TROG 03.04

TRANS-TASMAN RADIATION ONCOLOGY GROUP INCORPORATED

A RANDOMISED TRIAL INVESTIGATING THE EFFECT ON BIOCHEMICAL (PSA) CONTROL AND SURVIVAL OF DIFFERENT DURATIONS OF ADJUVANT ANDROGEN DEPRIVATION IN ASSOCIATION WITH DEFINITIVE RADIATION TREATMENT FOR LOCALISED CARCINOMA OF THE PROSTATE

Version 1 – 17 April 2003
Version 2 – 13 October 2003
Version 3 – 20 November 2003
Version 4 – 16 July 2004
Version 5 – 14 October 2004
Version 6 – 10 January 2007
Version 7 – 1 December 2011
Version 8 – 23 October 2013
Version 9 – 1 September 2016

Trial Management Committee:

Trial Executive:	Professor David Lamb (Wellington Hospital, New Zealand) Co-Chair Clinical Professor David Joseph (SCGH, Perth, WA) Co-Chair Professor Jim Denham (Calvary Mater Hospital Newcastle, NSW) Trial Director Professor Gillian Duchesne (Peter Mac, Melbourne, VIC)
Other Members:	Associate Professor Chris Atkinson (St George's Cancer Care Centre, Christchurch Hospital, NZ) Dr Lizbeth Kenny (QRI Royal Brisbane Hospital, QLD) Dr Kumar Gogna (QRI Mater Hospital, QLD) Dr John Matthews (Auckland Hospital, NZ) Dr Nigel Spry (SCGH, Perth, WA) Dr Keen-Hun Tai (Peter Mac, Melbourne, VIC) Dr Sandra Turner (Westmead Hospital, NSW) Dr Terry Diamond (St George Hospital, NSW)
Trial Manager:	Mrs Allison Steigler (University of Newcastle, NSW)
Trial Statistician:	Professor John Attia
Trial Pathologist:	Professor Brett Delahunt (Wellington Hospital, NZ)
Trial Physicist:	Dr Annette Haworth (Peter Mac, Melbourne, VIC)

Foreword

This document is intended to describe a Trans-Tasman Radiation Oncology Group (TROG) study and to provide information about procedures for entering patients. It is not intended that the protocol be used as a guide for the treatment of other patients. TROG will not accept any data for analysis unless the local ethics committee has approved this study for patient entry.

Amendments to the document may be necessary; these will be circulated to known participants in the study, but centres entering patients for the first time are advised to contact the TROG Central Operations Office, Newcastle, to confirm the details of the protocol in their possession.

Contents

GLOSSARY OF TERMS

3DCRT	Three dimensional conformal radiotherapy
ACM	All-cause mortality (previously termed Overall survival)
AD	Androgen deprivation
AE	Adverse event
ASTRO	American Society for Therapeutic Radiation Oncology
BMD	Bone mineral density
BT	Bisphosphonate therapy
BP	Bony progression
CEBT (EBT)	Conventional external beam therapy
CR	Complete response
CRFs	Case report forms
CRT	Conformal radiotherapy
DEXA	Dual energy x-ray absorption
DP	Distant progression
DRE	Digital rectal examination
EBRT	External beam radiation treatment
EORTC	European Organisation for Research and Treatment of Cancer
FA	False assessment
HDR	High dose rate
HDRB	High dose rate brachytherapy
ICRU	International Congress of Radiological Units
IMRT	Intensity modulated radiotherapy
IMI	Intramuscular injection
ITAD	Intermediate term androgen deprivation
LP	Local Progression
LH-RHa	Luteinising hormone – Releasing hormone analogue
LTAD	Long term androgen deprivation
MAB	Maximal androgen blockade
MAD	Maximal androgen deprivation
Month	One calendar month
NP	Nodal Progression
ONJ	Osteonecrosis of the jaw
OPF	Osteopenic fractures
PCSM	Prostate cancer-specific mortality
PD	Progressive disease
PSA	Prostate Specific Antigen
PSA DT	PSA doubling time
PSA-P	PSA progression
PTV	Planning target volume
QOL	Quality of life
RADAR	Randomised androgen deprivation and radiotherapy
RCT	Randomised control trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SDIC	Safety and Data Integrity Committee
SREs	Skeletal related events
STAD	Short term androgen deprivation
STI	Secondary therapeutic intervention (also known as “salvage therapy”)
TACT	Technical Advisory Committee of the Trial
TMC	Trial Management Committee
Trial Centre	Treatment Centre/Hospital where local data management resources are located
TROG	Trans-Tasman Radiation Oncology Group

OVERVIEW

Objectives of the trial

The principal objective of the trial is to test the hypothesis that 12 months adjuvant androgen deprivation using Leuprorelin acetate starting immediately after standard therapy (ie 6 months of Leuprorelin acetate before and during radiotherapy) will reduce prostate cancer-specific mortality (PCSM) when compared with standard therapy alone.

There are three secondary objectives:

(a) to test the hypotheses that 12 months adjuvant androgen deprivation (specified above) will reduce local progression (LP), distant progression (DP), secondary therapeutic intervention (STI), all-cause mortality (ACM), and improve quality of life (QOL);
(b) to test the hypotheses that 18 months of bisphosphonate therapy using zoledronic acid will reduce osteopenic fractures (OPF), improve bone mineral density (BMD), delay or prevent the onset of bony progression (BP) or metastases at any site (distant progression [DP]), delay or prevent secondary therapeutic intervention (STI), and improve quality of life (QOL) when compared to patients in this trial who are not treated with bisphosphonate therapy;
(c) to determine the nature of interactions between the total duration of androgen deprivation and:
    i the addition of bisphosphonate therapy;
    ii increasing radiation dose, within the structured radiation dose escalation program built into the design of the trial, with respect to LP, DP and PSA progression;
    iii increasing Gleason score with respect to prostate cancer specific mortality (PCSM).

A tertiary objective of the trial is to determine whether intercurrent medical conditions will impact independently on delayed radiotherapy morbidity and other treatment related morbidity.

Study Schema

Eligibility

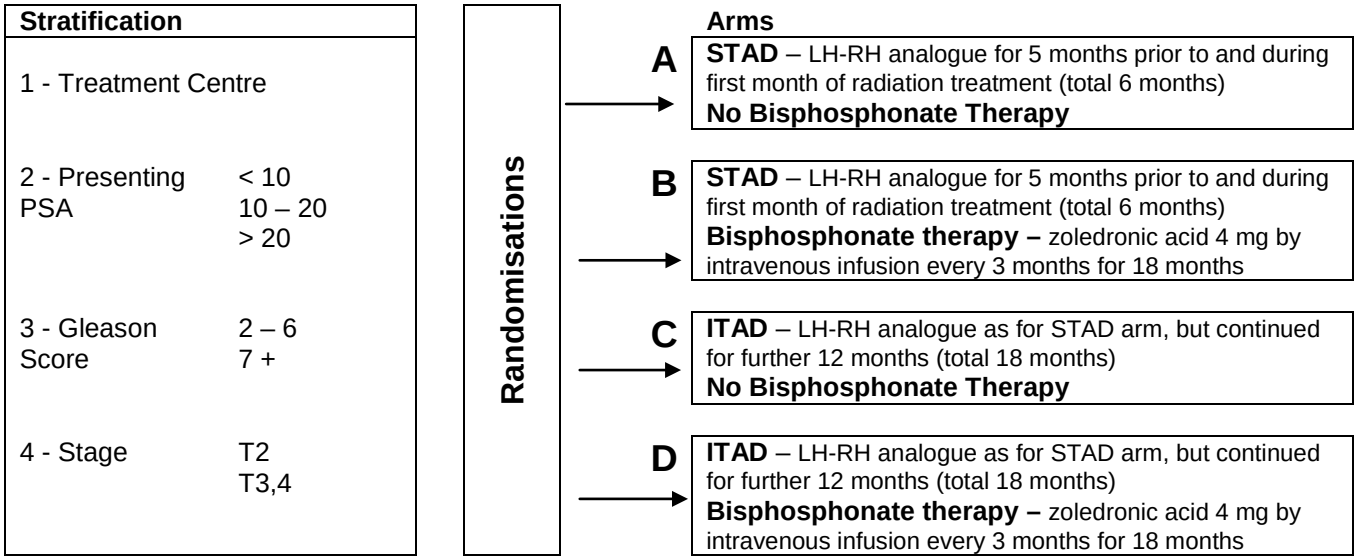
Patients with stage T2a (providing Gleason score 7 or more, **and** PSA 10 or more) and stage T2b-4 adenocarcinoma prostate without evidence of lymph node or distant metastases who agree to attend follow up clinics conducted by the Investigator.

Ineligibility

Patients who have had radical prostatectomy, any prior hormone or bisphosphonate treatment, or pelvic radiotherapy. Evidence of lymph node and/or distant metastases; other major cancer; other medical conditions seriously limiting life expectancy; poor performance status, and osteoporosis resulting in >30% loss in vertebrae height in one or more thoraco-lumbar vertebrae as measured by the treating clinician.

Randomisation

Eligible patients will be randomised by the minimisation procedure at the Newcastle Central Trials Office (Tel: +61 2 4921 1462; Fax: +61 2 4921 1153; after the treatment centre has nominated the patient's radiotherapy technique and dose (see below).



Radiation Treatment

Treatment will be delivered using a conventional technique, unless the treatment centre of the participating clinician demonstrates an ability to deliver the treatment using a CRT, IMRT, or HDRB technique verified by the trial TACT.

(a) **Conventional EBT**– 66 Gy in 33 daily fractions over 6.5 – 7 weeks prescribed to a volume that encompasses the prostate and potential local extensions only.

(b) **3DCRT and/or IMRT** – an escalating total dose of radiation delivered in daily fractions of 2 Gy when at least part of the treatment is delivered using an approved CRT or IMRT technique to a volume that tightly encompasses the prostate and potential local extensions only. Dose escalation will only occur when criteria agreed by the TACT have been satisfied.

(c) **HDR brachytherapy** – the trial allows a combination of initial external beam therapy (EBT) delivered using conventional or conformal EBT with a boost delivered using HDR brachytherapy.

At any time during the course of the study, the participating centre can elect to change from one method of delivery to another and one dose level to another, however verification from the TACT must be obtained before any change is initiated.

Drug Treatment

LH-RH analogue (LH-RHa) (Leuprorelin acetate 22.5 mg) will be delivered as a depot injection every 3 months. This will be administered as an intramuscular injection (IMI).

Zoledronic acid 4 mg will be delivered as an intravenous infusion over 15 minutes once every 3 months for 18 months, in patients randomised to this therapy. No placebo therapy will be given to patients randomised to 'no bisphosphonate therapy' treatment arm.

1 INTRODUCTION

1.1 Prostate cancer is an increasing health problem in Western countries. Approximately one in eight men will be diagnosed with prostate cancer during his lifetime[1], and a significant proportion of patients diagnosed will eventually die from progressive malignancy. In the United States, it is estimated that more than 3 million of the current male population will die from prostate cancer. Projections for 1998 indicate that the number of deaths from prostate cancer (39,200) will begin to approach breast cancer deaths (43,500). In 1996 Australia recorded 10,055 new cases with an age standardised rate of 117.4 per 100,000[2]. Since 1994 incidence rates have been falling. This has been attributed to the large increase in occult cancers that were detected when PSA testing became widely available in the late 1980s and early 1990s. Unfortunately few registries classify newly diagnosed cases according to degree of spread at presentation. Imprecise as they are, data from the NSW registry indicate that 70 – 75% of all newly presenting cases have cancer localised to the prostate, or have regional spread only.

In Australia in 1996, 2,644 deaths from prostate cancer were recorded, and 6228 person years of life were estimated to have been lost[2]. Data from the South Australian and Queensland cancer registries suggest that the development of prostate cancer will reduce survival expectation by approximately 30%. This figure has been decreasing steadily over the last two decades, which may reflect earlier detection and/or improvements in management.

In New Zealand, prostate cancer was the leading male site for cancer registrations in 1996 and had an age-standardised rate which was 97.7 per 100,000 population, higher than for all other sites, including those affecting both sexes[3]. There were 502 deaths from prostate cancer in 1996, with a mortality rate of 18.1 per 100,000.

1.2 Morbidity due to prostate cancer, with consequent need for medical intervention and hospitalisation, is perhaps an even more significant consideration in this age group, but is poorly quantified. The overall cost of treating prostate cancer is also difficult to estimate. Approximately $18 million were expended in Australia in 1999 on the surgical and radiotherapeutic treatments of localised prostate cancer, while $25 million and $54 million were spent on the anti-androgens and luteinizing hormone releasing hormone (LH-RH) analogues used for treating more advanced cancer. A large proportion of the drug bill was expended on treating progression after treatment of localised prostate cancer. The provision of palliative care (including palliative radiation [circa $4 million in Australia in 1999], drugs and hospitalisation) adds to the costs of treatment for progression, and treatment of this group of patients comprises a significant proportion of the total workload of cancer centres in Australia and New Zealand. These figures demonstrate that more effective strategies for the treatment of apparently localised prostate cancer could result in worthwhile financial savings.

1.3 Androgen blockade is the only treatment shown in randomised clinical trials to prolong life in prostate cancer patients, and this applies to patients with both localised and metastatic disease[4-10]. Each year, approximately 8000 men in Australia and New Zealand[2,3] develop localised prostate cancer amenable to attempted cure by surgery or radiation. Of these, approximately one half have cancers where 'adjuvant' androgen deprivation (AD) may be prescribed according to the registered indications. There are, however, enormous variations in prescribing practices, which reflects the uncertainty that exists as to the **appropriate** indications for AD.

At an international level, the contribution of adjuvant androgen deprivation strategies to improvements in outcome following surgery or radiotherapy in the curative management of localised prostate cancer is gradually becoming clearer as results emerge from large scale trials in the USA, Europe and Australia and New Zealand. For example it is now established that recurrence of the primary cancer and appearance of metastatic cancer are significantly delayed by adjuvant strategies[8,11-13]. In addition trial data are beginning to suggest that these improvements are translating into overall survival benefits[14-16]. What remains unclear, however, is which patients derive most benefit, whether androgen deprivation should begin before curative

surgery or radiation, or follow it, and how long androgen deprivation should be prescribed for. The present trial will address these issues.

The Trans-Tasman Radiation Oncology Group (TROG) became involved in adjuvant androgen deprivation trials in the early 1990's and has focussed its attention on the neo-adjuvant ('ante-hoc') use of androgen deprivation prior to and during curative radiation therapy in patients with locally advanced (but not metastatic) cancers. The neo-adjuvant use of AD is particularly attractive because it has the potential to reduce tumour cell number substantially prior to radiation[12]. This leads to a greater probability of eradication of the entire tumour cell population. In addition, the shrinkage of the prostate gland produced by neo-adjuvant AD leads to a reduction in the volume of adjacent rectum and bladder that needs to be included in the radiation target volume, so reducing the long-term toxicity of radiation treatment[17].

In 1996 TROG launched a large randomised three-arm trial (96.01). Two of the arms were the same as those in the US Radiation Therapy Oncology Group (RTOG) 86.10 trial, which was already showing early evidence of benefit for three months maximal androgen deprivation (MAD), using goserelin and flutamide, compared to radiation treatment alone[12]. MAD was given for two months before, and for one month during, radiation treatment. Work from Canada had shown that androgen deprivation (AD) continued for periods longer than three months produced additional shrinkage of the prostatic tumour and surrounding normal prostate, and this shrinkage continued for 6 – 8 months after starting AD[18]. The TROG 96.01 trial therefore compared radiation treatment alone (to 66.00 gray) with three months and six months MAD prior to and during the same radiation treatment. MAD was achieved with goserelin and flutamide as in the RTOG trial. The TROG trial completed its recruitment target of 800 eligible patients in early 2000.

1.4 The results of a number of major randomised clinical trials investigating adjuvant AD have been published since TROG 96.01 was initiated, and these have provided the stimulus for TROG to design a 'follow on' trial to 96.01. The European Organisation for Research and Treatment of Cancer (EORTC) trial, reported in the New England Journal of Medicine in 1997 [8] and subsequently in the Lancet in 2002 [19], suggested that 3 years of adjuvant ('post hoc') androgen deprivation (using goserelin alone) administered after radiotherapy reduced relapse and improved survival in patients with locally advanced prostate cancer. This publication was the first to indicate the possible advantages of much longer androgen deprivation, but on its own had little impact on prescribing practices in Australia and New Zealand. There were some concerns that patients on the radiotherapy alone (control) arm of the trial were not treated by salvage androgen deprivation as soon as relapse had become evident, and this could have led to a sub-optimal outcome in this treatment arm. In addition, there were conscientious concerns about the acceptability to patients, and the costs, of long term administration of androgen deprivation strategies in an adjuvant setting. However, the issue was raised again by the recent reporting of results from the RTOG 85.31 and 92.02 trials[15,20]. The issue of timely salvage therapy has not been questioned in these trials, and a survival advantage was again demonstrated. Many clinicians in Australia and New Zealand have therefore become anxious that their earlier conservatism was not well founded, as it now looks likely that at least some of their patients would benefit from long term androgen deprivation. Further confirmation has come from the industry sponsored bicalutamide adjuvant trials whose preliminary results were published in 2002[13].

Table 1 provides a brief overview of the trials conducted to date and their most recent findings.

Table 1~ Overview of trials conducted to date

Trial	Sample Size	Eligibility	Treatment Option	Results to Date		
RTOG 85.31 (USA)	992	• T2B, 2C, 3, 4 • RT alone or post prostatectomy • Node +ve and/or extracapsular extension	RT only Vs RT then long term Goserelin (LTAD)	At 8 years: Favours LTAD	• Local control • Rate of distant metastases • PSA control • Overall survival Gleason Score 8 – 10 only	} All } p<0.0001 }
RTOG 86.10 (USA)	456	T2B, 2C, 3, 4, N0	RT only Vs 3 months maximal androgen deprivation (MAD) Goserelin / Flutamide prior to and during RT	At 8 years: Favours MAD	• Local control • Rate of distant metastases • PSA control • Cause specific survival • Overall survival in Gleason score 2 – 6 only	} } All } $p \leq 0.05$ }
RTOG 92.02 (USA)	1554	T2C, 3, 4	4 months MAD prior to and during RT Vs 4 months MAD prior to and during RT then 24 months Goserelin (LTAD)	At 5 years: Favours LTAD	• Local control • Rate of distant metastases • PSA control • Cause specific survival NS p 0.07 • Overall survival NO difference	} All } p=0.0001 }
EORTC (Continental Europe)	415	T2B, T2C, 3, 4	RT only Vs RT then 36 months Goserelin (LTAD)	At 5 years: Favours LTAD	• Local control • Clinical disease free survival • Overall survival	} All } p < 0.001 }
TROG 96.01 (Australia and New Zealand)	802	T2B, 2C, 3, 4 N0	RT only Vs 3 months MAD prior to and during RT Vs 6 months MAD prior to and during RT	At 5 years: Favours 6mth MAD	Local control Rate of distant metastases PSA control Disease free survival Cause specific survival	p < 0.0001 p < 0.046 p < 0.0001 p < 0.0001 p < 0.04
RT = Radiotherapy MAD = Maximal Androgen Deprivation (Goserelin/Flutamide) LTAD = Long Term Androgen Deprivation (Goserelin)						

Although these trials have provided strong evidence that some patients benefit from long term AD, it is still not clear **which** patients derive a large enough advantage to justify the toxicity and expense of this treatment. The RTOG 86.10 trial suggests that just 3 months neo-adjuvant AD could confer a survival advantage to patients with low grade cancers[16]. However, data from RTOG 85.31 and 92.02 [15] suggest that long term AD is more beneficial to patients with high grade cancers. Roach et al suggested that mortality could be reduced by one third in these patients[21]. Adding to the uncertainties generated by these trial results, preliminary analysis of data from the TROG 96.01 trial raises the question as to whether long term AD is necessary in any patient. Analysis of two important trial end points was conducted in August 2001. The first end point was radiation target volume size. It is known that maximal androgen deprivation produces a reduction in volume of prostate cancer and normal prostatic tissue[17]. It is also known that reductions in volume continue for at least six months after commencement of androgen deprivation[18]. Volumetric reductions may be clinically important if they lead to reductions in radiotherapy 'target volumes', because reductions in delayed radiation injury may then follow[22]. As Table 2 indicates, reductions in target volume did accompany maximal androgen deprivation in the 96.01 trial. In fact, as had been anticipated, the greatest reductions were produced by six

months androgen deprivation. Unfortunately however, these reductions have not translated into a consistent reduction in delayed proctopathic symptoms[23].

Table 2 ~ Radiation Target Volume according to treatment arm (in mls)

	Treatment Arm	Target Volume (median)	Range
(A)	RT alone	912	405 – 2050
(B)	3 months MAD+RT	810	394 – 2511
(C)	6 months MAD+RT	765	333 – 2156
(Volumes are distributed log normally. Log transformed volume p values: A vs B = <0.001, A vs C = <0.001, B vs C = 0.04)			

In 2003 we reported that patients randomised to AD had experienced short-term side effects that had added temporary inconvenience only to the immediate toxicity experienced during and shortly after radiotherapy[24]. We conducted two sets of pre-planned preliminary analyses addressing the main trial hypotheses in 2005 when median follow-up time had reached 5.9 years. It was acknowledged a priori, and at the time of the analyses, that because the clinical evolution of prostate cancer is often slow this might be too soon to address the *survival* endpoints. However it was felt necessary to address the impression that most clinicians had developed in the clinic that patients treated with six months AD were experiencing better outcomes and that prescribing practices should change accordingly (see page 6). In fact, these impressions turned out to be correct. The results summarised in Table 3 were presented in our first report that dealt with treatment efficacy[25].

Table 3 ~ Summary of 5 year actuarial failure and failure-free probabilities

Endpoint	5 year failure and failure-free rates (%) (95% CI)			Hazard ratios for adjusted Cox proportional hazards model*					
				0 Mths* v *3 Mths		***0 Mths* v *6 Mths*†**		***3 Mths* v *6 Mths*‡**	
	***0 Mths* (*n*=270)**	***3 Mths* (*n*=265)**	***6 Mths* (*n*=267)**	**HR (95% CI)**	**p-value§**	**HR (95% CI)**	**p-value§**	**HR (95% CI)**	**p-value§**
Local failure	28 (23,34)	17 (12,22)	12 (7,16)	0.56 (0.39,0.79)	0.001	0.42 (0.28,0.62)	<0.0001	0.75 (0.49,1.16)	0.196
Distant failure	19 (14,24)	22 (17,28)	13 (8,17)	1.09 (0.76,1.56)	0.633	0.67 (0.45,0.99)	0.046	0.61 (0.41,0.91)	0.016
Biochemical failure-free survival	38 (32,44)	52 (45,58)	56 (50,63)	0.70 (0.56,0.88)	0.002	0.58 (0.46,0.74)	<0.0001	0.83 (0.64,1.07)	0.155
Disease-free survival	32 (27,38)	49 (42,55)	52 (45,58)	0.65 (0.52,0.80)	0.0001	0.56 (0.45,0.69)	<0.0001	0.85 (0.67,1.07)	0.165
Freedom from salvage therapy	63 (57,69)	68 (62,74)	78 (72,83)	0.73 (0.56,0.96)	0.025	0.53 (0.40,0.71)	<0.0001	0.73 (0.53,0.99)	0.043
Cause-specific survival	91 (88,95)	92 (89,96)	94 (91,97)	0.91 (0.56,1.48)	0.711	0.56 (0.32,0.98)	0.040	0.58 (0.33,1.05)	0.072

* Model covariates: treatment arm (0 Months/3 Months/6 Months), age (<70/≥70), Gleason score (2-6/7/8-10), initial PSA (<10/10-20/>20), stage (T2b,c/T3,T4)
† Reference group is *0 Months* ‡ Reference group is *3 Months* § p values for Wald test

We concluded that local failure (i.e., recurrence of the primary tumour in the prostate) had been reduced in relative terms by 44%* in the three month AD arm (when compared with the control radiotherapy alone arm of the trial). Six months AD had reduced local failure by 58%* (i.e., even further). Distant failure (i.e., the development of metastases outside of the prostate region) however, was not reduced by three months AD but was *reduced* by 33%* in the six month AD arm. As a result biochemical failure (i.e., the presence of rising PSA levels sometime after low levels had been reached after treatment) and disease-free survival (the absence of clinical or biochemical evidence of failure) were reduced significantly in the two androgen deprivation arms. This, in turn, was found to lead to corresponding reductions in the need for salvage therapy (amounting to a halving in the 6 month AD arm)*.

