisure

E9. How much time in total do you usually spend on one of those days doing moderate physical activities?

- [ ] hours per day

- [ ] minutes / day

---

*PLEASE CONTINUE TO SECTION G FROM SECTION E, AS THERE IS NO SECTION F.*
### PART 2 - FAMILY CANCER HISTORY

G1. Please complete the table below, as demonstrated in the examples at the top, for each relative listed on the left hand side.

<table>
<thead>
<tr>
<th>RELATIVE</th>
<th>IS THIS PERSON YOUR IDENTICAL TWIN?</th>
<th>HAS THIS PERSON BEEN DIAGNOSED WITH CANCER?</th>
<th>IF YES, WHAT TYPE OF CANCER?</th>
<th>IF OTHER TYPE OF CANCER, PLEASE SPECIFY BELOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES  NO</td>
<td>YES  NO</td>
<td>Prostate  DON'T KNOW</td>
<td>DON'T KNOW  OTHER</td>
</tr>
<tr>
<td><strong>EXAMPLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full brother</td>
<td>○  ●</td>
<td>●</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Half brother</td>
<td></td>
<td>○</td>
<td>○</td>
<td>BOWEL</td>
</tr>
<tr>
<td>Biological Father</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Full Brother 1</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Full Brother 2</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Full Brother 3</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Full Brother 4</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Full Brother 5</td>
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<td>Full Brother 7</td>
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<td>Half Brother 1</td>
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<td>Half Brother 2</td>
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<td>Half Brother 8</td>
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</tr>
</tbody>
</table>
### PART 2 - FAMILY CANCER HISTORY

G1. Please complete the table below, as demonstrated in the examples at the top, for each relative listed on the left hand side.

<table>
<thead>
<tr>
<th>Relative</th>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
<th>IF YES, WHAT TYPE OF CANCER?</th>
<th>IF OTHER TYPE OF CANCER, PLEASE SPECIFY BELOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE Full sister</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>EXAMPLE Half sister</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>BREAST</td>
</tr>
<tr>
<td>Biological Mother</td>
<td>○</td>
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<td>○</td>
<td>○</td>
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<tr>
<td>Full Sister 1</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Full Sister 2</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Full Sister 3</td>
<td>○</td>
<td>○</td>
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<td>○</td>
<td></td>
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<tr>
<td>Full Sister 4</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Full Sister 5</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Full Sister 6</td>
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<tr>
<td>Full Sister 8</td>
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<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Half Sister 1</td>
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<td>○</td>
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<tr>
<td>Half Sister 2</td>
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<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Half Sister 3</td>
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<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
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<tr>
<td>Half Sister 4</td>
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<tr>
<td>Half Sister 5</td>
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<td>Half Sister 8</td>
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</tr>
</tbody>
</table>

Page 8 of 12
Participant Questionnaire
RAVES Genetic Study
### PART 2 - FAMILY CANCER HISTORY

G1. Please complete the table below, as demonstrated in the examples at the top, for each relative listed on the left hand side.

<table>
<thead>
<tr>
<th></th>
<th>HAS THIS PERSON BEEN DIAGNOSED WITH CANCER?</th>
<th>IF YES, WHAT TYPE OF CANCER?</th>
<th>IF OTHER TYPE OF CANCER, PLEASE SPECIFY BELOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td><strong>EXAMPLE</strong> Son</td>
<td>●</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td><strong>EXAMPLE</strong> Daughter</td>
<td>○</td>
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<td><strong>SONS</strong></td>
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<td>Son 3</td>
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<tr>
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<tr>
<td>Son 8</td>
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</tr>
<tr>
<td><strong>DAUGHTERS</strong></td>
<td></td>
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<tr>
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<tr>
<td>Daughter 8</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
PART 2 - FAMILY CANCER HISTORY

G2. Please list any other BLOOD RELATIVES (i.e. apart from biological mother, biological father, siblings, half-siblings or children) who have been diagnosed with cancer.

G2a. Have any of your blood relatives been diagnosed with cancer? ☐ Yes  ☐ No  ☐ Don’t Know

<table>
<thead>
<tr>
<th>RELATIONSHIP TO YOU</th>
<th>WHAT TYPE OF CANCER?</th>
<th>IF OTHER TYPE OF CANCER, PLEASE SPECIFY BELOW</th>
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<tr>
<td></td>
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<td>GRANDFATHER</td>
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<td>AUNT</td>
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<td>Relative 10</td>
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Amendment 2: dated 29 May 2014
### PART 3 - CURRENT MEDICAL CONDITIONS

H1. Please list all current medical conditions.

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<th>Medical condition 1</th>
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<table>
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<th>Medical condition 9</th>
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<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
I1. Do you have any comments or information that you think we should have asked about?

[Blank space for comments]

Thank you very much for completing this questionnaire. We are very grateful for your time.
## Central Pathology Review Synoptic Report

**Submitting laboratory:**

Name: ________________________________  
Collection Date: ________________________  
Laboratory Ref. No: ____________________

<table>
<thead>
<tr>
<th>Review Component</th>
<th>Review Parameters</th>
</tr>
</thead>
</table>
| **Prostate Gland**        | Measurement: ___ by ____ mm  
                          | Weight: ____________gms                                                           |
| **Tumour**                | Type: NOS/ or subtype  
                          | Tumour Location  
                          | Regions: Anterior, Posterior  
                          | Zones: Peripheral, transitional, central |
| **Index Cancer**          | Block:  
                          | Gleason Score  
                          | Primary Grade  
                          | Secondary Grade  
                          | Tertiary  
                          | % High Grade (4/5) |
| **Intraduct Carcinoma**   | Present or Absent                                                                |
| **Extra Prostatic Extension** | Negative  
                          | Focal - 1 or 2 fields with EPE extending ≤1 HPF (0.5mm)  
                          | Established - 1 or more fields EPE extending >1 HPF (0.5mm)  
                          | Location: Bladder Neck, Anterior, Posterolateral |
| **Margin Involvement**    | Negative  
                          | Focal - 1 or 2 regions involved by ≤ 1 mm  
                          | Extensive - 1 or more regions involved by > 1 mm  
                          | Location: Bladder Neck, Apex, Posterolateral, Anterolateral  
                          | Grade at margin: Gleason Grade |
| **Seminal Vesicle**       | Right side Not Involved / Involved  
                          | Left side Not Involved / Involved                                                   |
| **Lymph Nodes**           | Involved / Not involved  
                          | Number of total involved: ... / ... (eg: 1/3 or 0/5 etc)                               |
| **Stage (pT)**            | 2 confined to prostate  
                          | 3A extra prostatic extension  
                          | 3B seminal vesicle involvement                                                     |
| **Variation from submitting pathologist** | Yes/No  
                          | If yes, brief comment                                                             |
APPENDIX XI: Sexual Health Inventory for Men (SHIM)

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME: ___________________________ TODAY'S DATE: __________

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual’s overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that best describes your own situation. Please be sure that you select one and only one response for each question.

OVER THE PAST 6 MONTHS:

<table>
<thead>
<tr>
<th>Question</th>
<th>VERY LOW</th>
<th>LOW</th>
<th>MODERATE</th>
<th>HIGH</th>
<th>VERY HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How do you rate your confidence that you could get and keep an erection?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. When you attempted sexual intercourse, how often was it satisfactory for you?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Add the numbers corresponding to questions 1-5. TOTAL: __________

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED  8-11 Moderate ED  12-16 Mild to Moderate ED  17-21 Mild ED
APPENDIX XII: Health Resource Usage Questionnaire

Have you been admitted to hospital in the last 12 months?  

☐ Yes  ☐ No

If yes:

How many times were admitted to hospital?

Please describe the reason you were admitted to hospital, and the number of nights you spent in hospital (please complete a separate line for each admission if more than 1):

1. Reason for admission:_____________________________________
   Number of nights in hospitals: ☐

2. Reason for admission:_____________________________________
   Number of nights in hospitals: ☐

3. Reason for admission:_____________________________________
   Number of nights in hospitals: ☐

Questionnaire developed by:

Jon Karnon
Professor in Health Economics
School of Population Health and Clinical Practice
University of Adelaide
APPENDIX XIII: RAVES Patient Information and Consent Form

PATIENT INFORMATION AND CONSENT FORM

Amendment 1: 8 July 2011

Site: [Add your institution’s name]

Full Project Title: A phase III multi-centre randomised trial comparing adjuvant radiotherapy (RT) with surveillance and early salvage RT in patients with positive margin or extraprostatic disease following radical prostatectomy

Short Title: RAVES: Radiotherapy – Adjuvant Versus Early Salvage

Study Number: TROG 08.03

Principal Researcher: [Add name]

Please make sure you have all [Add number] pages of this document.

Introduction
You are invited to participate in a clinical trial (a type of research study). This Patient Information Sheet explains the research project and the procedures involved. Its purpose is to help you decide if you want to take part in this research. Please take your time to make your decision. You may wish to discuss it with your friends and family.

Participation in this research is voluntary and you may refuse to participate or withdraw from the trial at any time, without penalty or loss of benefits to which you are entitled. If you decide you want to take part in the research project, then you will be asked to sign the Consent Form. By signing it you are telling us that you:

- Understand what you have read in the information sheet
- Consent to taking part in the research project
- Consent to the use of your personal and health information as described in the information sheet.

You will be given a copy of this Patient Information Sheet and Consent Form to keep as a record.

Background and Purpose of Study

You have been invited to take part in this research study because:

- You have already had surgery to remove your prostate cancer (called a “radical prostatectomy”)
- The features of your cancer (as determined by a pathologist after the surgery) indicate the risk of the PSA (prostate specific antigen) rising again may be higher than other patients. This rise in PSA can indicate the cancer is coming back although this can take months to years to occur. In some patients the cancer may never cause symptoms even though the PSA rises.
The features the pathologist describes which determine whether you are at higher risk of the PSA rising again include finding prostate cancer in one of the following areas:

- At the edges of the prostate gland and surrounding tissue that was surgically removed.
- Outside the capsule that encloses the prostate.
- In the seminal vesicles (the glands that sit above the prostate).

If you have one or more of these risk factors, you have nearly a 50% chance the PSA can rise again at some stage in the future. There are currently two ways of managing men who have these high risk features after a radical prostatectomy.

1. The first option is to give radiotherapy immediately after surgery to everyone. We know from several large studies that giving radiotherapy to everyone immediately after surgery will halve the risk of the PSA rising again. This means that only half of the men who have radiotherapy benefit from it. Unfortunately we don't know which men benefit from radiotherapy and which don't. It would be simple to give everyone radiotherapy if there were no side effects but many men experience unpleasant side effects (these are described in section 8).

2. The second alternative is to watch men very closely (“active surveillance”) with regular clinic visits and regular PSA blood tests. The PSA blood test can detect activity of the cancer months or years before other tests and usually long before any symptoms appear. Radiotherapy is only given if the PSA starts to rise. In this situation nearly half the patients would be spared the possible side effects of radiotherapy.

It is not known whether these 2 ways of managing men with high risk features are the same in controlling the PSA in the long term. In one group of men radiotherapy is given to everybody with high risk features after surgery where as in the other group radiotherapy is only given if the PSA starts to rise. The aim of the study is to therefore see whether patients treated with active surveillance (and giving radiotherapy as soon as the PSA rises) is as good as immediate radiotherapy. This study will also compare the side effects occurring in each treatment group and what affect the treatments have on quality of life. It will also compare whether the 2 ways of managing men with high risk features results in the same percentage of men who are alive and without prostate cancer.