In spite of causing reductions in local and biochemical failure, three months AD was *not* found to reduce prostate cancer mortality significantly. Six months AD, however, which caused reductions in distant failure as well as even greater reductions in local failure, *was* found to reduce prostate cancer mortality thereby producing a small improvement in five year survival which just reached statistical significance (p=0.04).

1.5 It was therefore logical for TROG to design a 'follow-on' trial to the 96.01 trial, to determine whether a longer period of androgen deprivation might lead to greater advantages than those seen with just 6 months treatment. The follow-on trial, which is described in this protocol, and is known as the RADAR (Randomised Androgen Deprivation and Radiotherapy) trial, uses the best arm of the 96.01 trial (6 months AD) as the short term androgen deprivation (STAD) 'control' arm. The 'experimental' arm comprises androgen deprivation extended to 18 months, and this is termed intermediate term androgen deprivation (ITAD), as the duration of treatment lies mid way in the range of durations that have been trialled. However, similarly to the STAD arm, androgen deprivation is commenced 5 months before start of radiotherapy, so all patients benefit from the reduced radiotherapy target volume which results from neo-adjuvant AD[17]. This has become standard prescribing practice in Australia and New Zealand.

In designing the RADAR trial, two important questions needed to be resolved. Firstly, when using chemical treatment to achieve adjuvant androgen deprivation, which drug(s) is optimal? Secondly, what is the *minimum* duration of androgen deprivation that is likely to lead to worthwhile survival gains, but at the same time limit the long term metabolic complications of this treatment?

1.6 At the time the protocol for the 96.01 trial was developed, there was much enthusiasm for 'Maximal Androgen Blockade' (MAB) (alternatively known as 'Maximal Androgen Deprivation', or 'complete Androgen Blockade') as the optimal hormonal treatment for prostate cancer. MAB comprises a combination of a treatment which stops production of androgens by the testes, together with an 'anti-androgen', which blocks the action of androgens at the cellular level. There are good theoretical reasons why MAB might be an advantage. Under normal circumstances, the androgens acting in the prostate originate from two main sources of approximately equal importance, namely the testes and the adrenal glands. Although surgical or chemical castration will result in a 90 - 95% drop in the concentration of circulating testosterone[24], there is only a 50 – 70% drop in the **intraprostatic** concentration of the potent androgen 5-dihydrotestosterone (DHT). This reflects the fact that a significant proportion of DHT originates from precursors secreted by the adrenal gland. However, an increasing number of publications over the last five years cast serious doubts as to whether these theoretical advantages of MAD are reflected in useful benefits to the patient. A recent review[26] of the five meta-analyses performed on trials of different hormone treatments for metastatic prostate cancer concluded that MAD did **not** lead to worthwhile survival advantages, but did reduce quality of life. The authors felt that the currently available data did not justify the routine use of an anti-androgen in addition to medical or surgical castration. TROG's experience with the 96.01 trial supports this conclusion. The anti-androgen

* Statistically significant differences which are quantified in Table 3.

component of MAD led to significant toxicity, which necessitated flutamide being stopped in 27% of patients in the 6 months MAD treatment arm. This was mainly due to disordered liver function, and bowel side effects. In contrast, only 6 patients out of 528, or 1.1%, had to stop the luteinizing hormone releasing hormone analogue (LH-RHa) goserelin because of unacceptable side effects. Therefore, for the RADAR trial, LH-RHa alone which is thought to produce greater and more rapid prostatic tumour volume shrinkage than anti-androgens alone[27] will be used to achieve androgen deprivation. Monotherapy has the additional advantage of costing considerably less than MAD.

1.7 The **reversibility** of androgen deprivation is clearly important in both arms of this trial, due to the metabolic consequences of persisting castrate levels of testosterone (see 1.9 and 1.10). A normal testosterone level also permits a return of sexual activity, although a disappointingly small proportion of patients will benefit from this. Acute toxicity data from TROG 96.01 has demonstrated that only 36% patients were sexually active **before** any treatment was initiated, and this had fallen to just 15% by 1 year after completion of radiotherapy, regardless of whether or not the patient received 3 or 6 months MAD in addition. The chance of being sexually active 1 year after treatment was very much dependent on age, and only patients less than 60 years had any real prospect (33%) of being sexually active at that time.

1.8 When considering the options for adjuvant LH-RHa, it is impossible for responsible clinicians not to consider the potential implications to funding bodies in Australia and New Zealand. The cost of providing LH-RH analogue in Australia is already 54m AUD. This figure could increase dramatically if all patients with locally advanced prostate cancer received 3 years of adjuvant treatment with LH-RHa, as was used in the landmark EORTC trial. The cost per patient for this drug would be more than 13,000 AUD (excluding consultation fees and ancillary investigations). The 18 months of LH-RHa selected for the experimental arm of this trial is therefore a responsible compromise. Should this duration of LH-RHa prove beneficial, it is an **affordable** treatment strategy for health funding bodies in Australia and New Zealand.

1.9 Loss of bone mineral density (BMD) as a result of low oestrogen levels in post-menopausal women has been recognised for a number of years; more recently it has been reported as a complication of androgen deprivation therapy in men with prostate cancer, particularly those undergoing more protracted treatment.

A number of authors have reported significant loss of BMD[28] and increased bone turnover[29] after a year or more of androgen deprivation. These changes may be more marked in men undergoing surgical rather than medical castration[28]. Duration of androgen deprivation of 4 years may reduce BMD from the middle of the normal range to the criteria for osteopenia[30]. An increase in osteoporotic fractures has also been reported, with a rate of approximately 50% at 9 years in androgen-deprived patients, compared with 10% in prostate cancer sufferers without androgen deprivation[31]. There is evidence that use of bisphosphonates may reduce the loss in density with its associated morbidity[32].

In patients with accelerated osteoporosis that is not associated with malignant disease or AD, zoledronic acid 4 mg given by infusion just once every 12 months may be sufficient to suppress increased bone turnover[33]. However, in patients with osteoporosis secondary to adjuvant AD for early prostate carcinoma, it is not known what is the optimum dose, frequency and duration of zoledronic acid therapy. In a small, randomised, controlled study of patients on AD for advanced prostate carcinoma, a single intravenous treatment with disodium pamidronate was shown to preserve BMD in the short-term[34]. Data referring to osteoporotic fracture rates and therapeutic interventions are more sparse but recent reports indicate an increase in fractures following all forms of AD[35,36]. To date an effective therapeutic program for severe osteoporosis resulting in fracture is not established.

The potent bisphosphonate, zoledronic acid (Zometa®), is effective in reducing skeletal-related events (SREs) in patients with hormone-refractory advanced prostate carcinoma involving bone[37]. In this setting, zoledronic acid 4 mg is regularly given by 15 minute intravenous infusion

every 3 - 4 weeks. Bisphosphonates may also be helpful in hormone responsive cancer. The MRC PR05 trial showed that the less potent bisphosphonate clodronate could delay the progression of bony metastases in patients responding to or initiating first-line hormonal treatment, particularly in patients with early bony metastatic disease[38]. Early treatment of patients with prostate cancer with zoledronic acid, as envisaged in this clinical trial, may prove helpful in preventing development of bone metastases. For example, a placebo-controlled trial of the much-less-potent oral bisphosphonate clodronate as part of adjuvant therapy in patients with breast cancer has shown a reduction in bone metastases and an increase in overall survival[39].

As a single agent, zoledronic acid strongly inhibits the growth of several prostate cancer cell lines in vitro at 100 µM concentrations, and has anti-proliferative effects at concentrations as low as 25 µM, despite the presence of serum growth factors[40]. Whilst these concentrations are reached transiently in plasma after intravenous infusions of 4 mg, concentrations of zoledronic acid in bone at the site of metastases may be many fold higher – potentially having an anti-tumour effect. In pre-clinical models, zoledronic acid directly decreases adhesion of prostate cancer cells to bone and reduces neo-angiogenesis – key steps in the formation of bone metastases[41,42]. The same researchers have shown that the invasion of prostate cancer cells into bone can be inhibited by nitrogen-containing bisphosphonates, and zoledronic acid was the most potent of the bisphosphonates tested[41].

These provocative pre-clinical and clinical data therefore raise the possibility that zoledronic acid given simultaneously with adjuvant LH-RHa will delay the onset of bony metastases as well as preventing LH-RHa induced osteopenia in patients with earlier stage disease in whom bony metastases cannot be detected.

Since the magnitude of benefits of zoledronic acid therapy in patients with early prostate carcinoma treated by radiotherapy with adjuvant AD remain uncertain, it is proposed in this trial to randomise patients to receive either no bisphosphonate therapy or zoledronic acid 4 mg by 15 minute intravenous infusion every 3 months for 18 months. This schedule of zoledronic acid therapy has been chosen as a reasonable compromise between the bisphosphonate schedules shown to be effective in osteoporosis alone and in those that delay progression of malignant disease involving bone; additionally, this schedule has not been associated with significant renal impairment. To help ensure renal safety, patients with evidence of underlying renal impairment (ie a serum creatinine > 2 times the upper limit of normal) will be excluded from zoledronic acid therapy. In addition renal function will be monitored through the course of the 18 months of bisphosphonate administration.

The RADAR trial will therefore provide randomisation into four arms to determine whether bony metastases **are** delayed and loss of BMD **is preventable** with zoledronic acid 4 mg infusions every 3 months for 18 months. Patients will be randomised to STAD or ITAD, and to zoledronic acid or to no bisphosphonate therapy. Hence, there will be four treatment arms: STAD + no bisphosphonate; STAD + zoledronic acid therapy and ITAD + no bisphosphonate; ITAD + zoledronic acid therapy.

In patients where x-ray demonstrates that BMD may be reduced and whose treatment centres can provide them ready access to the appropriate diagnostic facilities, measurement of lumbar and hip BMD will be undertaken prior to starting AD, and again at 2 and 4 years. Rates of porotic fractures in the thoraco-lumbar spine will be documented at baseline and 3 years, and comparisons made between the four treatment arms. The primary comparison will be the rates of porotic fractures sustained in zoledronate-treated patients relative to the controls.

With regard to safety issues, intravenous bisphosphonate therapy is generally well tolerated[43]. Patients may experience a 'flu-like' syndrome with their first infusion of bisphosphonate, but symptoms usually respond to paracetamol. Some patients also note upper GIT symptoms and easy fatigability. However, it is unusual for these symptoms to necessitate any reduction or interruption in bisphosphonate therapy.

An increasing number of reports have drawn attention to the possibility of developing osteonecrosis of the mandible during intensive bisphosphonate therapy for metastatic cancer in bone from a number of malignancies including prostate cancer. Avascular necrosis of the mandible has been recorded in the absence of bisphosphonate therapy in patients with advanced metastatic cancer who may or may not be receiving chemotherapy, and in patients treated by radiotherapy for head and neck cancer [44-49]. At the commencement of the RADAR trial osteonecrosis of the mandible was not expected to occur in patients with non-metastatic prostate cancer treated with the low dose intensity schedule of bisphosphonate described. However, as of October 2006, one patient without any known risk factors has experienced a relatively minor osteonecrosis, which fortunately has completely healed with conservative measures. In response, the Trial Management Committee has determined a stopping rule (for the use of bisphosphonates in the RADAR trial) if further cases become apparent (see Appendix 20.3(d)). It is advisable for patients to notify their doctors if a dental procedure (e.g. an extraction) is being considered during the course of bisphosphonate injections. In addition, patients who are allocated bisphosphonate should not begin receiving bisphosphonate treatment until any prior dental work or trauma to the jaw has completely healed. During bisphosphonate treatment, patients should, avoid invasive (traumatic) dental procedures (e.g. extractions) until at least three months have elapsed after the last dose of bisphosphonate in the treatment course. If a traumatic procedure is indicated during the planned course of bisphosphonate it is recommended that it occur at least 3 months after the last dose, and that the next dose of bisphosphonate be postponed for 3 months after the procedure[48,50-53]. If further cases of osteonecrosis of the mandible occur in the RADAR trial, it is recommended that patients involved are referred promptly to an oral surgeon with experience of this complication for diagnosis and management without further dental intervention.

1.10 Other undesirable sequelae following long term AD therapy have been reported. Anaemia, obesity, loss of muscular mass, fatigue, mood changes, depression and gynaecomastia have all been witnessed but their risks are poorly documented[54,55]. A detrimental impact on quality of life has frequently been assumed to accompany these sequelae but documentation is limited[26]. In the RADAR trial an attempt is therefore made to address this deficiency by the prospective assessment of health related (global) quality of life, using the instrument developed by the EORTC together with its organ specific (prostate) module.

1.11 Local persistence of prostate cancer after conventional external beam radiotherapy (EBRT) represents an important clinical problem. Post-treatment biopsy positivity may be as high as 64%[56-58] and increased local failure has been associated with a higher incidence of distant metastases and ultimate clinical failure.

Increasing the dose delivered to the prostate has the potential to increase local control (and hence ultimate control). Improved biochemical (PSA) and clinical local control have been reported with higher doses[11,59,60] but doses above 70 Gy utilising EBT have been associated with increased risk of long-term complications[61]. For example Smit reported[62] severe rectal toxicity of up to 60% in patients who had anterior rectal wall doses of 75 Gy using conventional EBT.

Using standard doses of RT with conventional EBT a number of series report a 2 – 3% severe complication rate. One of the aims of the present trial is to use modern techniques to allow increased dose intensity whilst maintaining the same level of severe late complications. At the Royal Marsden Hospital a randomised Phase III trial was performed to compare the use of conventional EBT with conformal radiotherapy[22,63]. This study demonstrated that at the same dose (64 Gy in 32 fractions of 2 Gy) conformal radiotherapy did reduce the amount of reaction in the high dose volume which, in turn, reduced late rectal complications. The same group estimated that 3DCRT reduces the volume of normal tissue treated by approximately 40 – 50%[64]. A phase III randomised study has also been performed at MD Anderson Hospital. This group has reported an acceptable acute toxicity with 3DCRT to 78 Gy versus conventional EBT to 70 Gy[65]. Preliminary control results from the same trial are encouraging with improved 4 year NED rates (as determined by PSA progression) for T_1 / T_2 disease with initial PSA of 10 ng/ml[66]. These results however are preliminary and have not been reported as enthusiastically as a number of

single institution series. The results of these studies have used PSA progression as defined according to the ASTRO consensus (3 consecutive rising PSA values from the nadir value) to report control[11,67,68]. All have reported that 3DCRT is well tolerated and all have concluded that better local control is achieved than in patients treated in previous years at their own institutions. A large multi-institution randomised controlled trial conducted in Holland has confirmed that better local control can be achieved without increased toxicity [69].

Although neo-adjuvant androgen deprivation may improve local control after conventional doses of prostatic irradiation (ie 65 – 70 Gy) it remains unproven that it will improve outcome in patients treated with higher radiation doses. The present trial will therefore provide complementary information to presently on-going trials in Canada and Europe that are deliberately testing this hypothesis.

The impact of increasing dose on outcome in the present trial will be assessed by using radiation dose as an explanatory variable in competing risks models of time to PSA progression and death. The possibility of an important interaction between duration of androgen deprivation (ie treatment arm) and radiation on probability of progression will be carefully addressed as part of the process.

1.12 The precise implications of PSA progression after radiation treatment for localised prostate cancer are poorly understood. It seems likely that PSA progression indicates an increased risk of dying of prostate cancer. However, some patients will enjoy prolonged survival with salvage treatment, and may eventually die of other causes. The significance of PSA progression probably also differs according to when it occurs in relation to adjuvant androgen deprivation, ie during or after, and this treatment clearly has the potential to significantly delay PSA progression, without necessarily having the same magnitude of effect on ultimate disease-free and overall survival[70]. As more data emerge, PSA doubling times of less than 8 months have been found to be predictive for the more sinister development of metastatic disease, rather than local recurrence[71]. Doubling times under 3 months are almost invariably associated with death due to prostate cancer[72]. The value of PSA doubling time as a predictor of subsequent outcome has now been confirmed and better quantified by the prospective anatomical site of relapse data from the 96.01 Trial. Notwithstanding these observations, management trends in Australia and New Zealand have followed those in the US and Europe. A rise in PSA is now widely being taken as an indication of progression without, in many instances, the presence of other corroborating evidence. Indeed, many patients are commenced on salvage therapy (usually androgen deprivation) without identification of site of progression.

1.13 The now standard practice of using PSA as a measure of disease control after treatment for prostate cancer has led to difficulties in determining the precise site of progression in many patients as indicated above. TROG trial 96.01, which used international guidelines to define PSA relapse[73], demonstrated that restaging investigations were often normal at the time of PSA relapse, presumably due to the volume of cancer being too small to be detected clinically or demonstrated radiologically. As there are no proven benefits from **immediate** salvage treatment for PSA relapse, a policy was adopted of allowing the PSA to rise to 20.0 ng/ml before repeating radiological investigations, unless the patient became symptomatic beforehand, which is not a common event. This allowed the site of failure to be identified in a higher proportion of patients, which is important because this may help to define the therapeutic options available to the patient. The RADAR trial has drawn extensively from experience obtained in the 96.01 trial. At the commencement of RADAR, it was still considered reasonable to use the ASTRO definition of PSA progression. However the high rate of false positive calls identified in the first analysis of the main endpoints of the 96.01 trial[25] mandated the choice of the Phoenix method[74] in its place. In addition a revised set of Relapse Diagnosis guidelines based on 96.01 experiences has been agreed upon for use in the RADAR trial (see Appendix Section 21). The alternative, ie the delay of salvage treatment until symptoms develop, has been demonstrated to compromise ultimate survival[75].

This trial differs from TROG trial 96.01 in that it does **not** recommend re-biopsy of the prostate if local recurrence is suspected on clinical and radiological grounds. Although re-biopsy of the prostate two years or more after definitive radiation treatment can help determine whether or not local control has been achieved[76,77], patients are generally reluctant to undergo this invasive procedure again and the result rarely influences patient management.

In analysing patterns of progression data from the present trial, it will be acknowledged that site of progression will be unknown in a proportion of cases for the reasons listed above. Potential biases from such missing data will therefore need to be taken into account when interpreting these analyses.

The present trial not only standardises the timing of salvage treatment, but also determines what salvage treatment is appropriate. This is prudent because in the two randomised trials[8,75] which demonstrated survival advantages when androgen deprivation (AD) is used earlier in the natural history of the disease, some patients in the delayed AD arms *never* actually received AD. Even more did not receive AD until in an advanced stage of progression. Omissions of this nature clearly have the potential to exaggerate differences in survival in trials where duration of androgen deprivation differs in treatment arms, as well as to disadvantage individual patients. Whilst there will always be some patients who decline a recommended treatment for progression, and it is the right of the patient to do so, the supervising clinician does have a responsibility to ensure that all patients who relapse are at least **offered** the treatment believed to be most effective.

1.14 The 2002 TNM staging of prostate cancer[78] is used to determine eligibility for the RADAR trial, even though it is recognised the distinction between T1 and T2 cancers on the basis of digital examination is highly subjective, and trans-rectal ultrasound often fails to demonstrate changes diagnostic of malignancy. The eligibility criteria for this study are similar to those for TROG study 96.01, and include higher risk T2a tumours, as well as T2b, T2c, T3 and T4 tumours. There is evidence that factors other than T stage have as much prognostic significance in patients with disease clinically confined to within the prostate gland. Patients have a worse prognosis if any Gleason pattern 4 cancer is detected, ie Gleason score 7 or more, and the presenting PSA is 10 or more. Patients who have T2a cancers with these characteristics are eligible for this trial. These patients are more likely to be treated with definitive radiation treatment, as they are at relatively high risk of positive margins and local progression after radical prostatectomy[79].

1.15 The two most significant long-term complications of definitive radiation treatment alone for localised prostate cancer are impotence, and the syndrome known as radiation proctitis, which is characterised by bowel urgency and rectal bleeding. TROG study 96.01 demonstrated that impotence had developed by 6 months after radiotherapy in approximately 60% of patients who were sexually active at randomisation. Moderate grades of radiation proctitis had developed in 8% of patients by 10 months after radiotherapy. Androgen deprivation may reduce the frequency and severity of this complication through a reduction in the radiation target volume. Delivering the radiation treatment using CRT or IMRT, as is optional in this trial, may further reduce this complication, or at least prevent a greater dose of radiation leading to a higher incidence of radiation proctitis. As in TROG study 96.01, the impact of short and long-term treatment side effects on the patient will be carefully evaluated by the clinician and by the use of self-assessment questionnaires.

1.16 This trial also attempts to identify whether there are underlying medical conditions that predict for a higher incidence of radiation proctitis. There is mounting laboratory evidence that radiotherapy induces long term endothelial injury. Just as endothelial injury is thought to be one of the initiating events in atherosclerosis[80,81] there is also reason to believe that it may contribute to the vasculopathies and fibroses that characterise delayed radiation injury[82]. Accumulated evidence from retrospective reviews and case reports of increased normal tissue complications in certain patient groups lend support to this suggestion[83]. A large study involving 944 patients treated for localised prostate cancer in Philadelphia suggested that late rectal and bladder complications were twice as frequent in diabetic patients[84] quite independently of other causative factors.

Peripheral vascular disease, hypertension, and obesity have also been identified as predisposing or contributing to increased risk of significant late complications[83,84].

As pointed out by Klotz[54] prolonged androgen deprivation may also be associated with reductions in HDL cholesterol levels. These, in turn, may place the patient at increased risks of cardiovascular disease and late radiation injury. In fact, changes in lipid profile produced are dependent on the type of endocrine manoeuvre performed[85,86] and thrombogenesis may in fact be due to changes in the coagulatory system, eg reductions in anti-thrombin 3[87] in some instances. Regardless of mechanism however, duration of androgen deprivation may therefore impact on risk of radiation injury as well as metabolic and quality of life consequences listed in 1.11.

This suggestion is supported by the toxicity data from RTOG 92.02[15] in which patients receiving prolonged androgen deprivation also experienced more toxicity. However, the role that changes in lipid profiles have in modifying radiation toxicity risks remains speculative. To date no prospective clinical research has been performed to address the impact of atherosclerosis, hypertension, glucose intolerance and abnormal lipid profiles on subsequent risk of radiation morbidity.

The strong circumstantial and retrospective evidence in favour of links between the disorders listed above and late radiation injury, coupled with an increasing number of interventions capable of modifying these disorders, mandates prospective research to determine their exact contribution to late radiation injury. This trial represents an excellent opportunity to do precisely this. Thorough pre-treatment general medical assessment, directed particularly at histories of the conditions detailed above, together with fasting plasma glucose and lipid profiles, will be performed. Multi-variate analysis of post-treatment toxicity data will determine whether the risk of late radiation injuries to rectum and bladder can be attributed to these conditions independently of treatment related factors.

1.17 The RADAR trial addresses several complex issues. A summary of these is therefore helpful:

(a) The trial seeks to determine whether ITAD produces better outcomes than STAD, in particular delays in PSA progression and reductions in mortality (1.5).
(b) Loss of bone mineral density, osteoporotic fractures, anaemia and other important physical and psychological sequelae can accompany more protracted androgen deprivation, but prospective documentation of their frequency and impact is limited. Measurement of these parameters and their impact on quality of life is an integral part of the trial design (1.9 and 1.11).
(c) The trial design will establish whether zoledronic acid will prevent osteopenia induced by adjuvant androgen deprivation (1.10).
(d) The trial also seeks to determine whether concurrent bisphosphonate therapy during androgen deprivation using zoledronic acid may produce further improvements in these outcome measures through delays in bony metastases (1.10).
(e) Local control of prostate cancer, PSA progression and radiation complications depend on radiation dose. The RADAR trial incorporates a carefully controlled dose escalation program that centres with CRT, IMRT or HDRB capability can enter. The risks that are inherent with the introduction of new technology are thus minimised (1.12).
(f) The magnitude of benefits following androgen deprivation may be influenced by histological grade (1.4), with reduction in mortality of **one third** predicted for patients with Gleason score 7 and above tumours who are treated with prolonged androgen deprivation. This potential interaction will be prospectively looked for in this trial.
(g) Intercurrent disorders that result in changes in lipid profiles, fibrinolysis, and endothelial injury may impact on cardiovascular disease as well as delayed radiation injury. The RADAR trial incorporates measurement of relevant blood parameters in its design (1.17).

1.18 Results from the TROG 96.01 10 year main endpoints data are summarised below. Several findings from 96.01 are of relevance to the RADAR trial.

(a) The 10 year data provide a much more reliable indication of the results from the TROG 96.01 trial than the 5 year data. In particular the effect sizes of 3 and 6 months NADT have become much clearer and the 95% confidence intervals are well separated from unity. An all-cause mortality benefit has been identified for 6 months NADT and the principal mechanism of mortality reduction (namely the reduction of metastases) has been established. Moreover subset analyses have now confirmed that men with T2c cancers derive similar benefits to those in men with T3,4 cancers. Based on these TROG 96.01 results, the decision to continue follow-up for RADAR patients to 10 years and report again at that timepoint is well justified.

Table 4. Summary of TROG 96.01 10 year endpoint data

Table 4A. Univariable analysis

Endpoint*	10 year cumulative incidence (%) (95% CI)			Pairwise trial arm comparisons of cumulative incidence (p values)	
	RT alone (n=270)	3 months NADT (n=265)	6 months NADT (n=267)	3 months NADT v RT alone	6 months NADT v RT alone
PSA progression†	73.8 (68.1-78.7)	60.4 (54.2-66.1)	52.8 (46.5-58.7)	0.0009	<0.0001
Local progression†	28.2 (22.9-33.7)	15.7 (11.6-20.4)	13.3 (9.5-17.7)	0.0003	<0.0001
Distant progression† (model 1) §	13.5 (9.7-17.9)	14.5 (10.6-19.1)	9.8 (6.6-13.7)	0.815	0.089
Distant progression† (model 2) §	20.6 (16.0-25.6)	18.3 (13.9-23.2)	10.9 (7.5-15.0)	0.497	0.0006
Prostate cancer-specific mortality†	22.0 (17.2-27.2)	18.9 (14.4-23.9)	11.4 (7.9-15.6)	0.394	0.0002
All-cause mortality‡	42.5 (36.7-48.7)	36.7 (31.1-42.9)	29.2 (24.1-35.1)	0.198	0.0005
Event-free survival‡	12.7 (9.0-17.1)	28.8 (23.4-34.5)	36.0 (30.2-41.8)	<0.0001	<0.0001

* Event-free survival and all-cause mortality were analysed using Cox regression models; all other endpoints used competing risks models

† Gray's test used to test treatment arm comparisons

‡ Log-rank test used to test treatment arm comparisons

§ Competing risks for distant progression model 1 are local progression, secondary therapeutic intervention and death, and for model 2 are secondary therapeutic intervention and death

Abbreviations: RT, radiotherapy; NADT, neo-adjuvant androgen deprivation therapy

Table 4B. Multivariable analysis

Endpoint	Multivariable Models‡			
	3 months NADT v RT alone§		6 months NADT v RT alone§	
	HR (95% CI)	p‖	HR (95% CI)	p‖
PSA progression*	0.72 (0.57-0.90)	0.003	0.57 (0.46-0.72)	<0.0001
Local progression*	0.49 (0.33-0.73)	0.0005	0.45 (0.30-0.66)	0.0001
Distant progression* (model 1)∏	1.03 (0.65-1.61)	0.912	0.66 (0.41-1.09)	0.106
Distant progression* (model 2)∏	0.89 (0.60-1.31)	0.550	0.49 (0.31-0.76)	0.001
Prostate cancer-specific mortality*	0.86 (0.60-1.23)	0.398	0.49 (0.32-0.74)	0.0008
All-cause mortality†	0.84 (0.65-1.08)	0.180	0.63 (0.48-0.83)	0.0008
Event-free survival†	0.63 (0.52-0.77)	<0.0001	0.51 (0.42-0.61)	<0.0001

* Competing risks models
† Cox regression models
‡ Model covariates: treatment arm (RT alone/3 months NADT/6 months NADT), age (<70/≥70), Gleason score (2-6/7/8-10), initial PSA (<20/≥20), stage (T2b/T2c/T3,T4)
§ Reference group is RT alone
‖ Fine and Gray p-value for competing risks models; Wald test p-value for Cox regression models
∏ Competing risks for distant progression model 1 are local progression, secondary therapeutic intervention and death, and for model 2 are secondary therapeutic intervention and death.

Abbreviations: RT, radiotherapy; NADT, neo-adjuvant androgen deprivation therapy; PSA, prostate-specific antigen

(b) In 2008[88] and 2009[89] we reported that survival is enormously variable following PSA progression in men treated on the 96.01 trial. In fact PSA progression is not the useful surrogate endpoint for prostate cancer outcome it was once thought to be. In the 96.01 dataset it was found that various cutpoints of two PSA progression derivatives were much more successful[88]. The implication of this for the RADAR trial is that PSA progression is an unsatisfactory primary endpoint and should be relegated to secondary endpoint status. Mortality reduction endpoints are commonly used as primary endpoints in prostate cancer trials, and there is no reason now to believe that the RADAR trial should be the exception. It will be noted in other sections of the protocol that prostate cancer-specific mortality and all-cause mortality are now the primary endpoints for the RADAR trial and that the protocol is amended accordingly. We therefore re-examined the power of the RADAR trial to detect differences in mortality, and its implications for the timing of pre-planned analyses.

The RADAR trial was powered to detect significant differences ($2\alpha = 0.05$) in PSA progression (60 vs 75%, $1-\beta=98\%$) and prostate cancer-specific mortality (92 vs 95%, $1-\beta=0.96$) at 5 years between the 6 month and 18 month ADT arms, assuming a 5% withdrawal rate. Accrual commenced in October 2003 and closed when it reached RADAR's target of 1050 eligible men (1071 randomised) in August 2007, a year ahead of schedule. It was originally hoped that this rapid rate of accrual would enable us to analyse the 5 year data in late 2012 when 5 years had elapsed from the last randomisation. However a recent independent review conducted in early 2011 has indicated that event rates for PSA progression and prostate cancer-specific mortality (PCSM) are lower in the RADAR trial than they were at the corresponding time in follow up for the 6 month NADT arm of the 96.01 trial

(i.e. the arm used to design the control arm of the RADAR trial). Since the prognostic features of men in the RADAR trial are very similar to those in the 96.01 trial, it was therefore important for us to learn that the power to detect a difference would be unlikely to reach 80% until early 2014 when 6.5 years will have elapsed from randomisation. This estimate is also of relevance to the overall duration of follow up in the RADAR trial. In the 96.01 trial 5 year main endpoints provided a reliable direction in which the outcomes of treatment were heading, but could not define the effect sizes of benefits from either the 3 or 6 months NADT (experimental) arms of the trial (the p values for the distant progression and PCSM endpoint comparisons of the control and 6 months NADT arms were both 0.04 i.e. barely reaching significance) or demonstrate an all-cause mortality benefit. However a further five years of follow up has enabled far more accurate quantification of the benefits of both experimental arms in the 96.01 trial for all endpoints, including all cause mortality. This makes it likely that accurate assessment of the magnitude of benefits achieved by the experimental arms of the RADAR trial will not emerge until 10 years of follow up has elapsed i.e. in 2017.

(c) Most leading journals are now reporting trial results using competing risk methodology. We therefore used this methodology for reporting the ten year results from 96.01. However to bring the 10 year main endpoints results of the RADAR trial in 2017 into line with other major trials groups reporting prostate cancer data, secondary therapeutic intervention will not be regarded as a competing risk for clinical progression endpoints. Also of relevance to the 2017 analyses is the multiplicative interaction we reported in 2014[90] between the use of zoledronic acid and Gleason score (GS) at the ≤7/>7 cutpoint for the endpoints bony progression and secondary therapeutic intervention. Since this interaction indicated that the use of zoledronic acid was beneficial in subjects with primary tumours graded >7 on the GS scale and detrimental in subjects with primary tumours graded ≤7 our 2014 endpoint data were analysed using Fine and Gray models comparing all four trial arms rather than the two treatment factors (i.e. the use of 12 additional months of androgen suppression and the use of 18 months of zoledronic acid)[90]. The same methodology will be used for our 2017 endpoint data if this interaction persists.

2 OBJECTIVES

2.1 Objectives

The principal objective of the trial is to test the hypothesis that 12 months adjuvant androgen deprivation using Leuprorelin acetate starting immediately after standard therapy (ie 6 months of Leuprorelin acetate before and during radiotherapy) will reduce prostate cancer-specific mortality (PCSM) when compared with standard therapy alone.

There are three secondary objectives:

(a) to test the hypotheses that 12 months adjuvant androgen deprivation (specified above) will reduce PSA progression (PSA-P), local progression (LP), distant progression (DP), secondary therapeutic intervention (STI), all-cause mortality (ACM), and improve quality of life (QOL);

(b) to test the hypotheses that 18 months of bisphosphonate therapy using zoledronic acid will reduce osteopenic fractures (OPF), improve bone mineral density (BMD), delay or prevent the onset of bony progression (BP) or metastases at any site (distant progression [DP]), delay or prevent secondary therapeutic intervention (STI), and improve quality of life (QOL) when compared to patients in this trial who are not treated with bisphosphonate therapy;

(c) to determine the nature of interactions between the total duration of androgen deprivation and:
   i the addition of bisphosphonate therapy;
   ii increasing radiation dose, within the structured radiation dose escalation program built into the design of the trial, with respect to LP, DP and PSA progression;
   iii increasing Gleason score with respect to all-cause mortality;
   and the interaction between the use of bisphosphonate therapy and Gleason score at the ≤7/>7 cutpoint identified in 2014 for the BP and STI endpoints. [90]

A tertiary objective of the trial is to determine whether intercurrent medical conditions will impact independently on delayed radiotherapy morbidity and other treatment related morbidity.

2.2 Endpoint hierarchy in 10 year analyses (2017)

Primary: Prostate cancer-specific mortality

Secondary:
(a) Distant progression
(b) Bone and nodal progression
(c) Secondary therapeutic intervention
(d) All-cause mortality
(e) PSA progression
(f) Local progression

3 TRIAL DESIGN

3.1 This is a randomised phase III multi-centre clinical trial.

3.2 After informed consent is given and eligibility is double checked patients will be randomised to one of four trial arms:

A. 6 months of androgen blockade with an LH-RH analogue (5 months before start of radiotherapy) (STAD),
B. 18 months of therapy with zoledronic acid 4 mg by intravenous infusion every 3 months for 18 months beginning concurrently with STAD
C. 18 months of androgen blockade with an LH-RH analogue (starting 5 months before start of radiotherapy) (ITAD),
D. 18 months of therapy with zoledronic acid beginning concurrently with ITAD.

Stratification will be according to the following criteria:

T2 / T3, 4
Gleason score 2 – 6 / 7+
Presenting PSA <10 / 10 – 20 / >20
Treatment centre*

* Note that centres opting to use both brachytherapy boost techniques and high dose conformal, or IMRT external beam techniques in different patient subgroups will be classed as two different centres for the purposes of stratification.

4 PATIENT ELIGIBILITY

4.1 Inclusion criteria

4.1.1 Histological confirmation of adenocarcinoma of the prostate taken within four months prior to the date of randomisation if the patient's Gleason Score is 6 or less, and six months prior to randomisation if the Gleason Score is 7 or more
4.1.2 Gleason primary and secondary pattern reported. If the volume of tumour in biopsies is too small for the pathologist to allocate a secondary pattern, the primary pattern alone is sufficient
4.1.3 Primary tumour stage T2b - 4 (UICC 2002), or T2a providing biopsies demonstrate Gleason score 7 or more, **and** presenting PSA 10 or more
4.1.4 PSA value obtained within one month of randomisation
4.1.5 No evidence of lymphatic or haematogenous metastases, as determined by negative chest x-ray, CT scan of abdomen and pelvis, and bone scan in the 3 months prior to randomisation
4.1.6 ECOG performance status 0 - 1
4.1.7 No concurrent medical conditions likely to significantly reduce prospects of 5 year survival
4.1.8 Patient accessible to follow up in the Investigator's clinic at intervals specified in protocol
4.1.9 Written informed consent given (signed by both patient and investigator prior to randomisation)

4.2 Exclusion criteria

4.2.1 Previous or concurrent malignancy within previous 5 years except for non-melanomatous skin cancer
4.2.2 Prostatectomy
4.2.3 Prior pelvic radiotherapy
4.2.4 Prior hormone treatment for prostate cancer
4.2.5 Inability to complete self administered QOL questionnaire
4.2.6 Prior bisphosphonate therapy
4.2.7 Serum creatinine > 2 x ULN
4.2.8 Osteoporosis resulting in >30% loss in vertebral height in one or more thoraco-lumbar vertebrae
4.2.9 Liver disease resulting in ALT or AST levels >3 x ULN
4.2.10 Prolonged continuous glucocorticoid therapy > 10 mg/day of prednisone equivalent (>6 months)
4.2.11 Current treatment with bisphosphonate
4.2.12 Inability to attend for follow-up at the Investigator's clinic

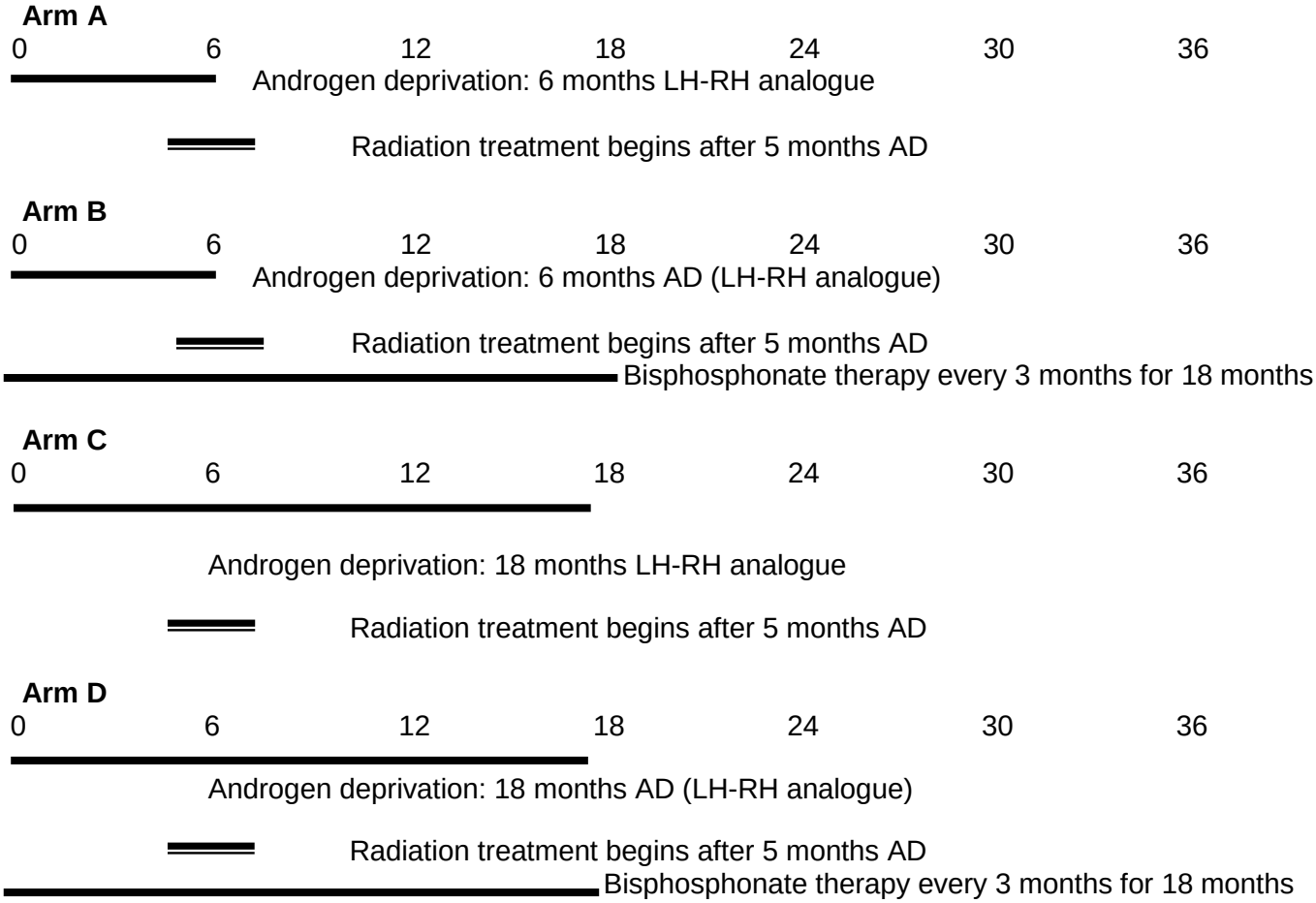
5 REGISTRATION AND RANDOMISATION

5.1 Registration and randomisation will take place at the Central Trials Office, Department of Radiation Oncology, Newcastle Mater Hospital, Waratah NSW 2298, Australia
Tel: +61 (0)2 4921 1462, Fax: +61 (0)2 4921 1153.

5.2 Registration should be performed by faxing completed Patient Registration Forms (BPT-Pre-Random, CA0, CP0, R0) to the Central Trials Office, together with a copy of the chest and thoraco-lumbar x-ray report. The Registration Form includes a checklist of eligibility / ineligibility criteria. Randomisation will normally be performed, and then confirmed by fax, within one hour (Office hours: 8.00am to 5.00 pm AEST).

6 TREATMENT PLAN

6.1 Summary



6.2 Radiation Treatment

6.2.1 General principles

Radiation therapy will start 5 months following initiation of drug administration. Radiation therapy must commence no more than two weeks prior to or two weeks post the 5 month RT start date given in the patient's trial treatment schedule. Technique and dose will be determined (see below) and declared to the Central Trials Office prior to each patient randomisation.

All centres may treat any number of patients using conventional external beam therapy (CEBT) as outlined in section 6.2.3. The prescribed dose will be 66 Gy in 33 fractions of 2 Gy to the ICRU 50 point utilising a minimum of three fields with $\geq$ 6 MV photons.

Centres utilising a 'conformal therapy' technique at any dose level will follow the requirements set out in section 6.2.4. MLCs or contoured blocks will be used to shape the portal to match the tumour volume in three dimensions. For the purpose of this trial, 'conformal therapy' will imply a treatment plan of up to two treatment volumes as defined in section 6.2.4.1 and a conformity index of no greater than 1.5 for each phase (PTV1 and PTV2) of treatment. Conformity index[91] is defined as the ratio of the volume of tissue encompassed by the 95% isodose surface divided by the prostate volume. Note that this definition is not strictly valid when the 95% isodose crosses the treatment volume. Where the volume of tissue outside this isodose is small compared to the prostate volume, the index will be measured according to the definition ignoring the violation of the definition.

The guiding principles that form the foundations of the technical requirements for dose delivery outlined below have been derived after acknowledging that competing priorities will affect the ultimate dose distribution achieved in an individual case. Of primary importance in the treatment of prostatic cancer is that the posterior aspects of the planning target volume do not fall within a zone in which the dose distribution achieved steeply declines. This is because prostatic cancer often begins its natural history in the posterior rim of the lateral lobes. Whilst maintaining an adequate dose on the posterior aspect of the prostate, it is also necessary to ensure that significant volumes of rectal tissue are not encompassed within the high dose volume. An important warning in this regard was sounded by Pollack et al (2002)[92], who found that delayed rectal injury was very significantly more likely if 25% of the rectal volume received doses of 70 Gy or more during a conventionally fractionated course of conformal radiotherapy. Making it more difficult to reconcile these competing objectives is the fact that the prostate has been shown to move during and between treatment fractions in the anterior-posterior direction and, to a lesser extent, in the cranio-caudal direction. Some authors have suggested that as much as 10 mm needs to be added to the posterior margin of the planning target volume to accommodate this movement[93-96]. Others have drawn attention to the observation that rectal filling is a key determinant of prostatic organ motion[97,98].

Some of these problems are overcome by the use of a HDR boost, which is an allowable option in this trial. Firstly, the dose gradients that exist around the HDR catheters allow more favourable posterior prostate to anterior rectal dose ratios to be achieved. Secondly, transfixion of the prostate by the catheters eliminates organ motion.

However, most centres will be using external beam conformal techniques exclusively as IMRT techniques gradually come on-line and so the guidelines below allow centres to exercise some flexibility around a set of guiding principles. The first is that it will be the final composite dose distribution that will be used to determine satisfactory rectal dose volume histogram profiles and adequate coverage of the prostate volume. That is to say that centres are permitted to reduce field sizes during delivery of treatment, and therefore use more than one planning target volume. When such reductions are made will be technique dependent and be at the discretion of the treating centre. The consensus

workshop in Melbourne 2002 indicated that this point would vary between 46 and 60 Gy across Australia and New Zealand. However reached, the final composite dose distribution will aim to achieve at least 95% of the prescribed dose in the planning target volume (PTV). It will also aim to ensure that the rectal constraints set out in the trial are maintained. Limitation of organ motion was an important concern at the Melbourne consensus workshop in 2002, and all centres will be encouraged to develop protocols to limit rectal filling during treatment [99]. In instances where the rectum on CT is shown to have excessive filling, the patient should be placed on a high fibre diet plus bulking agent, eg fibrogel, and the CT scan repeated until the rectum diameter is no larger than the maximum diameter of the prostate. An alternative approach is to encourage all patients to follow a high fibre diet plus bulking agent if desired, starting at least one week prior to the CT scan and continue with this diet throughout treatment. A suitable protocol for use has been designed in Melbourne and described in Appendix 20.5.