It is important to note that even if you have radiotherapy (either immediately after the operation or when the PSA rises after active surveillance) that the PSA may continue to climb afterwards indicating that the cancer is still active. Reasons why the radiotherapy may not be of benefit include that there are prostate cancer cells in some other part of the body or the radiotherapy did not get rid of the cancer remaining in the area where the prostate was.

**What Is Involved In The Study?**

**Participation:**

In order to clearly determine the most effective treatment, following surgery, in men that have been diagnosed with the particular type of prostate cancer that you have, approximately 470 men from New Zealand and Australia are required for this study.

**Randomisation (placement in a group):**

If you decide to participate you will be "randomised" into one of the study groups described below. Randomisation means that you are put into a group by chance. Neither you nor your
doctor can choose what group you will be in. You will have an equal chance of being placed in either group. You will be told which treatment you are to get.

1. Immediate radiotherapy (radiotherapy will start within 6 months of previous prostate surgery)
   
or
   2. To be watched very closely with regular clinic visits and PSA blood tests (“active surveillance”) and to receive radiotherapy only if your PSA level begins to rise.

Treatment:

Group 1: Immediate radiotherapy

If you are allocated to the immediate (within 6 months of surgery) radiotherapy group, you will receive a course of radiotherapy to the area where the prostate gland used to be (the prostate bed). Before starting the radiotherapy you will have a CT scan of this area, this is used to plan the radiotherapy. The radiotherapy is given over about 6 and half weeks. You will need to come in for treatment 5 times a week and you will have a total of 32 treatments. Each radiotherapy treatment will take approximately 15 minutes each day. Following the radiotherapy, review appointments and investigations will be carried out every 6 months including PSA blood testing. We are also interested in the after effects of radiotherapy and your doctor will ask you about any changes to your urinary, bowel or sexual function which may be side-effects of the radiotherapy.

Group 2: “Active surveillance” and delayed radiotherapy if necessary

If you are allocated to the “active surveillance” group, you will be seen in clinic at regular intervals by your doctor for routine check-ups and blood tests. The PSA blood test is done every 3 months in the first 5 years then every 6 months thereafter. It is expected that only half of the patients in the “active surveillance” group will have a rise in the PSA. If the PSA rises above a low set level you will receive radiotherapy in exactly the same way as Group 1 patients (described above). Following radiotherapy you will be clinically monitored every 6 months as described for Group 1.

Procedures and Medical Tests:

The following tests will be done at the hospital or clinic to make sure that you are eligible for this study. None of these tests are experimental. They are routine and would be done before starting your cancer treatment, even if you were not taking part in this study.

- Medical history
- PSA blood tests (2 teaspoons of blood required per test)

The needles used to take blood or inject substances for body scans might be uncomfortable. You might get a bruise, or rarely, an infection at the site of the needle puncture.

Many of these tests will also be repeated during the study. Some of these tests may be done more frequently than if you were not taking part in this research study.
Questionnaires:

Four (4) questionnaires are included in this study that are designed to help us understand how your treatment and illness affect your quality of life and feelings (mood).

You will be asked to complete most of these questionnaires at the following times:
- Before starting the study
- On the first day you receive radiation therapy,
- On the last day of radiation therapy,
- 6 weeks following the completion of radiotherapy
- Annually after enrolling on this study

The questionnaires ask about how you are feeling and take about 10 minutes to complete. Some of the questions are personal; you can refuse to answer these if you wish. One additional questionnaire will ask for information about some types of medical care you may have received between clinic visits. This questionnaire will be given to you annually throughout your participation in the study.

The information you provide is for research purposes only and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions—if you wish them to know this information please bring it to their attention.

Other Treatments Whilst on Study

It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies and any changes to these during your participation in the study. You should check with your doctor before taking any new medications while on the study, unless such medications are prescribed by another doctor in an emergency situation, in which case, you should notify the doctor who has enrolled you on this study of these medications as soon as possible.

Collection and Use of Tissue Samples

By consenting to take part in this study, you are also consenting to the collection and use of tissue samples for diagnostic testing as outlined below.

To confirm your cancer diagnosis

To make sure you have the type of prostate cancer that is being studied in this research study, a small sample of your tumour will be sent to a central laboratory in Australia where it will be examined to confirm your diagnosis. This is called “Central Pathology Review” and is a necessary part of this study. The tumour sample needed for this review will be from your cancer that has already been removed by surgery. The samples will be returned to your hospital's pathology department after completion of the review.

How Long Will I Be in the Study?

After enrolment into the study you will be followed for 10 years (minimum).

The researchers can take you off the study treatment early however for reasons such as:
- The treatment does not work for you
- You are unable to tolerate the study treatment
• New information shows that the study treatment is no longer in your best interest
• Your doctor no longer feels this is the best treatment for you
• Decisions made by the sponsor (TROG) or local regulatory/health authorities

Voluntary Participation and Withdrawal

Participation in this research is voluntary and you may refuse to participate or withdraw from the trial at any time, without penalty or affecting your routine treatment, your relationship with those treating you or your relationship with the institution where you are receiving your treatment.

If you join the research study and then decide to leave, please notify a member of the research team beforehand. This notice will allow a member of the research team to inform you of any health risks or special requirements linked to withdrawing or stopping your study treatment. If you do decide to leave the research study it will not be possible to withdraw the information that has been collected before your decision to withdraw.

What are the Risks of the Study?

Most men will experience some side effects from radiotherapy. Your doctor will watch you closely to see if you have side effects. Should you suffer any side-effects please notify the research team (your doctor or research nurse) as soon as possible. When possible other drugs will be given to you to make side effects less serious and uncomfortable. Many side effects go away shortly after therapy is stopped but in some cases side effects can be serious, long-lasting or permanent.