Institutions who can verify for the Technical Advisory Committee that they meet the requirements for technical accuracy set out in Technical Appendix 20.1 may proceed to the dose escalation component of the study. In this component of the study the dose will be increased in 4 Gy increments with at least 20 patients treated at each level to a dose of 78 Gy (ie dose levels of 66, 70, 74 and 78 Gy).

Radiation target volume will be tailored in the individual patient according to the risk criteria based on the risk of cancerous invasion of the seminal vesicles set out in the Table below:

Medium Risk	T stage < 3b, **and** Gleason score < 8 **and** PSA < 20
High Risk	T3b/c, T4a/b **or** Gleason score 8-10 **or** PSA > 20

6.2.2 Technique: Common to all patients

6.2.2.1 Treatment Position

The patient may be treated either prone or supine according to departmental preference. Bladder filling will be consistent between CT simulation and throughout the treatment, for example the patient may be asked to drink a volume of fluid ½ hour before each treatment fraction. It is recommended that patients be encouraged to maintain an empty rectum at simulation and during treatment.

6.2.2.2 Structure Definition

Planning of radiation treatment can take place during the fifth month of AD, but not before, to ensure that the radiation target volume is not unnecessarily generous by the time radiation treatment begins. CT slices will be taken covering the pelvic region from the bottom of the SI joints to the ischial tuberosities with contiguous axial slices with a maximum thickness of 5 mm. The patient position and bladder filling at CT shall be as in 6.2.2.1.

The following structures are to be defined (contoured) on the CT slices:

- The PTV as defined in sections 6.2.3.3 and 6.2.4.3 below;
- The outer wall of the rectum shall be defined superiorly from: the cranial border (where the rectum turns horizontally into the sigmoid colon, usually at

the caudal border of the sacroiliac joint) to inferiorly the caudal border (defined as 15 mm caudal to the apex of the prostate[100]).

- ❖ The left femoral head shall be defined from the acetabulum to the inferior edge of the treatment field.

6.2.2.3 Fractionation

Treatment shall be administered in daily fractions, 5 days per week or 9 days per fortnight as per departmental policies, with all treatment fields for the appropriate technique delivered each day.

6.2.2.4 Positioning / Immobilisation

Positioning / immobilisation will be as per departmental policy and in accordance with the technical requirements of the trial (see Technical Appendix 20.1).

6.2.2.5 Physical Factors

Beam energy of treatment fields will be 6 MV photons and above. Field arrangements will be capable of producing dose distributions as specified below using a minimum of three fields. A perineal boost field is not permitted.

6.2.2.6 *Technical Requirements*

- ❖ Each participating department shall provide a method for the independent assessment of monitor unit calculations (ie independent of the normal planning system).
- ❖ A CT scanner capable of taking contiguous axial slices of thickness 5 mm to cover the pelvic region.
- ❖ A megavoltage linear accelerator with the following facilities:
  - Capable of delivering at least 6 MV photons;
  - Beam modification (ie 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 (either electronically (EPID) or with radiographic film) which can be used to identify orientation and position of the radiation field relative to anatomical structures to within 1 mm compared with DRR images. See Technical Appendix 20.1 for further details.

6.2.3 Technique: Conventional External Beam Therapy (EBT)

In addition to points 6.2.2.1 to 6.2.2.6 above:

6.2.3.1 Dose Specification

- ❖ The radiation dose will be 66 Gy in 33 of 2 Gy fractions prescribed to ICRU 50 reference point, with the PTV fully encompassed by the 95% isodose.

6.2.3.2 Field Definition

- ❖ A three or four field technique will be used and rectal shielding in lateral fields is required.

6.2.3.3 Treatment Volume

GTV = Prostate + extra capsular extension (medium risk)

GTV = Prostate + SV + extra capsular extension (high risk)

CTV = GTV

PTV = CTV + 1.0 cm with a posterior margin of 0.5 cm

- The apex of the prostate will be determined from an assessment at CT planning. Urethrography may be used also but the possibility of this study leading to a significant superior shift of the prostate volume should be considered[101].

6.2.3.4 Port Films / In Vivo

- 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 (eg 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 treatment planning position and treatment position.

6.2.4 Technique: Three Dimensional Conformal Radiotherapy (3DCRT)

In addition to points 6.2.2.1 to 6.2.2.6 above:

6.2.4.1 Dose Specification

- The dose specified can increase at each institution in 4 Gy increments from 66 Gy up to 78 Gy.
- For total dose > 66 Gy, the dose delivered to the ICRU 50 reference point will be delivered such that the final composite dose distribution will satisfy the rectal and femoral head constraints set out in section 6.2.4.2. It is expected that the larger treatment volume (PTV1) will receive a dose of 46 to 60Gy to the ICRU point with the remaining dose delivered to the reduced treatment volume (PTV2). The final dose distribution will aim to achieve at least 95% of the prescribed dose to the planning target volume (PTV) in all <u>three</u> dimensions.
- Each institution will treat a minimum of 20 patients before escalating to the next dose level.
- Each institution will seek approval from the Technical Advisory Committee before proceeding to the next dose level.
- If a site feels ready to escalate dose from the level it is currently using it must notify the Central Office and Technical Advisory Committee (TACT) and submit fresh set-up accuracy data if requested by TACT confirming that the desired escalation can be undertaken safely. The timepoint from when dose escalation is permitted for use in the RADAR trial will then be advised by the Central Office. More details appear in Appendix Section 20.1.

6.2.4.2 Field Definition

- ❖ The field arrangement is to be determined by individual centres and where possible will meet the following criteria:
  - For the outer wall of the rectum, the maximum dose that will be delivered to a percentage of the rectal volume is shown below[100]:

65 Gy	40%
70 Gy	30%
75 Gy	5%

  - For the femoral head, the maximum dose that may be delivered to a percentage of the femoral head volume is shown below:

35 Gy	100%
45 Gy	60%
60 Gy	30%

- ❖ Use of compensators and IMRT techniques will be permitted where centres can demonstrate their Technique meets the requirements of the Technical Committee (Technical Appendix 20.1)

6.2.4.3 Treatment Volume

GTV	=	Prostate + extra capsular extension (medium risk)
GTV	=	Prostate + SV + extra capsular extension (high risk)
CTV	=	GTV
PTV1	=	CTV + 1.0–1.5 cm with a posterior margin of 0.5–1.0 cm
PTV2	=	CTV + 0.0–1.0 cm with a posterior margin of $\leq$0.5 cm

* All volumes will be defined on the CT slices using a 3D planning system.

6.2.4.4 Port Films / In Vivo

- ❖ To verify field size and shielding, each portal shall be visually checked on at least one occasion during the first week of treatment. This will be repeated in the first week of treating the reduced volume (PTV2).
- ❖ To verify patient position, at least two port films or images (eg AP and one lateral) will be acquired daily in the first week of treatment and then weekly. Films or images will be compared with DRRs to detect systematic differences between treatment planning position and treatment position – see Technical Appendix 20.1 for further details.
- ❖ In vivo dose measurements are encouraged and mandatory for a dose prescription > 74 Gy for at least 10% of patients. See Technical Appendix 20.1 for further details.

6.2.4.5 Structure Definition

In addition to defining the PTVs and rectal wall as defined in section 6.2.2.2 the additional structure will be defined:

- The bladder for patients receiving 78 Gy to the ICRU 50 point.

6.2.4.6 Technical Requirements

6.2.4.6.1 Treatment Planning System

A 3D planning system shall be available. The computerised planning system should have the following capabilities:

- Accesses CT data to be utilised in three-dimensional planning (including beams-eye-view and non-coplanar planning). System must be 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 (eg 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 downloaded onto a CD. See Technical Appendix 20.2 for further details.

6.2.4.6.2 Treatment Equipment

Participating centres should have the following equipment which should be utilised for the treatment (and treatment assessment) of trial patients:

- An in vivo dosimetry system capable of estimating entrance doses for each treatment field to within 5% is encouraged and is mandatory for prescribed doses > 74 Gy for at least 10% of patients. This can include any device (eg diodes, TLD, MOSFETs) which has been established as stable and reliable within each particular department. In vivo dosimetry for exit / midline dose would also be encouraged.
- Immobilisation devices. These may be as per departmental policy, though data on set-up uncertainty for prostate patients using a department's technique should be available. Demonstrable set-up accuracy shall be within the guidelines of the protocol as given in Technical Appendix 20.1.

All centres will participate in a phantom study under the guidelines of the dosimetry QA protocol.

6.2.5 Technique: high dose rate brachytherapy (HDRB)

6.2.5.1 External beam radiotherapy as Phase 1

Participating centres may elect to treat some of their patients with a combination of external beam radiotherapy and a HDRB boost. The treatment technique (set-up, planning and implementation) may be either conventional or conformal (as documented above). The recommended external beam phase dose will be 46 Gy in 23 fractions.

6.2.5.2 HDRB boost:

- The HDRB may be delivered either before or after the external beam phase of treatment. If given before EBRT there shall be an interval of 1 – 3 weeks. If HDRB is given after EBRT allow a gap of 2 – 4 weeks.
- A remote after-loading system with Iridium-192 should be used, and the needles inserted through the perineum under trans-rectal ultrasound guidance.
- CT or MR based planning should be employed with a maximum slice thickness of 0.5 cm. The planning target volume will be the gross tumour volume (the prostate gland and any identified spread eg extracapsular extension).
- The dose prescription will be 19.5 Gy delivered in three fractions over 2 days to the isodose encompassing the PTV. Each fractional dose of 6.5 Gy shall be delivered over a time interval of no more than 90 minutes.
- The dose to the urethra should generally be constrained to 120% of the prescribed dose. To meet this constraint it may be necessary to compromise on the dose coverage on the anterior part of base of the prostate to 80% of the prescribed dose. The dose to the anterior rectal wall should be no more than 70% of the prescribed dose. No more than 50% of the volume should receive a dose greater than 150% of the prescribed dose, and no more than 15% of the volume should receive a dose greater than 200% of the prescribed dose.

6.2.6 Delays in external beam radiotherapy or HDR boost enforced by SAEs or equipment related logistical issues

Unavoidable delays or breaks in treatment are unfortunately inevitable. In completing therapy after unscheduled breaks no dose supplementation scheme is recommended while it remains unclear that deleterious time factor considerations (eg treatment course prolongation increases the risk of local progression) are operative.

6.3 Hormone and Bisphosphonate Treatment

6.3.1 All patients entered into this trial begin their treatment program with 6 months androgen deprivation (AD), achieved as follows:

LH-RH analogue (Leuprorelin acetate, Lucrin®) depot every 3 months at 0, and 3 months.

Treatment should commence within seven days of randomisation.

Patients who experience disabling hot flushes after Lucrin may receive medication (including Cyproterone acetate) for this at the discretion of their treating clinician.

6.3.2 Patients will be monitored at the start of the third and sixth months to ensure that the PSA is falling, and to document toxicity of the treatment.

6.3.3 All patients will begin their radiation treatment at the end of month five of AD (no less than 4.5 months and no greater than 5.5 months after the initiation of AD). Planning of radiation treatment should take place no more than a month before radiation treatment is due to begin to ensure that the radiation target volume is not unnecessarily generous by the time radiation treatment begins.

6.3.4 Patients on Arms C and D will receive an additional 12 months of LH-RHa, delivered as a depot at months 6, 9, 12 and 15.

6.3.5 All patients will be randomised to either receive zoledronic acid 4 mg (bisphosphonate therapy) every 3 months for 18 months by intravenous infusion over 15 minutes or **no** bisphosphonate therapy. (Please see Arms A, B, C and D in Section 6.1 above).

Patients who experience disabling flu like symptoms after bisphosphonate infusion may receive medication for this (including hydrocortisone 50 mgs i.v.i at the time of the bisphosphonate infusion if paracetamol is unhelpful) at the discretion of their treating clinician.

6.3.6 Three monthly LH-RH analogue depot and bisphosphonate infusions must be administered no more than one week prior to, or one week post the treatment date listed in the patient's trial schedule (distributed from the Central Trials Office). If this is not possible, a reason for early or delayed drug administration must be provided to the CTO (either in writing on the BPT form or in the form of a file note, except around public holidays).

6.3.7 Patients on bisphosphonate therapy will have their serum creatinine, calcium and phosphate levels checked at baseline, then prior to their next infusion of zoledronic acid therapy (months 3, 6, 9, 12 and 15) and further tests at months 18 and 24 and then at every six months. At other times, serum creatinine monitoring should be done in accordance with clinical standard of care.

The serum creatinine result must be evaluated according to the following criteria:

- If the patient's baseline serum creatinine was <125 μmol/l at the time of study entry, an increase of 45 μmol/l or more will require the delaying of the dose of study drug until the patient's serum creatinine returns to no higher than 10% above the baseline value.

- If the patient's baseline serum creatinine was ≥ 125 μmol/l, then any increase in the serum creatinine of 90 μmol/l or more will require that the study drug be delayed until the patients serum creatinine returns to no higher than 10% above the baseline value.

- Any doubling of the baseline serum creatinine value will require that the study drug by delayed until the patient's serum creatinine returns to no higher than 10% above the baseline value.

Should the study drug need to be delayed, the patient's serum creatinine will continue to be followed at intervals according to the investigator's clinical judgement, but at least at the regularly scheduled study visits until full recovery (ie return to no higher than 10% above the baseline value). The patients should continue their regularly scheduled visits, even if they are not getting their infusion of study medication.

Minor degrees of hypocalcaemia induced by zoledronic acid can be managed with oral calcium supplements. Significant degrees of hypocalcaemia resulting in tetany necessitate dose delays or reductions after discussion with the Central Trials Office.

6.4 Treatment on Progression

6.4.1 This trial specifies the initial treatment to be used on relapse. This is to ensure that any differences that may be demonstrated in mortality reduction and PSA control cannot be attributed to under-utilisation of androgen deprivation in some patients.

6.4.2 The appropriate initial hormone treatment on relapse is independent of the **nature** of the relapse, ie it can be local progression, distant progression, or a combination of the two. In some instances, a rising PSA will be the only indicator of relapse, and the precise site of progression will be unknown. Because patterns of anatomical site of failure are so important in determining whether the additional interventions tested in this trial (ie 12 months additional AD and/or 18 months of zoledronic acid) are efficacious, salvage treatment is **not** recommended before site of progression is determined or before the PSA level reaches 20 *(see section 7.3 – Post Radiotherapy assessments)*. The Relapse Diagnosis Guidelines in Appendix 21 are mandatory reading and must be understood by all Investigators and Sub-investigators.

6.4.3 The appropriate initial androgen deprivation treatment on relapse is highly dependent on the **timing** of the progression in relation to previous, or even current, hormone treatment:

(a) Progression within 3 months of completing LH-RH analogue treatment (ie within 6 months of last depot injection) – initiate treatment with non-steroidal anti-androgen therapy of choice.

(b) Progression after completion of adjuvant LH-RH analogue treatment (STAD or ITAD), and 3 months has elapsed (ie 6 months since last depot injection) – initiate treatment with LH-RH analogue or bilateral orchidectomy. A non-steroidal anti-androgen may be used in addition, or alternatively held in reserve as second-line hormone treatment.

6.4.4 **In addition** to the androgen deprivation treatment detailed above, the investigator may deliver regionalised treatment, eg palliative radiotherapy, Strontium 89, as he/she sees fit. Treatment subsequent to failure of the androgen deprivation detailed above is entirely at the clinician's discretion.

7 PATIENT ASSESSMENT

7.1 Pre-treatment assessments

The following assessments will be done before the commencement of treatment:

(a) Registration form – inclusion and exclusion criteria ***(Form CA0)***
(b) Registration Physical Exam ***(Form CP0)***
(c) PSA/Testosterone Pre Registration ***(Form BPT)***
(d) Registration Biochemistry ***(Form BB0)*** (See ***Form BB0*** for complete list)
(e) Registration FBC ***(Form BH0)*** (See ***Form BH0*** for complete list)
(f) DEXA ***(Form DEXA) (required only if indicated by thoraco-lumbar x-ray)***
(g) Thoraco-Lumbar X-ray ***(Form TLX)***
(h) Quality of Life ***(Form QOL)***
(i) Randomisation – Bone scan, lymph node assessment ***(Form R0)***

Following randomisation the following assessments will be performed:

(a) Medical History Registration ***(Form CH0)***
(b) Symptomatology: Clinical Assessment ***(Form CS0)***

7.1.1 Clinical Assessment at Registration

Clinical assessment should focus on ***(Form CA0)***:

(a) Inclusion Criteria (see 4.1):
- Gleason Grade and Score;
- T Stage;
- Results of CX-Ray, CT Scan of abdomen and pelvis, and Bone Scan;
- ECOG.

(b) Exclusion Criteria (see 4.2):
- Concurrent/previous malignancy;
- Prior prostatectomy, pelvic radiotherapy, androgen deprivation, bisphosphonate or steroid therapy;
- Compromised renal or hepatic function;
- Osteoporosis resulting in spinal fracture (ie >30% compression in 1 or more vertebrae).

Physical examination should focus on ***(Form CP0):***

(a) pre-treatment assessment of the prostate gland with digital rectal examination. The Investigator should stage the primary tumour according to the UICC TNM Classification. The findings should be accurately recorded in the medical notes, as well as the registration form, for purposes of source data verification during monitoring.
(b) Summary of TRUS biopsy, nodal staging
(c) Bone scan results

The medical **history** should focus on ***(Form CH0)***:

(a) symptoms suggestive of active intercurrent medical conditions;
(b) any past medical history of intercurrent medical conditions.;
(c) current medications related to the listed conditions;
(d) alcohol and tobacco history;
(e) Blood pressure, ECOG, standing height and weight.

Symptomatology should focus on ***(Form CS0)***

(a) baseline urological symptoms;
(b) baseline gastrointestinal symptoms such as: CTC proctitis, lower bowel symptoms;
(c) Sexual function symptoms.

7.1.2 Imaging

All baseline imaging must be performed within 3 months prior to randomisation. (If imaging is performed outside 3 months, an eligibility query can be submitted to the Central Trials Office).

The following investigations will be used to exclude presence of macroscopic lymph node and bone metastases:

(a) chest x-ray – also required to check no radiological evidence of cardiac failure ***(Form CA0)***.
(b) radionuclide bone scan ***(Form R0)***.
(c) lymph node assessment ***(Form R0)*** *(*CT scan of pelvis and abdomen or nodal sampling).
(d) thoraco lumbar x-ray ***(Form TLX)***
(e) DEXA (only required if indicated by thoraco-lumbar x-ray)
(f) plain x-rays

The DEXA should only be performed at the time of the initial investigations in order to rule out osteoporosis if there is an indication that the patient has reduced bone mineral density. ***(Form DEXA)***.

Patients will undergo a bone mineral density (BMD) assessment, by dual energy x-ray absorption (DEXA) of the lumbar spine and hip and a lateral radiograph of the thoracolumbar spine. These will document initial bone mineralisation and the existence of osteoporotic fractures, and provide comparators for later assessments.

Other radiological investigations are optional, and at the discretion of the investigator, eg plain x-rays of an abnormality on bone scan. When results are equivocal for metastatic disease, the investigator will need to arbitrate on the basis of risk factors for metastatic disease, ie high PSA and/or Gleason score, and whether or not there is an alternative explanation for the radiological abnormality. If in doubt the patient should be excluded from the trial.

If a centre wishes to use MRI in place of CT in the assessment of the primary cancer and regional lymph nodes it is perfectly at liberty to do so but must use this method of investigation for all subsequent patients randomised at that centre (to avoid biases due to inappropriate stratification) and should notify the Central Office of this decision.

7.1.3 Histopathology and Blood Assessments

(i) Histopathological examination of prostatic tissue taken within four months prior to the date of randomisation if the patient's cancer is assigned a Gleason Score by the institutional pathologist of 6 or less, and six months prior to randomisation if the Gleason Score is 7 or more. Adenocarcinoma must be confirmed for entry into this trial. Prostatic tissue will generally be obtained by biopsy of the prostate under ultrasound control, but curettings obtained at trans-urethral resection are an acceptable alternative, recorded on ***Form CA0.***

The following baseline studies must be performed within one calendar month prior to randomisation:

(ii) Serum total PSA ***(Form BPT Pre Randomisation)***
(iii) Serum testosterone. ***(Form BPT Pre Randomisation)***
(iv) Full blood count. ***(Form BH0)***
(v) Serum alkaline phosphatase. ***(Form BB0)***
(vi) Fasting blood glucose. ***(Form BB0)***
(vii) Fasting cholesterol, HDL, LDL, triglycerides. ***(Form BB0)***
(viii) Serum creatinine – to be used to determine whether patient is suitable for bisphosphonate therapy. ***(Form P0)***
(ix) Serum phosphate. ***(Form P0)***
(x) Corrected serum calcium. ***(Form P0)***
(xi) 25 hydroxy-vitamin D. ***(Form BB0)*** It is recommended that the co-administration of Vitamin D and Calcium is the standard practice for those patients who are found to be Vit D deficient. For patients found to have 25 hydroxy-vitamin D levels below 25 nmol/L ergocalciferol (ostelin 1000) 1000 units together with Caltrate 500 mg daily or a calcium enhanced diet is considered appropriate.
(xii) Other Biochemistry as required. ***(Form BB0).*** The investigator can elect to perform other biochemistry more frequently if deemed necessary.

7.1.4 Other assessments

(a) Laparoscopic lymph node biopsies – generally, these are optional, and performed at the discretion of the investigator. However, they are recommended when the CT scan is equivocal for lymph node involvement, eg a single enlarged (>10 mm) pelvic lymph node. ***(Form R0)***

(b) A baseline Quality of Life (QOL) ***(Form QOL)***, EORTC QLC-PR25 ***(Form QP0)***, and Urinary Symptom Score (AUA IPSS) ***(Form QU)*** self-assessment questionnaires should be completed by the patient, **before** initiation of any treatment.

7.2 Assessments during treatment

7.2.1 Clinical assessments

(a) All patients will have a follow-up examination by the investigator at 3, 9 and 12 months ***(Form CS)***. At each assessment and at the 6 month point, the side effects of AD will be documented by the patient ***(Form QD)***.

(b) There will be a symptomatology assessment at the end of radiation treatment, approximately 30 weeks, ***Form CS EndXRT***.

(c) Further toxicity assessment after radiation treatment will be at 9 months ***(Form CS9),*** approximately 2 months after the end of radiation treatment. This corresponds to when the 4th dose of LH-RH analogue is due for those patients on ITAD (Arms C and D) and the 4th dose of bisphosphonate (Arms B and D).

(d) Patients on all four arms will have a clinical assessment for Symptomatology 3 monthly for 1 year after discontinuing AD in all four arms then every 6 months to five years. Depot injections of LH-RH analogue due between formal assessment visits can be administered by clinic staff or the general practitioner, whichever is more appropriate.