Radiotherapy Side Effects:

Short-term:

• Tiredness/fatigue during radiotherapy.
• You may pass urine more often, experience possible discomfort and slowing of the stream when passing urine.
• In patients with urinary incontinence (leakage of urine) after surgery the incontinence may become worse following radiotherapy. Radiotherapy may also cause urinary incontinence in patients who have no leakage after surgery
• You may notice more frequent bowel motions and there may be mucus or spotting of blood with the bowel motion. It may be uncomfortable to pass a bowel motion.
• Change in colouration of the skin (reddenning or tanning) and hair loss in the treatment area.

Long-term:

• Some men notice that their bowel habit changes permanently (often more frequent). It is quite common to have the occasional minor spotting (bleeding) with the bowel motion.
• A very few people have more persistent bleeding or bowel irritation, and this very occasionally (1-2%) needs surgery to deal with it.
Radiotherapy is also likely to have a negative effect on the recovery of erections or sexual functioning. This is more likely to happen if there were difficulties prior to treatment.
Serious injury to the bladder, bowel, urethra or other tissues in the pelvis is rare.

As with any medical treatment, there is also the chance of experiencing an unknown or unforeseen side-effect.

In the group of patients receiving radiotherapy straight after surgery there are the risks of the side effects of radiotherapy (as described above). However, if you start radiotherapy later, it is possible that the radiotherapy may be less effective. We do not know which is best, which is why we are conducting the study.

Are There Benefits to Taking Part in the Study?

If you agree to take part in this study, there may or may not be any benefit to you. We hope that the information from this study will benefit other patients in the future.

New Information Arising During the Study

During the research study, new information about the risks and benefits of the study may become known to the researchers. If this occurs, you will be told about this new information and your doctor will discuss whether this new information affects you.

Alternatives to Joining this Research Study

If you decide not to take part in this study, your doctor will discuss other treatment options with you. These may include other experimental therapy or no therapy at this time. Please talk to your doctor about the known benefits and risks of these other treatment options.

Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this research study that can identify you will remain confidential and will only be used for the purpose of this research study. It will only be disclosed with your permission, except as may be required by law.

Your medical records and any information obtained during the trial are strictly confidential and will not be made publicly available. Only authorised individuals from the following organisations will have access to your information:

- The Trans-Tasman Radiation Oncology Group (TROG) who co-ordinate the study in Australia and New Zealand
- Institution where you are receiving your treatment.
- Central review laboratories (because they examine tissue for confirmation of diagnosis)
- Regulatory Authorities

Your de-identified, trial-related information will be securely stored by Auckland Hospital for a period of 15-years. When the results of the trial are presented at scientific meetings or published in a medical journal no individual participant will be recognisable from the data presented. In any publication, information will be provided in such a way so you cannot be identified. By signing the attached Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities.
Your family doctor will be advised of your decision to participate in this study after you have signed the Consent Form. By signing this form you give permission for doctors, other health professionals, hospitals or laboratories outside this hospital to release information to \[\text{name of institution}\]. concerning your disease and treatment that is relevant for this study. This information will remain confidential as described above. By signing this form, you authorise the release of, or access to the information collected about you as described in this section, even in the event of your death.

In accordance with the *Freedom of Information Act* [Year, State], you have the right to access and to request correction of information held about you by \[\text{name of institution}\].

**Results of the Project**

It may be a number of years before the results of this research are available. The results are published in medical journals that are available to the public. Your study doctor will be informed of the results of the study once they are known. Please ask your doctor if you want to know more about this.

**What are the Costs?**

You will not be paid for taking part in this study.

Participating in this study will not incur additional costs to you compared to not participating and receiving standard treatment.

**Insurance and Compensation**

This cancer research trial is sponsored and coordinated by the Trans Tasman Radiation Oncology Group (TROG), a not-for-profit research group involving many cancer researchers in Australia and New Zealand, as well as internationally.

If you suffer any injuries or complications that may be as a result of your participation in this cancer research trial, you should immediately contact your doctor, who will assist you in arranging appropriate medical treatment, at no cost to you.

In the unlikely event of an injury caused by your participation in this cancer research trial, compensation may be payable to you. TROG maintains a clinical trials insurance policy to protect you in these circumstances.

The insurance policy has principles about when compensation is payable and the amount to which you may be entitled, which include:

- Compensation will depend on the nature, severity and ongoing nature of the injury.
- Compensation will only be paid for injury of a serious and enduring character and not for temporary pain or discomfort or less serious or readily curable complaints.
- Compensation will only be paid when, on the balance of probabilities, the injury was caused by the administration or use of any drug, product or treatment involved in the trial or was directly caused by your participation in the trial.
- Compensation will not be paid for the failure of a drug, product or treatment under trial to perform its intended purpose.
The amount of any compensation should be agreed between you and the sponsor of the cancer research trial (TROG), or by an independent lawyer if agreement cannot be reached.

Funding/Conflict of Interest

Apart from their standard salary, the researchers will not be paid for doing this research.

The institution where you are receiving your treatment is receiving funds from a number of funding bodies to help offset the costs of conducting this research.

Approval by a Research Ethics Committee

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to take part in research.

The ethical aspects of this research project have been approved by [add the name of the HREC that approved this study].

Further Information or Any Problems

If you have questions concerning this study or if you suffer a study-related medical problem (for example, any side effects) you can contact the principal researcher [insert name and ph. number] or any of the following people: [list names and contact phone numbers, including after hours number(s)].

Name: 
Telephone:

If you have a complaint about this project or would like any advice regarding your rights as a patient, you can talk to someone who is not involved in the study at all. That person is:

Name: [e.g. Executive Officer of the HREC]
Position: 
Telephone: 

You will need to tell [insert name] the name of one of the researchers given above.
CONSENT FORM
Amendment 1: 8 July 2011

Site: [Add your institution’s name]

Full Study title: A phase III multi-centre randomised trial comparing adjuvant radiotherapy (RT) with surveillance and early salvage RT in patients with positive margin or extraprostatic disease following radical prostatectomy.

Short Title: RAVES – Radiotherapy Adjuvant versus Salvage

Study Number: TROG 08.03

Principle Researcher: [Add name]

My signature on this consent form means the following:

- The study has been fully explained to me and all of my questions have been answered,
- I understand the requirements and the risks of the study,
- I agree to be selected, at random, into one of the study groups as described in section 3 of this Patient Information and Consent Form,
- I authorize access to my medical records as explained in this consent form,
- I authorise the collection and testing of my tissue samples for the mandatory components of this study, and
- I agree to take part in this study.

Participant’s Name (printed) ………………………………………………………………………………..
Signature Date

Name of Impartial Witness as required (printed) ………………………………………………………
Signature Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher’s Name (printed) ………………………………………………………………………………..
Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.
REVOCATION OF CONSENT FORM

Site: [Add your institution’s name]

Full Study title: A phase III multi-centre randomised trial comparing adjuvant radiotherapy (RT) with surveillance and early salvage RT in patients with positive margin or extraprostatic disease following radical prostatectomy.  

Short Title: RAVES – Radiotherapy Adjuvant versus Salvage  
Study Number: TROG 08.03  

Principle Researcher: [Add name]

I hereby wish to WITHDRAW my consent to participate in the research proposal named above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with the institution where I am receiving treatment.

Participant’s Name (printed) …………………………………………………………………

Signature ................................................................. Date
APPENDIX XIV: RAVES Biological Sub-study Patient Information and Consent Form

PARTICIPANT INFORMATION SHEET
Optional Genetic Studies

TROG 08.03 RAVES: Radiotherapy – Adjuvant Versus Early Salvage
A phase III multi-centre randomized trial comparing adjuvant radiotherapy with surveillance and early salvage RT in patients with positive margin or extra prostatic disease following radical prostatectomy

OPTIONAL TISSUE STUDIES

A. RAVES Genetic Study: Genetic basis of response to radiotherapy in prostate cancer patients
B. RAVES Tissue Banking Study

PRINCIPAL INVESTIGATOR: Add local details here

If you require an interpreter, please let us know as one can be provided.

INTRODUCTION

You are invited to take part in two separate projects because you have consented to participate in the Trans-Tasman Radiation Oncology Group 08.03 (RAVES) study, which is looking at treatment for prostate cancer.

Participation is voluntary. You may choose to participate in both, one or neither of the projects. You will receive the best possible care whether you take part or not.

Please read this participant information sheet carefully. Feel free to ask questions about any information contained in this sheet. Before deciding whether or not to take part, you may wish to discuss the project with your family, friends, or your doctor.

If you decide to take part in any of the projects, you will be asked to sign the consent form(s). By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep for your records.

WHO CAN PARTICIPATE IN THE RESEARCH?
All patients who have been diagnosed with prostate cancer and are enrolled in the Trans-Tasman Radiation Oncology Group (TROG) 08.03 RAVES trial will be asked whether they would like to participate in the RAVES Genetic Study and/or the RAVES Tissue Banking Study.

WHAT DOES THE RESEARCH INVOLVE?
Both studies involve asking your permission for researchers to collect and store samples for future research projects:

• Option A: RAVES Genetic Study
  Donation of a saliva or blood sample and completion of one questionnaire

  You will be given the option of providing either a saliva or blood sample. Your saliva or blood will provide a sample of your DNA, which is the chemical compound that genes are made of. Genes are inherited from both parents. The mixture of genes a person has, or alterations in these genes, may lead to a medical problem or vary the response to the treatment of a medical problem.

  If you consent to the RAVES Genetic Study and wish to donate saliva, you will be asked to collect into a specially prepared container. Alternatively, if you would rather donate blood, the sample will be taken by a suitably qualified person at your local hospital. DNA will be extracted from your saliva or blood and stored in a small plastic tube in a secure freezer.

• Option B: RAVES Tissue Banking Study
  Donation of the prostate tissue sample already collected at the time of your surgery for prostate cancer and potential completion of questionnaires

  When your prostate was removed it was sent to a pathology laboratory for examination. The first step in this process was to put pieces of it into paraffin (wax) blocks. These blocks are cut into very thin slices so that a pathologist can examine them under a microscope and send a report to your doctor. After the diagnosis has been made, there is usually tissue left over in these wax blocks, which are generally stored or “archived” indefinitely in the laboratory. These blocks are normally not used again following your diagnosis, although on rare occasions they are retrieved and looked at again. We are asking for your permission to obtain this stored material so that it may be used for research in the future. A collection of many of these blocks for research purposes is termed a tissue bank.

  If you consent to Option B, there is no guarantee that any of your tissue will be able to be put into the tissue bank. The pathologist at your local laboratory will decide if there is enough tissue available to donate. We are asking your permission to contact the laboratory where your biopsy specimen is held, and ask them to give us a small piece of that specimen that they no longer needed. Retrieving and processing the tissue does not require anything extra from you.
For both Option A and Option B:

**Questionnaires:** For both studies, you will be asked to complete questionnaires about your personal background, ethnicity, family cancer history, current medical conditions and medications. This will help researchers understand how a person’s genetic makeup might affect response to treatment for prostate cancer.

**Access to your medical records:** We will ask your permission to access medical information collected from you for the RAVES trial and during your routine clinic visits. Your medical information from the trial is necessary to provide background information about you, as well as information about your diagnosis, treatment and response to treatment for prostate cancer. In addition, we would like to follow your progress after your treatment by collecting information from various health agencies (such as medical practitioners, pathology laboratories or hospitals), your medical records or cancer registries and attaching it to your specimen in an anonymous manner. This information is very important in understanding findings related to the specimens you have donated. No personal information will be collected without your permission. By signing this form you authorise the release of, or access to the information collected about you as described in this section, even in the event of your death.

**WHAT IS A TISSUE BANK?**

A Tissue Bank collects and stores tissue, blood and other samples for future research purposes. These samples are labelled with a unique code number so as to protect the identity of the donor. When researchers wish to study certain diseases, such as prostate cancer, they can apply to the Tissue Bank to obtain coded samples. These samples can only be released to future researchers if the Tissue Bank has written evidence of Human Research Ethics Committee approval for their research projects. Relevant medical history and clinical information of people who have donated tissue and blood samples are also collected by the Tissue Bank. This information is stored in a secure database in a separate location from the tissue.