(e) All patients will have a serum creatinine every 3 months for the first 24 months for toxicity known to be associated with bisphosphonate therapy.

(f) Patients on bisphosphonate therapy will only proceed with this therapy if their serum creatinine is within 110% of the baseline value.

(g) All patients, whether or not on bisphosphonate, will have any incidental non-metastatic fractures documented at the same time clinical assessments are performed ***(Form CS).***

7.2.2 Biochemical assessments

(a) Apart from PSA measurements at 6 and 18 weeks all serum PSA will be measured, just prior to each clinical assessment ***(Forms BPT or CFU)***. However, the Investigator can elect to perform the test more frequently if he/she is concerned that PSA progression may be occurring. These additional tests should be reported to the CTO on **Form BPTA**. It is recommended that the PSA be repeated no more frequently than once a month under such circumstances. Furthermore, uncertainties in PSA value should be taken into account before it is concluded that an upward trend is occurring.

(b) Serum total testosterone will be measured at the time of the second LH-RH analogue depot injection, to ensure that satisfactory androgen deprivation has been achieved ***(Form BPT3)***.

7.2.3 Imaging

Patients with symptoms suggesting fracture(s) should have appropriate imaging arranged when the fracture occurs or at the next clinical assessment.

7.2.4 QOL and Symptomatology Self-assessment

Patients will complete the EORTC global (QLQ-C30) ***(Form QOL)***, prostate specific (PR25) (***Form QP***), and the AUA (urinary assessment) ***(Form QU)*** modules at each quality of life assessment. These will be done at baseline, at 3 months to measure the impact of the initial testosterone suppression and at the end of radiotherapy to quantify the contribution of acute radiation toxicity. It will be necessary to do further assessments at months 12, 18 and 24 to characterise differences attributable to the 6 and 18 month period of testosterone suppression and also to measure the impact of late radiation effects.

7.2.5 Assessment procedures for patients ceasing Leuprorelin acetate or bisphosphonate therapy prematurely

Should a patient not complete the indicated course of Leuprorelin acetate or bisphosphonate:

(a) ***Form P*** should still be completed indicating the reason study drugs were ceased (eg clinical decision, patient decision, intolerable side-effects or other)

(b) **Arm A and B patients** – No change to CRF completion required

(c) **Arm C and D patients** – If a patient ceases Lucrin treatment after 3 or 6 months, CRFs are to be completed as normal until 9 months. At 9 months a ***CFU form*** should be completed in addition to CRFs required at 9 months. A ***CFU form*** is then required at each subsequent follow up until 15 months. If Lucrin is ceased at any other follow up a ***CFU form*** in addition to normal CRFs should be completed at that time. Subsequent follow ups until 15 months should also include the completion of a ***CFU form***. From 18 months onwards CRFs should be completed as normal. (For Arm D patients ceasing Zometa early there is no change to CRF completion)

7.3 Post Radiotherapy Assessment

7.3.1 Clinical assessments (Refer to appendix 19.2 for schedule of assessments)

(a) **STAD (Arms A and B)** – Following radiotherapy follow-up will be 3 monthly for 1 year then 6 monthly until 5 years post randomisation, then annually thereafter.

(b) **ITAD (Arms C and D)** – Follow-up assessment will commence 3 months after last LHRH depot and occur 3 monthly for 1 year then 6 monthly until 5 years post randomisation then annually.

Clinical Follow-up Forms will capture relapse data at these visits ***(Forms CFU).*** Symptomatology: Clinical Assessment will be continued simultaneously using the ***Forms CS***. (NB: Form CS will not be required from 2015 onwards after quality of life and toxicity reports have been completed.) The Drug Related Effects will be completed by the patient and recorded on the ***Form QD***.

Note on assessing local progression: DRE assessment of local progression is strongly recommended at all follow-up time points prior to the commencement of secondary therapeutic intervention. In order to assess a trial endpoint, it must be measured. Frequency of local progression is especially important to the trial outcome as it directly relates to future choices of radiation dose and technique. Data from the 96.01 trial indicate that higher rates of local progression occurred in centres following the protocol assessment schedule. This indicates that there was an under-diagnosis of local progression in centres that did not perform DREs as per the trial clinical assessment timetable.

7.3.2 Haematological and biochemical assessments

(a) Prior to radiotherapy serum PSA will be measured at baseline, 6, 12 and 18 weeks using ***Form BPT***. Subsequent serum PSA estimations will occur at months 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 and annually using ***Form BPT***.

(b) Total Testosterone will be measured for those patients in Arms A and B at months 3, 6, 12, 18, 24 and 30 ***(Form BPT or CFU Arms A&B).*** For patients in Arms C and D the test will be done at months 3, 6, 24, 30, 36, and 42 ***(Form BPT or CFU Arms C&D).*** This is to ensure that the level has returned to within normal limits and that false positive PSA progression is not called during rises in testosterone levels after completion of AD. If the value of the repeat testosterone is at least 75% of the initial value, but still below the lower limit of normal for the patients age this will be classed as acceptable. If recovery is not complete, the test should be repeated again 6 months later. If, at the subsequent test, the level of testosterone still has not recovered, a luteinizing hormone level test is to be ordered. The results are to be recorded on ***Form BPT (Arm A&B or C&D).*** For patients in all Arms who have not started salvage therapy a Total Testosterone will be measured at 8 years (to be reported on ***CFU Annual form).***

(c) Full blood count will be measured at months 12, 18, 24, 30, 36, 42, 48, 54, 60 and annually using ***Forms BH***. These will discontinue from 2015 onwards after toxicity reports are completed.

(d) Serum creatinine for patients in all arms will be measured at months 3, 6, 9, 12, 15, 18, 24. For patients in arms B and D, calcium and phosphate will be measured at months 3, 6, 9, 12, 15, 18, and 24 ***(Forms P)***.

(e) **PSA progression** is defined using the Phoenix definition[74]. In this method PSA progression is not "called" (declared) until the PSA value rises 2ngs/ml above the absolute nadir value recorded after completion of therapy. PSA rises during testosterone recovery (ie a post treatment "rebound") or while some function returns in normal prostatic epithelial cells (ie rises to a PSA post treatment "plateau") must be viewed cautiously in the context of serum testosterone levels of the time. Some Phoenix fails are falsely positive during these events, and in cases of doubt Phoenix fail should not be called until further PSA values have been obtained to establish what is happening (see Relapse Diagnosis Guideline in Appendix Section 21). The timing of Phoenix failure is the date of the first PSA reading that rises 2ng (or more) above the nadir value.

The diagnosis of PSA progression is not necessarily a reason to immediately initiate salvage therapy, as usually the patient will be completely asymptomatic at the time. Also, the PSA is often still quite low, so it is unlikely that restaging investigations will detect such a small tumour burden. In this trial, patients who undergo PSA progression, and who remain asymptomatic, will normally be just monitored until the PSA exceeds 20 ng/ml. Chest x-ray, bone scan, and CT scan will then be repeated. Re-biopsy of the prostate is not routinely recommended in this trial, as the result is unlikely to influence clinical management. It is particularly important that PSA doubling time be estimated accurately prior to diagnosis of relapse site or institution of salvage therapy as suggested in the Relapse Diagnosis Guidelines (Appendix Section 21). This may be valuable in the derivation of a surrogate marker for pre-radiological evidence of bone metastases.

Once failure site is determined management **should** then be instituted according to the guidelines in section 6.4.3 of this protocol. Patients do, however, retain the right to request earlier initiation of salvage treatment, if they believe this is in their best interests.

Rate of change of PSA and PSA doubling time will be calculated for all relapsing patients for subsequent exploratory prognostic analyses.

The relapse follow-up form ***(Form CFU -ST)*** is to be completed at least 6 monthly once salvage therapy is initiated.

7.3.3 Imaging

(a) Imaging to be performed in the event of PSA progression is specified in section 7.3.2 above.

(b) All patients who have previously had a DEXA performed at baseline whether on bisphosphonate or not, will have their bone mineral density assessed by DEXA (dual energy x-ray absorption) scans of the lumbar spine and hip after 2 and 4 years on the trial ***(Form DEXA)***.

(c) Lateral thoraco-lumbar spine x-rays will be performed for all patients at 3 years ***(Form TLX)***. Osteoporotic fracture will be defined as a difference between the heights of the anterior and posterior borders of the vertebral bodies. All TLX films will be reviewed centrally by an expert radiologist.

(d) All other imaging performed is entirely at the discretion of the Investigator.

7.3.4 Quality of Life and Symptomatology Assessments

QOL assessment in the follow up period will occur at 18, 24, 36 and 60 months, as well as post-salvage therapy according to the schedule provided in Appendix 19.2. These post treatment assessments are necessary to document the prolonged effects of testosterone suppression and radiation dose utilised. **Form QOL** can be completed during or post salvage therapy either 6 monthly or annually as CFUST forms are completed. Patient self-assessments will no longer be required from 2015 onwards after quality of life and toxicity reports have been completed. Patients participating in the "Life 10 years after Prostate Cancer Treatment" Substudy (Section 21.2) will also complete a final comprehensive survivorship questionnaire at 10 years.

7.4 Procedures in the event that patients are lost to hospital follow up visits

Every effort must be made to collect minimum levels of information concerning each patient's medical status, even if the patient becomes too elderly and/or infirm to attend regular hospital follow up review.

7.4.1 Remote follow-up patients

Usually, patients who are unable to or do not wish to attend regular hospital follow-up visits are perfectly willing to provide information concerning their health to their trial centre by telephone or allow trial management staff to collect their pathology/other results remotely. These patients should be given the opportunity to maintain contact (telephone or other) with data management staff at the treatment centre according to trial schedule.

Some may arrange for their local practitioner (GP, urologist or other) to return information to the trial centre (including PSA estimates). Some may be willing to complete self assessment questionnaires through the post. These patients will be known as 'remote follow-up patients'. ***Form W*** should initially be completed for these patients which enables the reason for and method of remote follow-up to be documented.

Remote follow-up patients will continue on their usual trial schedule (6 monthly or annual visits) so that as much information as possible can be collected using ***Form RF***. Q forms (QOL, QP, QU) may be sent to the patient for completion and returned to the data manager.

7.4.2 Total Withdrawal Patients

Patients who choose to discontinue contact with their treatment centre as well as further collection of follow-up information must have this right respected. Under these circumstances the patient is withdrawing his consent to participate in any way in the trial and becomes a 'total withdrawal'. Information concerning his continuing medical status will therefore be curtailed. Total withdrawal from the trial should be the decision of the patient (or his guardian) exclusively (i.e. not staff from the treatment centre itself). The treatment centre will complete ***Form W*** which enables the patient (or his guardian) to provide a reason for his withdrawal if he so wishes.

7.4.3 Deceased patients

Cause of Death: Every effort must be made to ascertain date and cause of death in patients who have **not** withdrawn totally from the trial. These data will be recorded on ***Form D.*** Additional information about the death may be recorded using the ***Supplementary Death Form*****.**

7.5 Procedures in the event that a patient transfers to another institution

Should a patient participating in the RADAR Trial wish to transfer to another institution:

7.5.1 Patients transferring to a hospital participating in the RADAR trial

For patients who wish to transfer to another hospital, and who still wish to continue with trial treatment, every effort must be made to ensure that the patient is transferred to a trial centre participating in the RADAR Trial (*please contact the Central Trials Office before the patient is transferred*). This is to ensure that the centre has the necessary ethical approval and resources to monitor patient care and collect trial data in accordance with protocol requirements.

Once a participating hospital has been identified, the Central Trials Office must be notified of the transfer and the following documentation should occur:

(a) All assessments, laboratory tests, etc due up until the transfer date will need to be performed at the original trial centre, and CRFs completed and processed accordingly by the original trial centre

(b) Copies of all CRFs completed up to the transfer date need to be retained by the original trial centre, as well as all source documentation for this time period

(c) A second copy of all CRFs and source data need to be provided by the original trial centre to the new trial centre (including copies of laboratory tests and imaging)

(d) The transfer should be thoroughly documented in the source data at both the original and new trial centre

(e) The patient is required to re-consent at the new trial centre

It is important to note that, for analytical purposes, the patient will be recorded as a patient of the original trial centre. The new trial centre will be responsible for completing all CRFs, sending originals to the Central Trials Office (CTO) and keeping copies of CRFs on site.

Also, in terms of radiation treatment, the total dose (Gy) for the patient will need to remain identical to that at randomisation (refer to the patient's Randomisation Form (RO) for details of dose level selected). Exceptions may need to be considered if the 'new' treatment centre is not using conformal treatment techniques or has submitted set-up accuracy data to the TACT for a lower total dose than that of the original treatment centre.

7.5.2 Patients transferring to a hospital not participating in the RADAR Trial

Patients who transfer to a hospital, not participating in the RADAR trial and who want to continue their participation, will become "remote follow-up" patients (see 7.4.1)

7.5.3 Patients transferring who do not wish to continue participating in the RADAR trial

Patients who transfer to another hospital, and do not wish to continue their participation in any way in the RADAR trial, will be considered as total withdrawals regardless of whether they are still receiving treatment or are on follow-up (see 7.4.2)

7.6 Procedures for "Out of Town" patients

Timeframes specified throughout the protocol reflect the acceptable timeframes for treatment, assessment, etc. These timeframes may not correspond with available clinic times for those patients who live out of town, and who are receiving Drug Treatment or Assessment by the Investigator at a centre different to the Trial Centre. In these cases, every effort should be made to schedule a visit as close to the protocol timeframe as possible.

8 PATHOLOGY

Central pathology review will be performed in Wellington, New Zealand, by Professor Brett Delahunt, Department of Pathology and Molecular Medicine, Wellington School of Medicine & Health Sciences. The purpose of the review is:

(a) To standardise the process involved in allocation of Gleason grade (pattern) and score, and to determine the magnitude of inter-observer variation between local and central pathologist. This is appropriate because of evidence that pathologists have a tendency to **under**grade prostate cancer[102]. The presence of patterns in addition to the primary and secondary pattern will also be noted.

(b) To quantify the **extent** of involvement of the prostatic biopsies. This will involve quantification of the number of cores containing tumour, and the percentage of malignant to benign tissue within each core. Extension of malignancy into extra-prostatic tissues, and perineural invasion, will be recorded, if present.

(c) To re-classify the biopsy material according to the criteria defined by the International Society of Urological Pathologists (ISUP)[103].

As soon as possible after randomisation, the Investigator should arrange for one H&E and three unstained sections of **each** positive core biopsy to be forwarded to Wellington, New Zealand (see address below), together with a copy of the local pathology report (to allow the biopsy site of each core to be determined). The office in Wellington will batch this pathological material, and forward it to Professor Delahunt. Once review has been performed, slides will be returned to the local pathologist. A copy of the report issued by Professor Delahunt will be sent to the Central Trials Office.

Judy Murray
Wellington School of Medicine & Health Sciences
Dept. of Pathology & Molecular Medicine
PO Box 7343
Wellington South
New Zealand

Please note the following definitions used in this trial:

(a) Gleason Primary Pattern – this is the predominant grade of malignancy seen in a biopsy specimen (scale 1-5).

(b) Gleason Secondary Pattern – this is the next most common grade of malignancy seen in a biopsy specimen (scale 1-5). This can be the same as the primary grade.

(c) Gleason Score – this is the summation of the primary and secondary pattern to produce a number between 2 and 10. A Gleason score can be for a single pathological specimen, or a summary of all the pathological material examined. If there is insufficient tumour to allocate a secondary pattern, then it is conventional to obtain a score by doubling the number of the primary pattern.

In this trial, the primary and secondary patterns will be requested at the time of registration, together with a copy of the pathology report. Stratification will be according to Gleason score (2 – 6 or 7+).

In accord with Australian and New Zealand ethical and regulatory guidelines[104,105], unstained slides will be retained for use in translational research studies, but will be processed for such purposes only after protocols for their use have been approved by the Trial Management Committee and appropriate patient consent and regulatory approvals have been obtained.

2014 main endpoint data from the RADAR trial were used to validate the newly proposed 2014 ISUP grading system.[106] This system was designed to replace the Gleason score with a simple 5 tier scale (grade 1, GS 3+3; grade 2, GS 3+4; grade 3, GS 4+3; grade 4, GS 8; grade 5, GS 9–10). The ISUP grading system will be used in sensitivity analyses for the 10 year main endpoints report in 2017.

9 CRITERIA FOR ASSESSING TREATMENT OUTCOMES

An Endpoints Audit Team performs annual case reviews of oncologic outcomes to ensure that assessment criteria have been applied correctly by the treating clinician. These outcomes include local progression, bony progression, nodal progression and prostate cancer-specific mortality. The Team consists of six senior radiation oncologists from RADAR sites in Australia and New Zealand who are blinded to treatment arm.

9.1 PSA Progression

(i) PSA Progression (PSA-P) will be determined according to the Phoenix definition. Date of progression is the date of the first PSA reading that exceeds the nadir value by 2ng/ml or more.

9.2 Local Progression

(i) Progressive Disease (PD): Signs of malignancy in the prostate not previously detected, in the presence of a rising PSA. These signs must be confirmed by the clinician (in charge) who routinely examines the patient at follow up.

(ii) False Assessment (FA): This rating will be assigned retrospectively, to a result previously assigned PD, if CR is recorded at the two next examinations.

9.3 Distant Progression

(i) Bony Progression: These should be confirmed by bone scan, Prostate Specific Membrane Antigen (PSMA) PET scan or plain x-rays, with the date of progression being the date the first abnormal result was obtained.

(ii) Nodal Progression: These should be confirmed by a CT scan of pelvis and abdomen or PSMA PET scan, with the date of progression being the date the first positive scan was performed.

Note: De-identified imaging reports must be provided to the CTO for all investigations regarding distant progression.

9.4 Secondary Therapeutic Interventions (STI)

The date and type of the first STI will be recorded for time to event analyses.

9.5 Prostate Cancer Specific Mortality (PCSM)

The date of death and its cause will be documented for time to event analyses. Death will be attributed to prostate cancer by the subject's treating clinician if the major contributing factor was prostate cancer or its treatment rather than an independent, intercurrent disease process.

9.6 All Cause Mortality (ACM)

Date of death due to any cause will be used in time to event analyses of ACM.

9.7 Transition to castrate resistant prostate cancer and tertiary therapy

Transition to castrate resistance and initiation of tertiary therapy occur when there is evidence of:

(i) a rising PSA in the presence of serum testosterone concentrations at castrate levels before, during and after the PSA rise; or

(ii) clinical progression following administration of at least 6 months LHRH ± anti-androgen preparation and rising PSA levels for at least 3 months prior to this progression (i.e. castrate testosterone concentrations are not required during this period).

9.8 Radiation Morbidity

Acute morbidity will be scored using the revised NCI Common Terminology Criteria for Adverse Events Version 3.0. Late effects (> 90 days from RT start) will be scored using RTOG/EORTC late radiation morbidity scoring criteria.

9.9 Quality of Life (QOL) Assessment

The analysis variable will be the difference in scores from baseline in each of the domains.

9.10 Treatment compliance

Treatment non-compliance: when a patient elects to stop treatment.

9.11 Time-to-event Definitions

All events are measured from the date of randomisation, unless otherwise stated. Data is censored at closeout date or loss to follow-up.

(a) PSA progression
competing risk — death from any cause

(b) Local progression
competing risk — distant progression diagnosed more than two months prior to local progression, death from any cause

(c) Distant progression
competing risk — death from any cause

(d) Bony progression
competing risk — Non-bony metastatic progression diagnosed more than two months prior to bony progression, death from any cause

(e) Nodal progression
competing risk — Non-nodal metastatic progression diagnosed more than two months prior to nodal progression, death from any cause

(f) All-cause mortality
competing risk — not applicable

(g) Prostate cancer-specific mortality
competing risk — death from cause other than prostate cancer

(h) Secondary therapeutic intervention
competing risk — death from any cause

10 DATA MANAGEMENT AND QUALITY ASSURANCE

10.1 Data Management

Case Report Forms (CRFs) will be supplied by the Central Trials Office, on CD. Investigators and/or data managers should complete the CRFs at the time of assessment, noting that Clinician (C) Forms as well as Death (D), Total Withdrawal (WT), and SAE forms must be signed by an Investigator (see section 15). At each clinic visit, Investigators and data managers should ensure that administration of hormone (LH-RH analogue) and bisphosphonate (zoledronic acid) treatment complies with the schedule described in this protocol. Radiotherapy treatment / planning data should be generated and collected in accordance with Technical Appendices 21.2, 21.3 and 21.4.

The completed originals of CRFs and QOL questionnaires should be forwarded to:

RADAR Data Management
Prostate Cancer Trials Group
University of Newcastle
University Drive
Callaghan NSW 2308
Australia

A copy of the completed CRF and QOL forms should be retained by the participating centre. When received at the Central Trials Office, the forms will be checked for legibility, accuracy and completeness. Staff at the Central Trials Office will follow up with the relevant institution on any deficiencies noted. The quality of data will be monitored during the trial, as high standards are considered essential for the success of the trial. The Safety and Data Integrity Committee will report to the Trial Management Committee (TMC) regarding accrual, timeliness of data return, missing data, protocol compliance and serious adverse events.

The Central Trials Office conducts eligibility checks for all patients at various stages. Throughout the study, copies of relevant documents (such as pathology reports, blood test results and CT reports) will be requested by the Central Trials Office if necessary for CRF edit checks and source data verification.

10.2 Source Documents

In accordance with Good Clinical Research Practice Guidelines, source documents must be maintained for all trial patients. The purpose of maintaining source documents is to document the existence of the subject and substantiate integrity of trial data collected.

Source documents include original documents related to the trial, to medical treatment and history of the subject, and include but are not limited to:

- Hospital records
- Clinical and office charts
- Laboratory notes including laboratory reports, each of which is to be reviewed and initialled by an Investigator
- Memoranda
- Subjects' diaries or evaluation checklists
- Pharmacy dispensing records
- Recorded data from automated instruments

- Copies or transcriptions certified after verification as being accurate copies
- Microfiches
- Photographic negatives
- Microfilm or magnetic media
- Subject files
- Records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinic trial
- Reports of all procedures, including X-Rays, Bone Scans (including original films). *In the case where scans are done off-site, or where the original scan is taken home by the patient, a copy of the Scan and Report should be filed in the patient's Medical Record for Source Data Verification purposes.*

Source documents must be retained for at least 15 years after completion of the trial and remain available for source data verification / audit if required in accordance with Good Clinical Research Practice Guidelines.

10.3 Investigators File

Each centre should keep documentation about this trial in an investigators' file, which should include the following essential documents:

- Protocol and appendices (including superseded versions)
- Amendments
- Signed Protocol Signature Pages
- Sample CRFs including blank SAE forms
- Patient information and Informed Consent templates approved by Ethical Committee
- Investigator's Brochure and updates
- Ethical Committee approval of protocol, Patient Information sheet and IC, amendments (current and previous)
- Ethical Committee review of SAE, investigators' alert, and other documents
- Correspondence with Ethical Committee
- Current and previous certificates of insurance
- Agreement with between parties (i.e contract of reimbursement for costs associated with participation in the RADAR trial)
- Monthly SAE reports from the RADAR Clinical Trials Office
- Monthly Accrual reports from the RADAR Clinical Trials Office
- Normal laboratory values and Laboratory Certifications
- CV of Principal Investigator and co-Investigators
- Trial Signature list
- Patient Screening log
- Patient Identification log
- Audits/monitoring reports
- Technical QA booklets (Physicist and Radiation Therapist)
- SOPs for:
  - Screening log
  - Registration and Randomisation
  - Special Eligibility
  - Monitoring and Source Data Verification
  - Pathology
  - SAEs

The above essential documents will be monitored throughout the course of the trial, and may also be audited by auditors / regulatory bodies as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

10.4 Treatment Verification

10.4.1 Site Technical Requirements

Specific details about Radiotherapy Treatment review processes are outlined in the Technical Appendices (Section 21).