The purpose of the tissue collection and “banking” is to enable future research to be done on cancer. In your case, researchers are interested in understanding how to make the treatment of prostate cancer better by examining the cancer (and sometimes normal tissue) in great detail in the laboratory.

The first step in doing this is to obtain sample(s) from many men with prostate cancer, along with their treatment records. This research depends on people like you to donate samples for research as a “gift.”

The Trans Tasman Radiation Oncology Group is collaborating with two established tissue banks to bank and process the specimens:

- **RAVES Genetic Study (Option A):** DNA will be extracted from your saliva or blood and stored at the Western Australian DNA Bank, which is led by the Centre for Genetic Epidemiology and Biostatistics (C Geb) at the University of Western Australia. The WA DNA Bank has received formal recognition from a number of Human Research Ethics Committees. It does not recruit donors but provides the infrastructure and personnel to handle and process the bio-specimens for medical researchers using this facility. For safety the DNA collections are housed in two secure cryo-facilities in the basement of E-Block at Sir Charles Gardner Hospital in Perth and Royal Perth Hospital.
RAVES Tissue Banking Study (Option B): Prostate specimens from your surgery will be banked at the Australian Prostate Cancer BioResource. The tissue bank maintains tissue storage facilities in several capital cities in Australia, which are linked by a comprehensive database. Each facility has received approval from its Institutional Ethics Committee to collect and store blood and tissue from patients for future research purposes.

WHAT WILL HAPPEN TO MY DONATED SPECIMEN(S)?
Your saliva, blood or tissue will be packaged in a secure manner and shipped to whichever facility will store it. Specimens will be stored indefinitely, until they are used up or until you contact RAVES trial staff in the event that you change your mind about participating. In the case of your surgery specimen, your local laboratory may request that it be returned, if needed.

Any DNA donated for research will be stored in accordance with the National Health & Medical Research Council's Guidelines for Genetic Registers and Associated Genetic Material. Storage will be conducted under a coded system, to ensure that your confidentiality is maintained.

WHAT KINDS OF RESEARCH WILL MY SALIVA, BLOOD OR TISSUE BE USED FOR?
Because new techniques to look at genes in relation to cancer treatment are regularly developed, it is not possible for researchers to specify now how your tissue or DNA will be studied. However, having access to a collection of donated specimens allows researchers to make discoveries as new techniques become available. The most important discoveries will be directed to improvements in the diagnosis, monitoring and treatment of prostate cancer.

In addition to providing information that will help develop future treatments, your blood or saliva sample will be used to investigate whether genetic make-up has an effect on radiation therapy adverse experiences or “side effects”. This information may identify new ways that DNA is linked with radiotherapy side effects, which in turn would require further investigation. Your DNA will not be used for research that involves reproductive cloning. No researchers will be permitted to derive a genetic profile of you as an individual.

Your sample may be provided to approved researchers from hospitals, universities, medical research institutes, government affiliated institutions and sometimes commercial organisations, such as pharmaceutical companies. Data provided for other research studies will be identified only by a study identification number and not with your name. Researchers will be required to have approval from a Human Research Ethics Committee, who will ensure access to the data abides by the Australian guidelines and statutes that govern the Tissue Banks. Some research studies in cancer may involve sending your DNA interstate and overseas. If this is the case, these researchers are required to demonstrate that they meet the appropriate Australian standards of ethics and privacy as detailed below.

WHAT ABOUT CONFIDENTIALITY?
The RAVES study managers are committed to making sure that information about you is kept safe and in strict confidence. Personal information that can identify you, such as your name or date of birth is removed and replaced with your RAVES identifying code before it is sent to the tissue bank. Only your local hospital staff will be able to link your name with your trial code. The Tissue Bank will assign a further unique number code to your specimen(s), and anyone who studies your specimens will only be supplied with your coded sample(s) and data. Only authorised Tissue Bank staff will be able to break this code. This ensures that nothing that can identify you or your family will ever appear on any public or published reports. Access to your DNA donation for future research will be managed by an Advisory Committee and only released where the research project that wishes to use it has been approved by a Human Research Ethics Committee. International research collaborations...
using your information and/or tissue or DNA sample will only take place where researchers abide by equal or more stringent regulations of privacy and ethics as those in Australia, as assessed by a Human Research Ethics Committee.

Personal information, such as health information will remain privileged and confidential, except as required by law. By signing the attached Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities.

To ensure that these policies are followed, Human Research Ethics Committees monitor all research projects they approve. This is usually done annually, by requesting a report from the Chief Investigator for the research project. This report covers matters such as the maintenance and security of records and compliance with the project as originally approved.

**WILL I FIND OUT THE RESULTS OF THE GENETIC STUDY OR TISSUE BANK RESEARCH?**

You have the legal right to access your permanent medical records at any time, but specific research results will not be part of this record. Information from the sample(s) you may donate is not intended to be used in your diagnosis or treatment. Feedback will not normally be given to participants regarding personal information. This is because prostate cancer is thought not to be a single-gene disease (such as cystic fibrosis), but a complex disease with many genes and other factors contributing to its development and progression. We do not yet know exactly how these elements all interact, so releasing personal information would not be clinically meaningful or useful to you or your family.

**WILL MY FAMILY BE ABLE TO REQUEST STUDY RESULTS IN THE FUTURE?**

You should consider whether or not any significant health information obtained as a result of the genetic studies should be disclosed to your family members or descendents in the future. We will ask whether you consent to the disclosure of your information to your family members or descendents on the attached consent form. Family members would have to supply a written request to the Chief Investigator, and a Human Research Ethics Committee would review and consider the request to disclose information. If you do decide to participate, please consider advising your family members of the purpose for which you have provided your samples.

**WILL MY SAMPLES EVER BE SOLD?**

Your samples will NOT be sold. The Tissue Banks may charge researchers a fee to recover some of the costs of storing and administering its collection of tissue. Although knowledge acquired through medical research may lead to discoveries that are of commercial value to the researcher and their institution, there will be no financial benefit to yourself, your family or the Tissue Banks.

**WHAT ARE THE BENEFITS OF TAKING PART?**

It is unlikely that there will be a direct benefit to you or your family from participating in these studies. Your samples may not be used for many years until a new and as yet undiscovered approach to study cancer is developed. These studies may ultimately benefit other patients with prostate cancer, through new understandings about treatment and responses to treatment. The aim of these sub-studies is to improve the health of patients with prostate cancer. However, sometimes research on your tissue may lead to findings that result in the development of a commercial test or treatment that may be overseen by other groups, including private companies. There will be no financial reward or payment to you in such an event and by participating, you will waive all claims to patents, commercial returns, property or any material or products which may arise from these studies.
WHAT ARE THE RISKS OF TAKING PART?

There are no documented risks or adverse experiences from saliva sample collection.

If you opt to donate a blood sample, it may hurt for a short time and you may get a bruise. The amount of blood to be taken is small and you should not notice its loss. Infection at the site where blood is taken is very unlikely, as the skin is cleaned first with an antiseptic and sterile equipment is used. This procedure can also occasionally cause light headedness or fainting. These reactions are usually mild, of short duration and limited to a feeling of weakness, accompanied by sweating, slowing of heart beat, and a decrease in blood pressure.

For the patient surveys, it is possible that answering the questions could be upsetting. For instance, the surveys may arrive at a time when you are not feeling well or you are feeling anxious. Of course, you may decline to participate in a survey or to answer a specific question in the survey.

There is a risk that your information may be released without your permission, and measures have been taken to minimize this risk, as described in the section on Confidentiality above. It is important to note that there may be circumstances where disclosure of your health information kept by the study teams could be obtained, for example, if requested by law as a result of a court order.

Genetic research risks:

Genetic research involves the study of genetic material (DNA), which is shared with your blood relatives. Genetic research raises many important issues. It is unlikely that these issues will arise, but you should think about them carefully. Genetic research is undertaken to discover more accurate ways of predicting diseases within a group of people or in people where there is a strong family history or predisposition of disease. To perform such studies, a researcher must demonstrate to a Human Research Ethics Committee that procedures are in place to deal with certain issues which may arise.

The vast majority of research projects for which your tissue might be used are unlikely to reveal anything of medical importance specifically for you or your family. However, if that should happen and a discovery is made that predicts a possible medical condition, the researcher is required to inform the appropriate Human Research Ethics Committee. If the Committee considers that this knowledge may be of medical significance to you and/or your family, a member of the research team would contact you through your doctor and give you the option of learning more about the findings. If we are unable to contact your doctor, we will make a reasonable attempt to contact you at your address provided or any updated address that you might care to provide.

Learning the results from genetic research might create uncertainty or be upsetting; if for instance, the risk of developing a disease is identified which has no known prevention, treatment or cure. Some people may learn disturbing information about inherited diseases or a disorder involving their children, brothers or sisters. This could interfere with family relationships. You may be faced with the question of “Should I tell the family?” Other family members may or may not wish to know this information. It is important to understand that results from genetic research usually will not indicate that you have a disease or disorder, or whether you will develop it. The results can only show that you have an increased risk of developing a disease or disorder, but there would still be no guarantee that you will develop the condition. Any research results that could be of significance to you or your family will need to be repeated and verified. This may involve having a blood sample taken and having it retested in an official testing laboratory. This is standard practice for all patients receiving the results of genetic testing and would be provided free of charge to you. Counselling may also be provided free of charge if it is appropriate. Before a test is repeated to verify a
research finding you will be informed about the possible risks involved. This is especially important for individuals who are found to have a gene mutation, which increases their risk of disease or cancer. Knowing such information could lead to job discrimination and difficulties in obtaining some forms of insurance.

On the Consent Form you will be given the option of having your sample excluded from Study B (RAVES Tissue Bank) research that identify genes or diseases that run in families, for example, diseases that can be passed on (through DNA) to blood relatives. Whatever choice you make, your privacy will be protected and your decision will be respected.

We ask you to keep your local hospital up-to-date with your contact details even after the RAVES study has finished.

**WHAT ARE THE COSTS TO ME?**
You would not be charged for any tests or samples taken as part of the study. You will not be paid for taking part in this study. There will be no financial reward or remuneration to you. Participating in this study will not incur additional costs to you compared to not participating.

**WHAT HAPPENS TO MY SAMPLE(S) AFTER MY LIFETIME?**
In the event of your death, the study teams will continue to store your samples and make them available for use by researchers. Your gift will continue to be used in cancer and other bio-medical research subject to the same legal and ethical standards discussed in this document. On the Consent Form you may nominate a representative to be contacted about any matters that we would have contacted you about. This person should be a blood relative or spouse/partner and you should discuss the implications of your donation with whomsoever you nominate. If you decide to participate, please consider advising your family members or the Executor of your Will of the existence of your sample(s); perhaps even provide them with a copy of this Information Sheet and your signed Consent Form.

**WHAT DO I NEED TO DO TO PARTICIPATE?**
If you have read this information sheet and would like to participate, then please:

- Discuss any questions you may have with the clinic staff at your hospital.
- Once your questions have been answered, if you still wish to participate, please carefully read the consent form and sign it together with your doctor.
- Indicate which study option(s) you have selected.
- Clinic staff will then provide instructions about the study:

**WHAT IF I DO NOT WISH TO PARTICIPATE IN EITHER STUDY?**
If you do not wish to participate, you do not need to do anything further. Your decision will in no way affect your level of healthcare, your relationship with your doctor, or your continuing participation in the TROG 08.03 RAVES trial.