Participating centres must satisfy the requirements of the Technical Advisory Committee of the Trial (TACT) to proceed (at any dose level) with three dimensional conformal radiotherapy (3DCRT) (Technical Appendix 20.1). After commencing conformal therapy, a centre must treat at least 20 patients on the same dose level, and receive a renewal of verification (of technical accuracy) from the Technical Advisory Committee, before escalating treatment dose to the next level.

To treat trial patients using conformal therapy (3DCRT), a participating institution will be required to:

- Submit a set-up accuracy report (before treating any patients with 3DCRT);
- Perform in-vivo dosimetry (mandatory for at least 10% of patients receiving 78 Gy);
- Participate in a dosimetric intercomparison phantom study (this will be conducted during the active accrual phase of the trial).

10.4.2 Patient Technical Reviews

In accordance with TROG policy (Section 8, Policy and Procedures Manual: Quality Assurance Statement of Minimum Requirements for Clinical Trials) technical reviews will be conducted for this study. The reviews will be coordinated by the Technical Advisory Committee of the Trial (TACT) and results will be reported to the TMC and the TROG Trials Scientific Committee at least 6 monthly, and to the Safety and Data Integrity Committee as required.

Radiotherapy Technical Reviews will be conducted in 2 stages:

Stage 1: The first 10 patients entered from each institution will be reviewed. If major violations are identified this rate of sampling will continue until an acceptable level of quality is maintained. Sites then progress to Stage 2 auditing.

Stage II: All institutions will continue to be reviewed based on a ‘spot check’ 1-in-10 sampling of patients registered for this trial (or one patient every 6 months, whichever is sooner).

- Checklists outlining the patient information required for technical reviews will be provided by the Central Trials Office.
- All required information should be forwarded to the Central Trials Office within 2 weeks of each patient completing radiation therapy.
- All radiotherapy documentation and planning data for trial patients should be archived once patients have completed treatment and remain available if required for audit.

10.4.3 Patient Eligibility and Treatment Monitoring

Three monthly reviews of hormone and bisphosphonate treatment data will be undertaken to assess and verify compliance with the protocol by the Safety and Data Integrity Committee. The CRF will capture sufficient data to enable assessment of potential treatment violations. Any violations will be categorised according to TROG policy. Results of monitoring will be reported to the TMC at least 6 monthly, and to the TROG Scientific Committee biannually.

Site visits are intended to be conducted as part of the source/data and pharmaceutical prescription verification activities of this trial. Monitoring visits will commence at the discretion of the Trial Management Committee (subject to available funding). The purpose of monitoring visits will be to ensure trial protocol is being followed, and to perform source data verification on patient eligibility and all endpoint data. Formal monitoring reports will be completed following each visit.

11 SAFETY AND DATA INTEGRITY COMMITTEE

This committee comprising senior data management staff from centres in Australia and New Zealand will be established and chaired by the Safety & Data Monitoring Officer.

11.1 Purpose

The main purpose of the committee is to provide monitoring of recruitment information, serious adverse events, adverse events, compliance with pharmaceutical administration protocols, data returns and source data verification. It will report to the TMC. It will also assist in assembling data for the Independent Data Monitoring Committee (Section 13).

11.2 Meetings

Meetings may be held via teleconference or, if convenient, face-to-face, and members should be in email or other contact between meetings.

11.3 Replacement Members

The SDIC will decide on a replacement in the event that any member of the SDIC is unable to continue serving on the SDIC.

11.4 Roles and Responsibilities

The SDIC will:

- Monitor safety data: incidence and grade of severity of toxicities, (especially serious adverse events) and occurrence of unexpected toxicities.
- Monitor accrual data: to ensure trial goals can be met within a reasonable time.

11.5 Data reviewed

- recruitment
- eligibility criteria violations
- safety data: SAEs, toxicities (by modality, type and grade)
- deaths and their causes, especially treatment-related deaths
- pharmaceutical protocol compliance
- patient withdrawals (withdrawn consent and losses to follow-up): frequency and causes
- data quality (timeliness of returns and source data verification)
- outcomes

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1 Adverse Events (AEs)

Information about all adverse events (AEs), whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be documented in the patients' medical record and followed up as appropriate by the Investigator. Treatment specific adverse events will be recorded on the CS Forms.

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Study treatment includes the study therapy given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History Registration Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded on the appropriate forms (ie ***Forms QD, BPT or CFU)***.

12.2 Serious Adverse Events (SAEs)

Investigators are responsible for monitoring the safety of patients treated according to this protocol and must report any Serious Adverse Event (SAE) within 24 hours of its detection.

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in another medically significant event

Events **not** considered to be serious adverse events are hospitalisations for the:

- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen;
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission;
- Hospitalisation during the day and not involving an overnight admission;
- Basal cell carcinoma and squamous cell carcinoma;
- Laboratory events lower than grade 4 (ie grades 1 – 3 according to Common Terminology Criteria for Adverse Events Version 3), except where the investigator considers the event to fulfil the seriousness criteria;
- Hospitalisation overnight when only occurring due to distance travelled by patient.
- Prostatectomy

12.2.1 Reporting of Serious Adverse Events

All Serious Adverse Events that occur whilst the patient is receiving Lucrin or Zometa are required to be reported **whether or not considered related to** the treatment under investigation. An SAE must be reported for all events occurring within 30 days of the patient receiving their final dose of Lucrin or Zometa. A Serious Adverse Event that occurs more than 30 days after the final dose is required to be reported only if the event is considered related to Lucrin or Zometa or to radiation therapy.

SAEs should be reported to the Safety & Data Monitoring Officer (fax: +61 (0)2 4921 1153) within 24 hours by completing the SAE form ***(Form SAE1)***.

The Safety & Data Monitoring Officer will forward a copy of all SAE reports (as required) to TROG Central Operations Office, and 'suppliers' of Leuprorelin and Zoledronic Acid.

All SAE forms must be signed by the **Investigator**. Should the investigator not be available to sign the SAE1 Form within the 24 hour period, a **comment** to that effect should be written on the form and the form faxed without signature to the Safety & Data Monitoring Officer as above. The investigator should sign the form as soon as possible, and all 6 pages of the form should be re-faxed to the Central Trials Office.

If all details are not available at the time of the initial report, a completed report must be sent within the next 10 days. If the event is not resolved (or 'on-going') at the time of the initial report, a new SAE Form ***(Form SAE1), with mandatory sections completed at minimum,*** must be submitted to the Safety & Data Monitoring Officer every 30 days until the event is resolved or has stabilised. If a change occurs in a stable condition (ie it either worsens or improves), then a follow-up ***Form SAE1*** should be faxed to the Safety and Data Monitoring Officer. Supplemental pages ***(Form SAE2)*** can be used to accompany ***Form SAE1*** if extra space is required for relevant information.

The Investigator is responsible for ensuring their institutional Ethics Committee are notified of SAEs in accordance with local requirements.

Serious Adverse Events reported for this trial will be reviewed by the TMC and reported to the TROG Scientific Committee biannually.

13 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee will be established, comprising at least 3 persons with knowledge of prostate cancer and/or medical statistics, but without any direct involvement in the trial.

13.1 Purpose

The main purpose of the Independent Data Monitoring Committee (IDMC) is to independently monitor the conduct of the trial and where necessary perform interim analyses in order to ensure its ethical and scientific integrity[107,108]. The IDMC can make recommendations concerning amendments to the protocol and premature closure of the trial. Recommendations (and their rationale) of the IDMC will be made to the TMC, which will be the final authority for all decisions made. The priorities of the IDMC are, in order, to patients, investigators entering patients and the TMC.

13.2 Meetings

Meetings may be held via teleconference or, if convenient, face-to-face, and members should be in email or other contact between meetings. The IDMC will be disbanded after close of accrual following final assessment of all on study and treatment data.

13.3 Replacement Members

The TMC will decide on a replacement in the event that any member of the IDMC is unable to continue serving on the IDMC.

13.4 Roles and Responsibilities

- Monitor safety data: incidence and grade of severity of toxicities, (especially serious adverse events) and occurrence of unexpected toxicities.
- Monitor accrual data: to ensure trial goals can be met within a reasonable time.
- More generally, to assess and advise on criteria for early stopping of the trial.
- Request any data or analyses of data that will be of assistance to them in carrying out their responsibilities. Analyses of comparative efficacy data should be sought only if there is a strong indication for it, for example in order to adequately assess the importance of differential rates of toxicity between the two treatment arms.
- Review factors external to the trial when interpreting data, such as scientific or therapeutic developments that may impact on the safety of participants or ethical aspects of the trial.

13.5 Data reviewed

- eligibility criteria violations
- safety data: SAEs, toxicities (by modality, type and grade)
- deaths and their causes, especially treatment-related deaths
- protocol compliance
- patient withdrawals (withdrawn consent and losses to follow-up): frequency and causes
- data quality
- outcomes

Prior to each meeting, the IDMC will receive a report from the trial central data management centre. This report may include data requested by the IDMC.
The format of the meetings may be:

- open session with the trial statistician and, possibly, another TMC representative
- executive session

The Chair of the IDMC will send a formal report of each IDMC meeting to the Chair of the TMC.

14 STATISTICAL CONSIDERATIONS

14.1 Trial Design

This is a randomised, open label, 2×2 factorial design trial. The 'factors' are androgen deprivation duration (STAD versus ITAD) and bisphosphonate therapy (BT) (not given versus given). The primary aim of the trial is to determine, in patients with localised prostate cancer treated with radiation, whether ITAD is superior to STAD with respect to prostate cancer-specific mortality (PCSM). There are a number of secondary aims including: (i) to determine whether duration of androgen deprivation and/or BT is related to PSA progression (PSA-P), all-cause mortality and quality of life (QOL); and (ii) to determine whether bisphosphonate therapy is effective in reducing the risk of osteoporotic fractures (OPF), the risk of bony progression (BP) and all metastases (distant progression [DP]), and loss of bone mineral density (BMD). In this trial STAD represents the control arm and ITAD the experimental arm in the absence of interaction with BT.

14.2 Randomisation and Stratification

Patients will be randomly allocated to the four treatment arms (STAD, STAD+BT, ITAD, ITAD+BT) in a ratio of 1:1:1:1, subject to maintaining approximate balance with respect to the levels of the stratification variables: stage (2 levels), Gleason score (2 levels), presenting PSA (3 levels) and treatment centre (radiation oncology department). Balance will be achieved using the minimisation technique with a random element. Absolute confidentiality will be maintained as to the identity of the next treatment to be assigned.

14.3 Statistical Methods

The primary analyses will be performed according to the intention-to-treat policy; that is all patients with a histological diagnosis of adenocarcinoma of the prostate will be included and analysed according to the arm to which they were randomly assigned, regardless of treatment compliance or deviation from the protocol.

Baseline characteristics by treatment arm (STAD versus ITAD and no BT versus BT) will be summarised, in frequency tables and descriptive statistics. The summarised baseline characteristics will include the stratification variables, age, QOL score, urinary and rectal symptoms, performance status, intercurrent medical conditions, osteoporotic and sporadic fracture status, BMD, and type of RT used. Summary tables by treatment arm giving numbers of patients by completion of assessments, treatment compliance, dropouts and randomisation errors will be prepared.

Additive interactions between the trial factors will be explored for each endpoint by comparing the point estimates and confidence intervals for all four trial arms in the regression model. If there is no evidence of interaction, arms can be collapsed to compare STAD versus ITAD and no BT versus BT. If there is an interaction, comparisons of the individual trial arms will be undertaken. Due to the interaction between BT and GS at the ≤7/>7 cutpoint identified in 2014 (described in Section 2), a specific procedure is outlined below for the 10 year data analyses.

1. For every endpoint 10 year cumulative incidence will be calculated and compared by univariable analysis to estimate unadjusted sub-hazard ratios for treatment arm effects. To avoid inflating type 1 error for secondary endpoints with multiple pairwise comparisons, all four treatment arms will be kept separate by coding as a four level dummy variable. Omnibus (global) testing for significant treatment group effects will then proceed.
2. For endpoints in which omnibus tests are positive, interactions between the treatment factors and GS at the ≤7/>7 cutpoint will be tested on additive and multiplicative scales according to STROBE recommendations [109,110].
3. In the absence of interactions unadjusted pairwise cumulative incidence comparisons by treatment factor will be undertaken. In the presence of interactions pairwise comparisons between the trial arms will be undertaken and stratified by GS as defined in Section 8.

4. Subgroup analyses deemed necessary to explore important aspects of the overall findings will be undertaken using Forest plots.

Close-out dates will be determined at the time of main analyses usually 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 possible bias arising from the earlier reporting of follow-up for patients who experience an event.

Ninety-five percent confidence intervals (95% CI) for differences between arms of all important endpoints will be calculated. All p-values will be two-sided.

14.3.1 Analyses of Primary Objective

The cumulative incidence method will be used to estimate PCSM and treatments will be compared using Gray's test. If the interaction between GS and the use of BT identified in 2014 is confirmed in 2017, it will necessitate pairwise comparisons of all four trial arms and thus substantially reduce the powers to discriminate between the effects of the experimental trial arms when compared with the STAD control arm. If trial factor or trial arm differences for PCSM cannot be resolved in the 10 year analysis in 2017 due to lack of power, a sensitivity analysis will be performed using a composite endpoint of PCSM and transition to castrate resistant prostate cancer status events.

2014 PSA and distant progression data and secondary therapeutic intervention data provide evidence that the ITAD trial arms will have fewer PCSM events than the STAD arms in 2017. As these endpoints are upstream of PCSM, this would suggest that the composite PCSM/CRPC endpoint will not be necessary in 2017. However the PCSM event numbers for the STAD/ITAD arms in 2014 provide no such suggestion.

14.3.2 Analyses of Secondary Objectives

In the event that there are no interactions between AD duration and BT the competing risks cumulative incidence methodology of Gray's test will be used to compare duration of AD subgroups. Fine and Gray modelling will be used to derive sub hazard ratios and 95% confidence intervals for PSA progression, local and distant progression, and secondary therapeutic intervention. The Kaplan-Meier method will be used to estimate all-cause mortality and treatments will be compared using the log-rank test.

The effectiveness of the radiation dose escalation scheme will be assessed using cumulative incidence of PSA, local and distant progression in Fine and Gray models[111] adjusted for trial arm and baseline covariates (age, PSA, stage and Gleason score).

14.3.3 Timetable for Analysis of the Main Endpoints

Two main endpoint analyses are planned at 6.5 and 10 years from randomisation i.e. February 2014 and August 2017. The 10 year power calculations may require modification when 6.5 year data become available in 2014.

14.4 Power Calculations

It is aimed to accrue 1000 eligible patients over four years and to follow up patients indefinitely. There is one primary objective but also many important secondary objectives and the following power calculations indicate the adequacy of this number of patients to carry out these objectives.

14.4.1 Power Estimates

Two scenarios need to be addressed for the 10 year main endpoints analysis in 2017. Firstly, if an interaction between the use of BT and GS 8-10 tumours for multiple endpoints is confirmed, the power to detect differences between trial arms stratified by GS grade ≤7/>7 is important. Secondly if such an interaction is not confirmed, the power to detect differences between the trial factors alone (i.e. the use of BT and the use of an additional 12 months of AD) is permissible and important.

Based on 2014 main endpoint data the power to detect reductions in the primary endpoint, PCSM, from the use of an additional 12 months AD is low (see Section 14.3.1). Assuming 148 events at data closeout and two-sided type 1 (α) error of <0.05, relative reductions less than 25% are unlikely to be detectable with a power greater than 50%.

However the trial will have sufficient event numbers in 2017 to provide a power exceeding 90% to detect differences with a two-sided α error of <0.05 between one or more of the experimental treatment arms and the control arm for the main secondary endpoint, distant progression, as well as for the lower hierarchy secondary endpoints, PSA and time to secondary therapeutic intervention. It will have a power exceeding 80% to detect treatment arm differences for the secondary endpoints bone and nodal progressions. If no interactions between the use of BT and GS persist and no new ones are detected, comparisons of each endpoint by trial factor (ie an additional 12 months AD and 18 months BT) will be undertaken, with powers exceeding 90% to detect differences between factors for all endpoints at p-values <0.025.

The projected effect sizes of treatment group differences are summarised in the Table below:

Assuming GS/BT Interaction (comparison of trial arms)		
	ITAD v STAD	ITAD+BT v STAD
Distant progression All	0.61	0.56
GS ≤7	0.36	0.68
GS 8-10	0.70	0.40
Bony progression All	0.61	0.53
GS ≤7	0.30	0.53
GS 8-10	0.85	0.50
Nodal progression All	0.66	0.60
GS ≤7	0.46	0.72
GS 8-10	0.68	0.47

Assuming No GS/BT Interaction (comparison of trial factors)		
	BT v No BT	ITAD v STAD
Distant progression	1.00	0.57
Bony progression	1.02	0.54
Nodal progression	0.88	0.67

15 RESPONSIBILITIES OF THE INVESTIGATOR

The study will be performed in accordance with the CPMP/ICH Notes 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.

This trial protocol, including the patient information sheets and informed consent form, must be approved by an ethics committee before entry of patients onto the trial. The patient information sheets are designed to be generic for all investigators, and contain information that TROG is legally obliged to supply to all potential trial participants. The text must therefore not be deleted, although it is perfectly allowable for additional information to be provided to suit local requirements.

Before entering patients, the Investigator must forward a copy of the ethics committee approval and a copy of the approved patient information sheet and consent form to the Central Trials Office, making it clear which version of the protocol was submitted for review. The Principal Institutional Investigator should chair a local 'start up' meeting involving all parties involved in the care of patients participating in this study.

The investigator (ie the Specialist (Radiation Oncologist) who enrols the patients) is required to ensure compliance with all aspects of this protocol. In particular, it is the responsibility of the Principal Institutional Investigator to ensure that all Investigators and their delegees (ie their registrar staff – referred to as "Sub-investigators" in ICH GCP guidelines) are familiar with all provisions of the protocol (including its appendices and modifications) and comply fully (except in instances where it is unsafe to do so). In the event that a patient moves away from the area or becomes too infirm to attend follow-up with the Investigator, (after treatment is complete), the Investigator may seek the support of the patients' GP or Urologist to continue follow-up contact. In doing so the GP or Urologist must agree to take on the role of a Sub-investigator (and become familiar with and apply the protocol in consultation with the Investigator) (See Section 7.5).

It is the responsibility of the investigator to maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. It is the responsibility of the Investigator to maintain adequate and accurate case report forms (CRFs). The investigator may give authority for adequately qualified data management staff to complete and sign clinical case record forms accurately from source documentation on his/her behalf. This arrangement is only available via consultation with the Central Trials Office and requires the completion of a Clinic Data Authorisation Form. Should a correction be made to the CRF, the information to be modified should not be overwritten. The corrected information should be written next to the previous value, along with the initials of the person making the change, and the date the change was made.

The investigator is responsible for informing the ethics committee of any SAE and/or amendments to the protocol as per local requirements.

16 REPORTING OF RESULTS

The Central Trials Office will prepare interim reports every 6 months (for presentation to the Trial Management Committee) summarising protocol compliance and the quality of the submitted data. Investigators will be advised of these results, but they will not be reported externally.

The timing of external reporting after completion of treatment of all trial patients will be advised by the trial statistician. It is anticipated that definitive reporting on the primary end-points will be in one of the major medical journals.

17 PUBLICATION POLICY

The Trial Management Committee (TMC) has full responsibility for primary presentation and/or publication of results. Individual clinicians/investigators must not publish any trial data without the approval of the Trial Management Committee. Authorship of any publications arising from this study will be defined according to the Vancouver agreement of the International Committee of Medical Journal Editors, ie substantial contribution to the following criteria:

(i) study conception and design, or analysis and interpretation;
(ii) drafting article for presentation or publication, or critical revision;
(iii) final approval of version to be published.

In addition, investigators who are major contributors of evaluable cases may also be listed as authors.

18 REFERENCES

1. Labrie F. Combined androgen blockade: its unique efficacy for the treatment of localised prostate cancer. *Principles and Practice of Oncology Updates.* 1999;13(2).
2. Cancer in Australia 1996: Incidence and mortality data for 1996 and selected data for 1997 and 1998. Canberra: Australian Institute of Health and Welfare (AIHW) and Australasian Association of Cancer Registries (AACR); 1999.
3. New Zealand Health Information Service. New Zealand cancer registrations and deaths 1995. 1999.
4. Labrie F, Dupont T, Belanger A, al e. New hormonal therapy in prostatic cancer: combined treatment with an LHRH agonist and an anti-androgen. 1982;5:267-275.
5. Janknegt RA, Abbou CC, Bartoletti R, al e. Orchiectomy and Nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomised trial. *J.Urol.* 1993;149:77-83.
6. Denis LJ, De Moura JLC, Bono A, et al. Goserelin acetate and flutamide versus bilateral orchiectomy: A phase III EORTC trial (30853). *Urology.* 1993;42(2):119-130.
7. Crawford DE, Eisenberger MA, McLeod DG. A controlled trial of leuprolide with and without flutamide in prostate carcinoma. *N.Engl.J.Med.* 1989;321:419-424.
8. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. 1997;337(5):295-300.
9. Beland G, Elhilali M, Fradet Y, al e. Total androgen blockade versus castration in metastatic cancer of the prostate. In: Motta M, Serio M, eds. *Hormonal therapy of prostatic diseases: basic and clincal aspects*. The Netherlands: Medicom Europe; 1988:302-311.
10. Denis LJ, Keuppens F, Smith PH, al e. Maximal androgen blockade: final analysis of EORTC Phase III trial 30853. *Eur.Urol.* 1998;33:144-151.
11. Hanks GE, Lee WR, Hanlon AL, et al. Conformal technique dose escalation for prostate cancer: Biochemical evidence of improved cancer control with higher doses in patients with pretreatment Prostate-Specific Antigen > 10ng/ml. *International Journal Radiation Oncology Biology Physics.* 1996;35(5):861-868.
12. Pilepich MV, Sause WT, Shipley WU, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: A randomized comparative trial of the Radiation Therapy Oncology Group. *Urology.* 1995;45(4):616-623.
13. See WA, Wirth MP, McLeod DG, et al. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localised or locally advanced prostate cancer: First analysis of the early prostate cancer program. *J.Urol.* 2002;168:429-435.
14. Bolla M, Collette L, Gonzalez D, al e. Long term results of immediate adjuvant hormonal therapy with goserelin in patients with locally advanced prostate cancer treated with radiotherapy - A phase III EORTC study. *Eur.J.Cancer.* 1999;35(Supplement 4):S82.
15. Hanks GE, Lu JD, Machtay M, al e. RTOG Protocol 92.02: A Phase III trial of long term total androgen suppression following neo-adjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate. *International Journal Radiation Oncology Biology Physics.* 2000;48(Suppl 3):112.
16. Pilepich MV, Winter K, Byhardt RW, et al. Androgen ablation adjuvant to definitive radiotherapy in carcinoma of the prostate: Year 2000 update of RTOG phase III studies 86-10 and 85-31. *International Journal Radiation Oncology Biology Physics.* 2000;48(Suppl 3):169.
17. Shearer RJ, Davies JH, Gelister JSK, Dearnaley DP. Hormonal cytoreduction and radiotherapy for carcinoma of the prostate. *Br.J.Urol.* 1992;69:521-524.
18. Gleave ME, Goldenberg SL, Jones EC, Bruchovsky N, Sullivan LD. Biochemical and pathological effects of 8 months of neoadjuvant androgen withdrawal therapy before radical prostatectomy in patients with clinically confined prostate cancer. *J.Urol.* 1996;155:213-219.
19. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet.* 2002;360(9327):103-108.
20. Pilepich MV, Caplan R, Byhardt RW, al e. Phase III trial of androgen suppression using goserelin in unfavourable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of the Radiation Therapy Oncology Group Protocol 85-31. *J.Clin.Oncol.* 1997;15:1013-1021.

21. Roach MI, Lu J, Pilepich MV, et al. Predicting long-term survival and the need for hormonal therapy: A meta-analysis of RTOG prostate cancer trials. *International Journal Radiation Oncology Biology Physics.* 2000;47(3):617-627.
22. Tait DM, Nahum AE, Meyer LC, et al. Acute toxicity in pelvic radiotherapy; a randomised trial of conformal versus conventional treatment. *Radiother.Oncol.* 1997;42:121-136.
23. Christie DRH, Denham JW, Steigler A, et al. Delayed rectal and urinary symptomatology in patients treated for prostate cancer by radiotherapy with or without short term neo-adjuvant androgen deprivation. *Radiother.Oncol.* 2005;77(2):117-125.
24. Belanger A, Brochu M, Cliche J, al e. Levels of plasma steroid glucuronides in intact and castrated men with prostate cancer. *J.Clin.Endocrinol.Metabolism.* 1986;62:812-815.
25. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol.* 2005;6:841-850.
26. Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA, Eisenberger MA. Complete androgen blockade for prostate cancer: what went wrong? *J.Urol.* 2000;164(1):3-9.
27. Henderson A, Langley SEM, Laing RW. Is Bicalutamide equivalent to Goserelin for prostate volume reduction before radiation therapy? A prospective, observational study. *Clin.Oncol.* 2003;15(6):318-321.
28. Kiratli BJ, Srinivas S, Perkash I, Terris MK. Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology.* 2001;57:127-132.
29. Stoch SA, Parker RA, Chen L, et al. Bone loss in men with prostate cancer treated with gonadotropin- releasing hormone agonists. *J.Clin.Endocrinol.Metabolism.* 2001;86:2787-2791.
30. Wei JT, Gross M, Jaffe CA, et al. Androgen deprivation therapy for prostate cancer results in significant loss of bone density. *Urology.* 1999;54:607-611.
31. Daniell HW. Osteoporosis after orchiectomy for prostate cancer. *J.Urol.* 1997;157:439-444.
32. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer.* 1998;83:1561-1566.
33. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in post-menopausal women with low bone mineral density. *N.Engl.J.Med.* 2002;346(9):653-661.
34. Diamond TH, Winters J, Smith A, et al. The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomised placebo-controlled crossover study. *Cancer.* 2001;92(6):1444-1450.
35. Melton LJ, Alothman KI, Khosla S, Achenbach SJ, Oberg AL, Zincke H. Fracture risk following bilateral orchiectomy. *J.Urol.* 2003;169:1747-1750.
36. Diamond TH, Higano CS, Smith MR, Singer FR. Osteoporosis in men with prostate cancer receiving androgen deprivation therapy: Recommendations for diagnosis and therapies. *Cancer.* 2004;100(5):892-899.
37. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J.Natl.Cancer Inst.* 2002;94(19):1458-1468.
38. Dearnaley DP, Sydes MR, Mason MD, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J.Natl.Cancer Inst.* 2003;95(17):1300-1311.
39. Powles T, Paterson S, Kanis JA, et al. Randomised, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J.Clin.Oncol.* 2002;20(15):3219-3224.
40. Lee MV, Fong EM, Singer FR, Guenette RS. Bisphosphonate treatment inhibits the growth of prostate cancer cells. *Cancer Res.* 2001;61(6):2602-2608.
41. Boissier S, Magnetto S, Frappart L, et al. Bisphosphates inhibit prostate and breast carcinoma cell adhesion to unmineralised and mineralised bone extracellular matrices. *Cancer Res.* 1997;57:3890-3894.
42. Fournier P, Boissier S, Filleur S, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res.* 2002;62(22):6538-6544.
43. Ali SM, Esteva FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. *J.Clin.Oncol.* 2001;19(14):3434-3437.

44. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors. *J.Clin.Oncol.* 2005;23(34):8580-8587.
45. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases. *J.Oral Maxillo.Surg.* 2004;62:527-534.
46. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J.Oral Maxillo.Surg.* 2005;63:1567-1575.
47. Durie BGM, Katz M, Crowley J. Osteonecrosis of the Jaw and Bisphosphonates [Letter]. *N.Engl.J.Med.* 2005;353(1):99-100.
48. Tarassof P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. [Letter]. *J.Oral Maxillo.Surg.* 2003;61(10):1238-1239.
49. Lenz J-H, Steiner-Krammer B, Schmidt W, Fietkau R, Mueller PC, Gundlach KKH. Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? *Journal of Cranio-Maxillofacial Surgery.* 2005;33:395-403.
50. Marx RE. Pamidronate (Aredia) and zolendronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. [Letter]. *J.Oral Maxillo.Surg.* 2003;61(9):1115-1117.
51. Migliorati C. Bisphosphonates and oral cavity avascular bone necrosis. [Letter]. *J.Clin.Oncol.* 2003;21(22):4253-4254.
52. Assael AL. New foundations in understanding osteonecrosis of the jaws [Editorial]. *J.Oral Maxillo.Surg.* 2004;62:125-126.
53. Carter GD. Bisphosphonates and avascular necrosis of the jaws. *Aust.Dent.J.* 2003;48(4):268.
54. Klotz L. Hormone therapy for patients with prostate carcinoma. *Cancer.* 2000;88(12):3009-3014.
55. Stege R. Potential side-effects of endocrine treatment of long duration in prostate cancer. *Prostate Suppl.* 2000;10:38-42.
56. Crook JM, Perry GA, Robertson S. Routine prostate biopsies following radiotherapy for prostate cancer. *Urology.* 1995;45:625-632.
57. Scardino PT, Frankel JM, Wheeler TM, et al. The prognostic significance of post-irradiation biopsy results in patients with prostate cancer. *J.Urol.* 1986;135(3):510-515.
58. Sewell RA, Braren V, Wilson SK. Extended biopsy follow-up after full course radiation for prostate cancer. *J.Urol.* 1975;113:371-373.
59. Roach MI, Meehan S, Kroli S, et al. Radiotherapy for high grade clinically localised adenocarcinoma of the prostate. *J.Urol.* 1996;156(5):1719-1723.
60. Pollack A, Zagars GK. External beam radiotherapy dose - response of prostate cancer. *International Journal Radiation Oncology Biology Physics.* 1997;39(5):1011-1018.
61. Hanks GE, Martz KL, Diamond JJ. The effect of dose on local control of prostate cancer. *International Journal Radiation Oncology Biology Physics.* 1988;15:1299-1305.
62. Smit WGJM, Helle PA, van Putten WLJ, Wijnmaalen AJ, Seldenrath JJ, van der Werf-Messing BHP. Late radiation damage in prostate cancer patients treated by high dose external radiotherapy in relation to rectal dose. *International Journal Radiation Oncology Biology Physics.* 1990;18:23-29.
63. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet.* 1999;353:267-272.
64. Dearnaley DP. Radiotherapy of prostate cancer: established results and new development. *Semin.Surg.Oncol.* 1995;11:50-59.
65. Pollack A, Zagars GK, Starkschall G, et al. Conventional vs conformal radiotherapy for prostate cancer: Preliminary results of dosimetry and acute toxicity. *International Journal Radiation Oncology Biology Physics.* 1996;34(3):555-564.
66. Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J.Clin.Oncol.* 2000;18(23):3904-3911.
67. Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *International Journal Radiation Oncology Biology Physics.* 1998;41(3):491-500.
68. Zelefsky MJ, Leibel SA, Kutcher GJ, al e. The feasibility of dose escalation with 3 dimensional conformal radiotherapy in patients with prostatic carcinoma. *Cancer J.Sci.Am.* 1995;1:42-40.

69. Peeters ST, Heemsbergen WD, van Putten WL, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *International Journal of Radiation Oncology, Biology, Physics.* 2005;61(4):1019-1034.
70. Zagars GK, Pollack A, Kavadi VS, von Eschenbach AC. Prostate-specific antigen and radiation therapy for clinically localized prostate cancer. *International Journal Radiation Oncology Biology Physics.* 1995;32(2):293-306.
71. Zagars GK, Pollack R. Kinetics of Serum Prostate Specific Antigen after external beam radiation for clinically localised prostate cancer. *Radiother.Oncol.* 1997;44(3):199-302.
72. D'Amico A, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate End Point for Prostate Cancer-Specific Mortality After Radical Prostatectomy or Radiation Therapy. *Journal of the National Cancer Institute.* 2003;95(18):1376-1383.
73. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: Guidelines for PSA following radiation therapy. *International Journal Radiation Oncology Biology Physics.* 1997;37:1035-1041.
74. Thames H, Kuban D, Levy L, et al. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. *International Journal Radiation Oncology Biology Physics.* 2003;57(4):929-943.
75. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br J Radiol.* 1997;79:235-246.
76. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. *J Clin Oncol.* 1997;17:1155-1163.
77. Gaudin P. Histopathologic effects of radiation and hormone therapies on benign and malignant prostate tissues. 1998;8:55-67.
78. Cancer IUA. *TNM Classification of Malignant Tumours.* New York, USA: Wiley-Liss; 2002.
79. Ohori M, Wheeler TM, Kattan MV, al e. Prognostic significance of positive surgical margins in radical prostatectomy specimens. 1995;154:1818.
80. Kumar V, Cotran RS, Robbins SL. Disorders of Vascular Flow and Shock. *Basic Pathology*. 6th ed. Philadelphia: W.B. Saunders, Harcourt Brace Jovanovich, Inc.; 1992:61-70.
81. Ross R. Atherosclerosis - an inflammatory disease. 1999;340(2):115-126.
82. Denham JW, Hauer-Jensen M. The radiotherapeutic injury - a complex 'wound'. *Radiother.Oncol.* 2002;63(2):129-145.
83. Busch DB. Pathology of the radiation-damaged bowel. In: Galland RB, Spencer J, eds. *Radiation Enteritis*. London: Edward Arnold; 1990:66-87.
84. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor for late radiation morbidity. *International Journal Radiation Oncology Biology Physics.* 1999;43(3):475-479.
85. Denti L, Pasolini G, Cortellini P, et al. Effects of androgen suppression by gonadotropin-releasing hormone agonist and flutamide on lipid metabolism in men with prostate cancer: focus on lipoprotein (a). *Clin.Chem.* 1996;42(8):1176-1181.
86. Moorjani S, Dupont A, Labrie F, et al. Changes in plasma lipoproteins during various androgen suppression therapies in men with prostatic carcinoma: Effects of Orchiectomy, Estrogen and combination treatment with luteinizing hormone-releasing hormone agonist and flutamide. *J.Clin.Endocrinol.Metabolism.* 1988;66(2):314-322.
87. Henny CP, Cate H, Dabhoiwala NF, Buller HR, Cate JW. Effect of hormonal manipulation on antithrombin III activity in patients with prostatic carcinoma. *Eur.Urol.* 1984;10:202-206.
88. Denham JW, Steigler A, Wilcox C, et al. Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. *Lancet Oncol.* 2008;9:1058-1068.
89. Denham JW, Steigler A, Wilcox C, et al. Why are pretreatment prostate-specific antigen levels and biochemical recurrence poor predictors of prostate cancer survival? *Cancer.* 2009;115:4477-4487.
90. Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic

acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): An open-label, randomised, phase 3 factorial trial. *The Lancet Oncology.* 2014;15(10):1076-1089.
91. ICRU (International Commission on Radiation Units and Measurements) ICRU 62. *Prescribing, recording and reporting photon beam therapy (Supplement to ICRU Report 50).* Bethesda1999.
92. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomised trial. *International Journal Radiation Oncology Biology Physics.* 2002;53(5):1097-1105.
93. Beard CJ, Kijewski P, BussiŠre M, et al. Analysis of prostate and seminal vesicle motion: implications for treatment planning. *International Journal Radiation Oncology Biology Physics.* 1996;34(2):451-458.
94. Dawson LA, Mah K, Franssen E, Morton G. Target position variability throughout prostate radiotherapy. *International Journal Radiation Oncology Biology Physics.* 1998;42(5):1155-1161.
95. Roeske JC, Forman JD, Mesina CF, et al. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder and rectum during a course of external beam radiation therapy. *International Journal Radiation Oncology Biology Physics.* 1995;33(5):1321-1329.
96. Vigneault E, Pouliot J, LaverdiŠre J, Roy J, Dorion M. Electronic portal imaging device detection of radiopaque markers for the evaluation of prostate position during megavoltage irradiation: a clinical study. *International Journal Radiation Oncology Biology Physics.* 1997;37(1):205-212.
97. Padhani AR, Khoo VS, Suckling J, Husband JE, Leach MO, Dearnaley DP. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *International Journal Radiation Oncology Biology Physics.* 1999;44(3):525-533.
98. Zelefsky MJ, Crean D, Mageras GS, et al. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. *Radiother.Oncol.* 1999;50:225-234.
99. de Crevoisier R, Tucker SL, Dong L, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *International Journal of Radiation Oncology, Biology, Physics.* 2005;62(4):965-973.
100. Boersma LJ, van den Brink M, Bruce AM, et al. Estimation of the incidence of late bladder and rectum complications after high-dose (70-78 Gy) conformal radiotherapy for prostate cancer, using dose-volume histograms. *International Journal Radiation Oncology Biology Physics.* 1998;41(1):83-92.
101. Te V, Haken RK, Perez-Tamayo C, Thesser RJ, al e. Boost treatment of the prostate using shaped, fixed fields. *International Journal Radiation Oncology Biology Physics.* 1989;16:193-200.
102. Iczkowski KA, Bostwick DG. The pathologist as optimist: Cancer grade deflation in prostatic needle biopsies. *Am.J.Surg.Path.* 1998;22(10):1169-1170.
103. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. ISUP Grading Committee. *Am.J.Surg.Path.* 2005;29(9):1228-1242.
104. NHMRC., ARC., Australian Vice-Chancellors Committee. *National Statement on Ethical Conduct in Human Research: Second consultation draft (2006).* Canberra2006.
105. Ministry of Health. *Guidelines on the Use of Human Tissue for Future Unspecified Research Purposes 2006.* Wellington2006.
106. Delahunt B, Egevad L, Srigley JR, et al. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data. *Pathology.* 2015;47(6):520-525.
107. Ellenberg SS. Independent data monitoring committees: rationale, operations and controversies. *Statistics in Medicine.* 2001;20:2573-2583.
108. Fda. *Guidance for Clinical Trial Sponsors: On the establishment and operation of Clinical Trial Data Monitoring Committees (draft).* 2001.
109. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology.* 2007;18(6):805-835.
110. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol.* 2012;41(2):514-520.
111. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. . *J Am Stat Assoc.* 1999;94:496-509.

19 APPENDICES

19.1 Information Sheet and Patient Consent Form

INFORMATION SHEET

The 'RADAR' Trial – a Study of Radiation, Hormone and Bone Density Therapy for the Treatment of Localised Prostate Cancer

Coordinated by the Trans-Tasman Radiation Oncology Group (TROG)

INTERPRETER FOR MEDICAL INFORMATION *(NZ Sites to include this section)*:

English	I wish to have an interpreter	Yes	No
Maori	E Hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai
Cook Island	Ka inangaro au I tetai tangata uri reo	Ae	Kare
Niuean	Fai manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai

INTRODUCTION

This information sheet gives you more detail about the clinical research study your Doctor or Research Nurse discussed with you. This study will involve approximately 1000 men from Australia and New Zealand.

Your participation is entirely voluntary (your choice). Before deciding whether or not to take part in this study you should know the possible risks and benefits. If you decide to participate you will need to sign the consent form. You will be a 'study participant' during treatment and throughout the standard follow up period (at least 5 years).

It is your right to decide not to take part and if you decide not to participate in this study you can still receive standard treatment and care for your prostate cancer.

Discuss all treatment options with your doctor before consenting to participate in this study.

PROSTATE CANCER TREATMENT

As your doctor has explained, you have been diagnosed with localised cancer of the prostate.

STANDARD TREATMENT:

1. Radiation therapy: is the standard treatment for localised prostate cancer. High energy x-rays are directed at your prostate. The total amount of radiation therapy you can receive for your prostate cancer is limited by the 'radiation tolerance' of normal (non-cancer) tissue in that area. Treatment will usually be 5 days a week (not on weekends) with at least 33 treatments in total.

2. Hormone therapy: can be used before and during radiation therapy to help control prostate cancer. Prostate cancer needs male hormones (androgens) to grow. Drugs (such as 'Lucrin') 'deprive' your body of these hormones. Hormone therapy drugs are commonly given for a total of 6 months (starting 5 months before radiation therapy). The drugs are given every 3 months via an injection into muscle tissue.

NEW TREATMENT DEVELOPMENTS:

1. **Conformal Radiation Therapy**: is achieved by new technologies* and enables the shape of the area receiving radiation to be closely matched to the shape of your prostate. This reduces the amount of normal tissue in the treatment area. The total amount of radiation can be increased but side effects may also increase. Strict criteria must be followed for planning and monitoring conformal radiation treatment techniques. Clinical research studies can help provide hospitals with some of the resources required to develop this technique.

2. **Longer Hormone Therapy**: may improve the treatment of localised prostate cancer but this is not known for certain. Extending the overall time of your hormone therapy program to 18 months may be more inconvenient for you as it means that your hormone therapy would continue for approximately 1 year after radiation therapy has finished. You would have 4 more hormone injections than if you were on a standard (6 month) hormone therapy program.

3. **Bone Density Therapy**: using drugs called 'bisphosphonates' (such as 'Zometa') may reverse or prevent the loss of bone density that can sometimes occur with hormone therapy. It may also reduce the risk of secondary cancers developing in your bones but this is not known for certain. The drugs are given every 3 months via an 'infusion' injection into a vein. 18 months of bone density therapy may inconvenience you as it would continue for approximately 1 year after radiation therapy has finished. You would have 6 more injections than if you were receiving the 'standard' treatment of hormone therapy alone (no bone density therapy).

A clinical research study is needed to assess the actual benefits and risks and answer the questions:

1	Is 18 months Hormone Therapy better than 6 months Hormone Therapy?
2	Is Hormone Therapy With Bone Density Therapy better than Hormone Therapy Alone?

STUDY DESIGN

All participants on this study will have radiation therapy (RT). Whether or not you will receive 'conformal radiation therapy' depends on your hospital. They may elect to use the resources provided by this study to develop a conformal radiation therapy technique. Please discuss with your doctor whether or not 'conformal radiation therapy' will be part of your treatment.

If you consent to participate in this study, neither you or your doctor can choose whether you have 6 or 18 months of hormone therapy, or whether or not you receive 18 months of bone density therapy. This is a 'randomised controlled trial' (RCT) which means a computer will randomly allocate you to a standard or 'experimental' hormone therapy treatment program and a standard or 'experimental' bone density therapy treatment program. In this study, you will have an equal and un-biased chance (like tossing a coin) of being allocated to one of the 4 treatment groups. You will be told which group you have been randomised to before any treatment is given.

The 4 treatment groups (and their treatment programs) are:

GROUP A - RT and 6 months Hormone therapy
Radiation therapy begins after 5 months of hormone therapy.

GROUP B - RT, 6 months Hormone therapy and 18 months Bone Density Therapy
Hormone and bone density therapy start at the same time, radiation therapy begins 5 months later.

GROUP C - RT and 18 months Hormone therapy
Radiation therapy begins after 5 months of hormone therapy. Hormone therapy continues for 12 months after RT.

* these include the use of multi-leaf collimation, intensity modulation and high dose rate brachytherapy to confine radiation dose to the prostate itself. Ask your doctor for further details.

GROUP D - RT, 18 months Hormone therapy and 18 months Bone Density Therapy
Hormone and bone density therapy start at the same time. Radiation therapy begins 5 months later. Hormone therapy continues for 12 months after RT.

Rarely, study treatment may need to be stopped early if any of the following occur:

- the treatment does not appear to be controlling your cancer
- you experience a serious side effect that can not be controlled with medication
- you develop another serious medical condition (not related to your prostate cancer)
- you are unable to meet the requirements of the study (eg. unable to attend follow-up visits)
- new information becomes available about the treatment of localised prostate cancer

If any of these events occur, your doctor will discuss it with you so that you can make a decision about your continuing care. Once treatment is completed, you will need to attend routine follow up clinics at least once a year to be checked for any signs that your prostate cancer has returned and to monitor any long term side effects you may experience. Follow up usually continues for at least 5 years for localised prostate cancer.

MEDICAL ASSESSMENTS AND TESTS

STANDARD: Before and during treatment you will be assessed by your doctor. You should tell them about any other medical conditions you have, any medication you are taking and if you are participating in any other clinical research studies. If you have not recently had them done, you will require routine pre-treatment tests including a CT scan of the pelvis/abdomen, chest x-ray, bone scan, DRE (digital rectal examination), PSA (a specific blood test for prostate cancer) and other blood tests for chemistry analysis, such as testosterone levels.

ADDITIONAL TESTS and ASSESSMENTS: Samples of biopsy material taken to diagnose your prostate cancer will be sent to Wellington Hospital in New Zealand for pathological review for this study only. Once the review is complete the biopsy material will be returned to your hospital. Prior to starting treatment you will be asked to complete a questionnaire relating to symptoms you may experience as a result of your prostate cancer treatment, including changes in bowel, urine and sexual function. At follow up visits you will be asked to complete the questionnaire again. If your treatment centre has access to additional scanning facilities you will have 2 extra x-rays taken of your spine and 3 bone density ('DEXA') scans will be required.

MEDICAL INFORMATION: After each of your assessments some of your medical information will be recorded on study reporting forms and forwarded to the study centre in Newcastle, Australia. All information will be treated confidentially and handled according to international guidelines for research security. Copies of study records will kept for at least 15 years at your hospital and at the study centre. Auditors may be granted access to the study information to verify that it was collected and recorded accurately. The results of the study may be published, but will comply with privacy standards and your identity will not be revealed.

KNOWN SIDE EFFECTS, RISKS AND BENEFITS

The information obtained during this study may benefit other people in the future rather than directly benefiting you. You could potentially experience some of the known side effects (listed below) for radiation, hormone and bone density therapy. Your doctor should discuss these side effects with you. The side effects experienced and their severity varies from person to person. Occasionally side effects may be long lasting, and in rare cases, life-threatening. You will be regularly assessed and medication may be prescribed or treatment modified to control side effects. Your GP will also be kept informed.