**WHAT IF I CHANGE MY MIND?**
You are free to withdraw from either study at any point without giving a reason. If you decide to withdraw from the study, you can choose to let the tissue banks keep and use the DNA sample or tumour block for future cancer research or request that the sample(s) be destroyed or returned. If you would like to withdraw from either study, please contact study staff in writing:

[Insert details of local Principal Investigator or Study Coordinator]

XXXXX
XXXXX
XXXXX
STATEMENT OF APPROVAL:
The [INSERT LOCAL ETHICS COMMITTEE NAME] has reviewed this study and has given its approval for the conduct of this research trial. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

All current and future studies will only be conducted after approval of an Institutional Review Board (IRB)/Human Research Ethics Committee (HREC). No tissue or health information will be released to a third party unless it is to carry out research that has been approved by a Human Research Ethics Committee.

CAN I CONTACT ANYONE WHO IS INDEPENDENT OF THE STUDIES?
If you have a complaint about this project or would like any advice regarding your rights as a patient, you can talk to someone who is not involved in the study at all.

Name:
Position:
Telephone:

You will need to tell [INSERT LOCAL CONTACT] the name of one of the researchers listed at the beginning of this document.

FURTHER INFORMATION
Please feel free to ask your doctor any questions at your next clinic appointment. If you need further information, please contact:

[Insert local study coordinator details here]

Thank you for considering this invitation.

You will be given a copy of this Participant Information Sheet to keep for your records.
PARTICIPANT CONSENT FORM

TROG 08.03 OPTIONAL TISSUE STUDIES

Study A. RAVES Genetic Study: Genetic basis of response to radiotherapy in prostate cancer patients

Study B. RAVES Tissue Banking Study

TROG 08.03 RAVES: Radiotherapy – Adjuvant Versus Early Salvage
A phase III multi-centre randomized trial comparing adjuvant radiotherapy with surveillance and early salvage RT in patients with positive margin or extra prostatic disease following radical prostatectomy

PRINCIPAL INVESTIGATOR: Local Investigator Details

Please read this consent form carefully.

My signature on this consent form confirms the following:

- I have read, or have had read to me in a language I understand, the Patient Information Sheet and Consent Form (Version 2, dated 10/05/11).
- I have had an opportunity to ask questions, and I am satisfied with the answers I received. The research objectives have been fully explained to me. I have understood the Patient Information Sheet, which describes the purpose of the studies and what my participation involves. I have been given the opportunity to have a member of my family or a friend present while the study was explained to me.
- I understand that my involvement in the study is voluntary and it will not affect my relationship with my medical advisers in their management of my health. I also understand that I am free to withdraw from the study at any stage without my future treatment being affected. I may do this by contacting RAVES trial staff at my local hospital.
- I understand that the results of the research may be of interest to my immediate family, including my descendants, and I may decide whether or not the information may be disclosed to my family in accordance with ‘Options for disclosure to family members’ section detailed below.
- The Chief Investigator of this project and his associates involved with this project will not be liable for any loss or damage to the saliva, blood or tissue taken or used in accordance with this form.
- I give permission for the release of information concerning my disease and treatment as outlined in the Patient Information Sheet.
**Consent to participate in Study A and/or Study B:**

### Study A:

<table>
<thead>
<tr>
<th>I consent to donate a saliva or blood sample to the RAVES Genetic Study / Centre for Genetic Epidemiology for DNA extraction, storage, testing and research. I have been advised what sample is being collected, what the purpose of this is and what will be done with the sample.</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>I give my consent for the RAVES Genetic Study, the Centre for Genetic Epidemiology and Biostatistics at the University of Western Australia to use my information and samples, including my health information collected in this study, for future medical research.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I consent to my information and tissue sample to be available to researchers working with the Western Australia DNA Bank, some of which may be in different countries.</td>
<td>Yes</td>
<td>No</td>
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### Study B:

| I agree to allow my archived tissue surplus to diagnostic requirements to be obtained from the place of its storage and provided as a “gift”.
- I understand that the tissue samples (including their constituents and anything derived from them) will be stored indefinitely in the Australian Prostate Cancer BioResource Tissue Bank
- I understand that my tissue may be used for future studies of prostate cancer. These may be biochemical or genetic studies provided I have not stipulated otherwise below.
- I give permission for my tissue to be used in any way that The Australian Prostate Cancer BioResource and the RAVES study managers deem beneficial. | Yes | No |
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<tr>
<td>I consent for genetic research to be performed on my tissue samples</td>
<td>Yes</td>
<td>No</td>
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### Options for disclosure to family members: Please tick one box only

I understand that future DNA (genetic) testing may result in new information about diseases or potential diseases that may have health implications for my family, including my descendants. I understand that extensive testing and validation would be required before the information can be determined to be useful and that information can only be provided after careful consideration by a Human Research Ethics committee, through approved medical channels, and when there is clear evidence of the medical importance to my family.

- [ ] I DO consent to genetic information obtained from my DNA as a result of this study being revealed to my family members, upon their written request to the Chief Investigator, in the event of my death.

- [ ] I DO nominate a representative to be contacted about any matters that study staff would need to contact me about, in case I am unable to be reached:

  Name: ________________________________

  Address: ________________________________

- [ ] I DO NOT consent to genetic information obtained from my DNA, as a result of this study, being revealed to my family members, upon their written request to the Chief Investigator, in the event of my death.
If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your doctor before signing this Consent Form.

**PATIENT STATEMENT & SIGNATURE**

**Statement by Participant:** *I hereby consent to take part in this study and I will be given a copy of this signed and dated consent form.*

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<th>Printed Full Name</th>
<th>Signature</th>
<th>Date (Personally Dated)</th>
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**Witness** *(optional)*
In my opinion consent was given freely

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**Interpreter** *(if applicable)*
In my opinion consent was given freely

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**Statement of Investigator**
In my opinion consent was given freely

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