- **Radiation Treatment (all GROUPS – STANDARD TREATMENT)**

Radiation treatment will be administered using your hospitals treatment technique. Side effects experienced during radiation treatment are usually *temporary* and should gradually get better once the treatment has finished. Some bowel symptoms may potentially be experienced long term. It is not known

if patients who have 'conformal' radiation treatment techniques could experience ***more severe*** side effects, or if the new conformal techniques combined with hormone therapy provide a better chance of preventing your prostate cancer from returning.

*Likely to be experienced by more than **50%** of participants*	*May be experienced by **5-50%** of participants:*	*Likely to be experienced by less than **5%** of participants*
Frequent need / stinging when urinating (Cystitis)	Mucus/pain or bleeding from the rectum (Proctitis)	Red / inflamed / sore skin in radiation treatment area
Increased number of bowel motions per day	Urgent bowel motions (need to immediately go to toilet)	Weakened / reduced 'flow' when urinating
Tiredness	Fewer or no erections	Blood in urine

- **Hormone therapy (both 6 and 18 Month Groups)**

Most of the side effects you may experience are due to lowering the levels of male hormones in your body. All treatment groups (6 + 18 months) may experience short-term side effects that should gradually improve 3-6 months after the last injection. Reduced bone density can be a long-term side effect of hormone therapy. Usually this does not cause problems but occasionally it may increase your risk of fractures. Groups C+D (18 months) may have a greater risk of ***long term or permanent*** side effects. 18 months of hormone therapy may be beneficial in terms of preventing the cancer returning and reducing the risk of dying from prostate cancer, but this is not yet known for certain.

*Likely to be experienced by more than **50%** of participants*	*May be experienced by **15-50%** of participants*	*Likely to be experienced by less than **15%** of participants*
Fewer or no erections	Loss of bone mineral density	Redness /pain /swelling at injection site
Reduced sex drive (Libido)	Increased need to urinate during the night	
Tender / swollen breast tissue		Joint pain
Hot flushes	Change in blood pressure	Headaches
	Mood changes	Weakness/loss of body strength
	Depression	Skin rash*:*
Rare Side Effects: Blocked urinary tract; Allergic reaction to injection (may be **life-threatening)**		

- **Bone Density Therapy (Groups B and D)**

Bone Density Therapy works by driving calcium and phosphate from your blood into your bones, causing them to 'harden'. Side effects from Bone Density Therapy drugs are usually mild, do not require treatment and are usually temporary. If you are allocated to a bone density therapy group (Group B or D) you should maintain your normal fluid intake as dehydration may increase the likelihood of side effects. Bone density therapy may decrease your risk of fractures and may also decrease the risk of secondary cancers developing in your bones but this is not yet known.

*Likely to be experienced by more than **10%** of participants*	*May occur in **1-10%** of participants*	*Likely to be experienced by less than **1%** of participants*
Low blood phosphate levels (unlikely to require treatment)	Low blood calcium levels (if very low may need treatment to prevent muscle spasms)	Redness/pain/swelling at injection site
		Itchy skin, rash, sweating
	Reduced kidney function *(if not treated, may result in **kidney failure**)*	Numb/tingling fingers, cramps, spasms, muscle weakness
		Weight gain, altered taste
	'Flu-like' symptoms – eg. fever, chills, tiredness, loss of appetite, headaches, aching bones / muscles / joints	Diarrhoea, constipation, sore stomach, indigestion
		Chest pain, difficulty breathing
		Dizziness, anxiety or confusion
	Nausea, vomiting	Blurred vision
	Inflammation of the lining of the eye (conjunctivitis)	→ *and rarely:*
		Allergic reaction to injection (*may be **life-threatening)***

There have been reports of 'osteonecrosis' (a condition leading to fracture) of the jaw in patients with advanced cancers receiving prolonged courses of the bone drug (Zometa) used in this trial. The causes of osteonecrosis are not clear, but when patients using this type of bone drug have a tooth removed or other invasive dental procedure, it appears that the bone in the jaw is not able to heal adequately. The risk of osteonecrosis occurring during this trial is very minimal, but as it is a serious condition it is advisable that patients maintain good oral health and have any required dental procedures attended to before commencing on the trial. If a dental procedure is required during the course of Zometa injections, please advise your doctor before proceeding.

WHAT ARE MY RIGHTS?

- **Participation:** It is your right to decide whether or not to take part in this research study. Do not sign the consent form unless you have had the chance to ask questions and have received satisfactory answers. You can withdraw from this study at any time. You will not be paid for your participation or for any associated costs such as travel.
- **Fully Informed:** Your doctor will keep you fully informed. If new information about treatment for prostate cancer develops that is relevant to your treatment, your doctor will discuss this with you. Please keep staff informed of your current contact details.
- **Compensation:** ***(NZ Sites)***: In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the New Zealand Accident Compensation (ACC) legislation within its limitations. Your claim for cover may be accepted by ACC but your entitlement to compensation will depend on a number of factors.

WHO CAN I ASK IF I HAVE QUESTIONS?

- **Clinical Trial:** For questions about this study, please contact ***Local Principal Investigator (insert name, title, treatment centre and contact phone number)*** or ***Local Research Coordinator (insert name, title and contact phone number)***.
- **Urgent Medical Assistance**: If at any time during your treatment you require urgent medical assistance after-hours, contact ***(insert treatment centre/oncology ward after-hours contact details)*** or your nearest hospital emergency department. You should tell the medical staff if you are participating in this clinical research study.
- **Ethical Approval**: This study has received ethical approval from the ***(insert name of Institutional/Local Ethics Committee)***. For questions about your rights relating to participation in clinical research, or any concerns about this trial; please contact the ***(insert contact details for representative if appropriate).***

CONSENT FORM

The 'RADAR' Trial – a Study of Radiation, Hormone and Bone Density Therapy for the Treatment of Localised Prostate Cancer

Co-ordinated by the Trans-Tasman Radiation Oncology Group (TROG)

Principal Investigator: Insert Local Principal Investigators Name and Title
Insert Treatment Centre name and Contact phone number

I have been given and read a copy of the Information Sheet for this research study. I have had the opportunity to discuss this study with my doctor and am satisfied with the answers I have been given. I have had time to consider whether to take part.

I understand that my participation in this study is voluntary (my choice) and that I may withdraw at any time and this will in no way affect the quality of my health care. I understand I am a study participant during treatment and throughout the follow up period (at least 5 years).

I know who to contact if I have any questions or side effects. I understand that the treatment or investigation will be stopped if it should appear harmful to me, and that my GP will be kept informed. ***(NZ Sites)***:I understand the compensation provisions for this study in the event of serious medical injury.

I understand that my participation in this study is confidential and that I will not be identified in any publication or reports. I understand that auditors may review my medical information to ensure this study is conducted safely and that information reported for this research study is accurate.

I agree that biopsy samples from my prostate cancer will be sent to Wellington Hospital, New Zealand for the sole purpose of review for this study. I understand that the samples will be returned to my hospital once the review is complete.

I understand that my treatment **will/will not *(delete as appropriate)*** involve 'conformal' radiation treatment techniques.

I understand the treatment program for all study groups and that this is a 'randomised controlled trial'. I agree to be 'randomised' to a study group and intend to have the 'hormone therapy' and 'bone density therapy' treatment that is allocated to me.

Signatures *(a copy of this signed form must be given to the patient)*

Patient's Name _____

Patient's Signature _____ Date: _____

(delete only if a 'witness' is not required for informed consent at this institution - otherwise this section must be included in the consent form and completed)

Witness' Name _____

Witness' Signature _____ Date: _____

I have discussed the purpose, procedures and risks of this research study with the patient.

Investigator's Name _____

Investigator's Signature _____ Date: _____

19.2 Schedule of Assessments and Follow-up visits

RADAR ASSESSMENT SCHEMA		0 MONTHS	6 WEEKS	3 MONTHS	18 WEEKS	5 MONTHS	6 MONTHS	END-XRT	9 MONTHS	12 MONTHS	15 MONTHS	18 MONTHS	21 MONTHS	24 MONTHS	27 MONTHS	30 MONTHS	36 MONTHS	42 MONTHS	48 MONTHS	54 MONTHS	60 MONTHS	ANNUALLY	POST SALVAGE	SAE	REMOTE FU
BLOOD TESTS	FBC**	ABCD								ABCD		ABCD		ABCD		ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD			
	Es + Us	ABCD																							
	AST + ALT	ABCD																							
	OTHER LFT	ABCD																							
	VIT D	ABCD																							
	FAST LIPIDS	ABCD																							
	FAST LDL	ABCD																							
	FAST HDL	ABCD																							
	FAST GLUCOSE	ABCD																							
	CREATININE	ABCD		ABCD			ABCD		ABCD	ABCD	ABCD	ABCD		ABCD											
	PO4	ABCD		BD			BD		BD	BD	BD	BD		BD											
	CA	ABCD		BD			BD		BD	BD	BD	BD		BD											
	TESTOSTERONE	ABCD		ABCD			ABCD			AB		AB		ABCD		ABCD	CD	CD				ABCD#	ABCD##		ABCD†
	PSA	ABCD	ABCD	ABCD	ABCD				ABCD	ABCD	ABCD	ABCD	CD	ABCD	CD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD		ABCD†
IMAGING	TLX	ABCD															ABCD								
	CT ABDO/PELVIS	ABCD																							
	BONE SCAN	ABCD																							
	DEXA*	IF REQ												IF REQ					IF REQ						
TREATMENT	XRT	ABCD				ABCD	ABCD	ABCD																	
	Lucrin	ABCD		ABCD			CD		CD	CD	CD														
	Zometa	BD		BD			BD		BD	BD	BD														
CRF	BB0	ABCD																							
	BH**	ABCD								ABCD		ABCD		ABCD		ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD			
	BPT	ABCD	ABCD	ABCD	ABCD				CD	CD	CD														
	CA0	ABCD																							
	CFU								AB	AB	AB	ABCD	CD	ABCD	CD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD			
	CFU-ST																						ABCD		
	CH	ABCD																							
	CP0	ABCD																							
	CS**	ABCD		ABCD				ABCD	ABCD	ABCD	ABCD	ABCD	CD	ABCD	CD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD	ABCD			
	DEXA*	IF REQ												IF REQ					IF REQ						
	P	ABCD		ABCD			ABCD		ABCD	ABCD	ABCD	ABCD		ABCD											
	QD**			ABCD			ABCD		BCD	BCD	BCD	BCD													
	QOL**	ABCD		ABCD				ABCD		ABCD		ABCD		ABCD			ABCD				ABCD	ABCD	ABCD		
	QP**	ABCD		ABCD				ABCD		ABCD		ABCD		ABCD			ABCD				ABCD	ABCD	ABCD		
	QU**	ABCD		ABCD				ABCD		ABCD		ABCD		ABCD			ABCD				ABCD	ABCD	ABCD		
	RF							ABCD																	ABCD^
	R0	ABCD																							
	SAE‡																							IF REQ	
	SAE2‡‡																							IF REQ	
	TLX	ABCD															ABCD								
	W																								ABCD

* DEXA to be performed if clinically indicated to rule out osteoporosis. If performed please repeat at 24 and 48 months

^ If a patient can no longer attend normal follow-up but is happy to continue to participate in the RADAR trial RF forms should be completed every 6 months

† Where possible

‡ See SAE guidelines for when SAE are to be reported. After initial report folow-up SAE form to be completed every 30 days until condition resolved or stable

‡‡ Only completed if all information could not be provided on SAE form

2015-17 assessments:

** CRFs and tests no longer required

One testosterone required at 8 years or later

A testosterone should be done with every PSA (to estimate when patient develops castrate-resistant prostate cancer)

19.3 Historical Protocol Sections

The sections below which appeared in earlier protocol versions have been transferred from the body of the protocol to the Appendices and are retained as an historical record of trial activities which have been completed.

19.3.1 Criteria for assessing Treatment Outcomes

Osteoporotic and Sporadic Fracture Events

(i) Asymptomatic osteoporotic fractures are considered as adverse events and will be documented using morphometry of the plain radiographs of the thoracolumbar spine. Sporadic fracture will also be documented.

(ii) The incidence and timing of symptomatic osteoporotic fractures, which are also considered as adverse events, will be documented independently.

(iii) Loss of bone mineral density will be documented using DEXA scans of the hip.

19.3.2 Early Closure Criteria

The SDIC will review data relevant to the decision to modify or discontinue one or more of the trial arms. It will report to the TMC, whose role is to determine whether remedial steps can be taken or whether early closure of one or more trial arms must occur after consultation with the IDMC. The following criteria will be used to determine if closure is to be considered:

(a) If inadequate recruitment occurs. If less than 25 patients are recruited in the first year after activation or less than 100 in the first two years, it will be deemed unlikely that the trial will meet its recruitment target of 1000 within a reasonable, ethical time frame.

(b) The incidence of toxic (adverse) events will be continuously monitored and rates will be reviewed by the SDIC every 3 months. If a persistent and unexpected high incidence of one or more of the adverse (toxic) events (defined below) is recorded then one or more trial arms will be discontinued unless alternate means can be devised to prevent toxicity. [Percentage cited below are crude percentages of patients affected by event specified.]

1 Radiation toxicities:

(i)	Grade 3 Bleeding per rectum	> 50%
(ii)	Grade 3 Urgency / incontinence of faeces	> 50%
(iii)	Grade 3 Skin reactions	> 50%
(iv)	Complete urinary obstruction	> 20%
(v)	Grade 3 Haematuria	> 50%

2 LHRH toxicities:

(i)	Osteoporotic fracture within 3 years of randomisation	> 50%
(ii)	Severe mood changes / depression	> 75%
(iii)	Tiredness / fatigue	> 80%
(iv)	Joint pains	> 30%
(v)	Complete urinary obstruction	> 10%
(vi)	Allergic reactions	> 10%

3 Bisphosphonate toxicities:

(i)	Hypocalcaemia	> 25%
(ii)	Elevated serum creatinine levels	> 25%
(iii)	Flu-like symptoms	> 50%
(iv)	Conjunctivitis	> 25%
(v)	Irritating skin rashes	> 10%
(vi)	Chest pain and dyspnoea	> 10%
(vii)	Allergic reactions	> 5%

(c) If data emerge from other trials which indicate that it is unethical to continue to randomise patients to one or more of the trial arms, or to continue treatment on one or more of the trial arms.

(d) Should 3 cases of osteonecrosis of the mandible be observed during or before treatment of all 500 recipients of zoledronic acid on the RADAR trial then zoledronic acid will be terminated immediately in all patients undergoing therapy, and no further patients will be enrolled on Arms B or D of the trial. This rule is subject to:

i. Any suspected case must have the diagnosis of osteonecrosis of the mandible confirmed by an experienced oral surgeon

ii. The Trial Management Committee must meet as soon as practicable (and within 2 weeks) when 3 cases are observed to discuss the application of this stopping rule in the light of knowledge at that particular time (ie before making a decision).

19.3.3 Statistical Considerations: Analysis of Secondary Objectives

Risk of osteoporotic fracture: The effect of bisphosphonate on the risk of osteoporotic and sporadic fractures will be tested by comparing the proportions of patients at three years with new fractures, between the arms, no BT and BT, using an exact test of proportions, stratifying for type of androgen deprivation arm (STAD or ITAD) and age (<60, 60 – 70, 70+). Patients eligible for this analysis will be those alive and who have been examined for presence of fracture by plain radiograph at baseline and at three years. The proportions of patients in each arm who have died before three years or who are otherwise not included in the comparison will be taken into account in the interpretation of the results.

Loss of BMD: The primary analysis for the effect of bisphosphonate on loss of BMD will be tested using multiple linear regression analysis on the change from baseline at two years of BMD, with a further analysis at 4 years, adjusting for baseline BMD and type of androgen deprivation received (STAD or ITAD). It is intended to log-transform data prior to analysis, however the pooled data will be examined prior to analysis to see whether a different transformation or the use of a nonparametric test is appropriate. Patients eligible for these analyses are those alive and who are tested for BMD by DEXA scan at baseline and at two years. The proportions of patients in each arm who have died before two years or are otherwise not included in the comparison will be taken into account in the interpretation of the results. Testing for, and interpretation of, interaction between BPT and AD will be as for OPF.

BT and risk of bony progression: The effect of bisphosphonate on risk of bone and other metastasis will be tested using competing risks methodology to compare the no BT and BT arms, adjusting for duration of androgen deprivation (STAD, ITAD), with respect to time to bony progression.

Quality of life: QOL will be measured at baseline, 3 months, at end of RT and at 12, 18, 24, 36 and 60 months, and annually thereafter. Mean change from baseline in global and domain scores will be plotted by time and by treatment arm. The primary analysis of QOL will be a comparison between treatments of the change from baseline of the global QOL score at three years, adjusted for baseline QOL score, using multiple linear regression. Patients included in

this analysis will be those who are alive at three years and who have completed both baseline and three-year questionnaires. Pooled data will be examined prior to analysis to see whether transformation or use of a nonparametric test is appropriate.

Radiation induced morbidity: This refers to urinary and rectal function which will be analysed at four cross-sectional time points: 1. At baseline prior to any treatment; 2. At the end of radiotherapy; 3. At 18 and 24 months (ie approximately 12 and 18 months post radiation); 4. At 36 months (ie 30 months post radiation). Individual function scores and composite scores will be compared between trial arms using non-parametric uni-variable and multi-variable techniques.

Subgroup Analysis: In addition to addressing the possible interactions described above, differences in effect size for PCSM will be looked for across patient subgroups based on prognostic co-variables (Gleason Score, stage and initial PSA) and D'Amico risk category (low, intermediate and high). Subgroup effect sizes will be estimated using competing risk modelling and will be presented in Forest plots.

19.3.4 Power Calculations

It is aimed to accrue 1000 eligible patients over four years and to follow up patients indefinitely. There is one primary objective but also many important secondary objectives and the following power calculations indicate the adequacy of this number of patients to carry out these objectives.

The trial was originally powered to detect differences in endpoints five years from randomisation of the last patient (ie August 2012). The power calculations were recalculated in 2011 when it became obvious that important efficacy endpoints (notably prostate cancer related deaths) were lower than expected. As a consequence the first main endpoints analysis was rescheduled to occur in February 2014, 6.5 years after randomisation. The revised power calculations are summarised below.

(a) Method

The sample size calculation was conducted using the power procedure in SAS v9.2. Rather than make any parametric assumption about the distribution of the survival curves, the observed survival probabilities in the RADAR trial at the time of the sample size recalculation were used. The sample size calculation was based on the log-rank test.

The calculations were conducted for a range of options. Calculations were based on conducting the analysis 5 years after the last person was randomised and separately based on conducting the analysis 5 years after the last person had their last dose of treatment. For each of these scenarios the calculations were conducted assuming that patients receiving ITAD would have:

- A 50% reduction in the risk of events
- A 33% reduction in the risk of events
- A 25% reduction in the risk of events.

(b) Assumptions

- Significance level was set at 5%
- All statistical tests are 2-sided
- The total sample size is 1050 (525 per group)
- The estimated rate of events were based on the observed rate of events in the combined groups of the RADAR trial at the time of the sample size recalculation

(c) Results

Based on the assumptions of the sample size calculation, it is a necessary condition that the study will have more power to find a statistical significant difference between groups if the analysis is conducted at the later time point (see Table 5).

Similarly, in a comparison of calculations with the same level of follow-up and the same estimated benefit, the study will have more power to find differences between groups for outcomes that have more events. Therefore, assuming a similar benefit for each of the endpoints, the study will have its maximum power to find a difference in PSA progression, which is over 80% for all scenarios considered. However, for the outcomes with lower event rates such as death, the study will have less power. The study will be underpowered (ie < 80%) to find a statistically significant difference in prostate cancer-specific survival (PCSM) 5 years after the last person is randomised even if the benefit is as great as 50%. It will have 92% power to find a difference in PCSM 6.5 years after the last person is randomised if the benefit is as great as 50% but will be underpowered if the benefit is 33% or less.

Similarly for all-cause mortality, where you would expect the relative benefit to be less than for PCSM, the study will have over 90% power to detect a difference at 6.5 years if the benefit is greater than 33% but will be underpowered for this difference at 5 years.

(d) Conclusion

The likelihood of finding a statistically significant benefit of treatment with ITAD compared to treatment with STAD in terms of all-cause mortality or prostate cancer-specific survival, if it truly exists, will increase as the length of follow-up increases. The results presented in Table 1 below indicate that if treatment with ITAD reduces the risk of prostate cancer death from any cause by 50% compared with STAD, then conducting the analysis 6.5 years after the last person is randomised will give the study a more than 90% chance to find a statistically significant difference between groups, whereas conducting the analysis 5 years after the last person is randomised will only give the study a 74% chance of finding a statistically significant difference. A similar benefit in terms of power exists for all-cause mortality if the true difference in risk between the groups is at least 33%.

Toxicity and QoL-related Endpoints

BT and loss of BMD: It is assumed that BMD at two years in the control arm (no BT) will decrease on average by 5%. It is further assumed that the standard deviation of the percentage change in BMD between patients in either arm is 5% [34]**.** It is planned to assess this outcome on only a subset of the patients. If 200 patients are alive and available for analysis at two years, the trial will have 95% power to detect a difference in percentage change between arms of 2.6% (a 5% drop in the control arm versus a 2.4% drop in the BT arm). This difference corresponds to an effect size (difference / standard deviation) of 0.52, which represents a moderate difference [112]**.** The trial will have powers of 80% and 90% to detect differences in percentage change between arms of 2% (-5% vs -3%) and 2.3% (-5% vs –2.7%), respectively.

Quality of life: About 800 patients are likely to be available (alive and disease-free and have completed the three-year questionnaire) for the primary analysis. This number of patients will enable a difference in change from baseline in global QOL score corresponding to an effect size of 0.23 to be detected with 90% power. An effect size of 0.23 represents a small difference between arms [112]. If the standard deviation between patients in the standardised global QOL score were 25 (eg Aaronson et al) [113] this would correspond to a QOL difference of 5.7.

Table 1. Summary of power calculations

Outcome	Timing of analysis (Years after final patient randomised)	Event rates at a range of follow-up times at the time when the analysis would be conducted - based on all groups in the RADAR trial	Proportional Reduction in risk in treatment group	Power (%)
All-cause mortality	5 (2012)	5 yrs = 10.1; 6 yrs = 14.0; 7 yrs = 20.1	25%	48
			33%	74
			50%	99
	6.5 (2014)	6.5 yrs = 17; 7.5 yrs = 22; 8.5 yrs = 27	25%	72
			33%	95
			50%	>99
Prostate cancer-specific mortality	5 (2012)	5 yrs = 3.3; 6 yrs = 5.4; 7 yrs = 7.7	25%	20
			33%	33
			50%	74
	6.5 (2014)	6.5 yrs = 6.4; 7.5 yrs = 8.4; 8.5 yrs = 9.4	25%	30
			33%	52
			50%	92
PSA Progression	5 (2012)	5 yrs = 28; 6 yrs = 34; 7 yrs = 36	25%	89
			33%	>99
			50%	>99
	6.5 (2014)	6.5 yrs = 35; 7.5 yrs = 37; 8.5 yrs = 39	25%	94
			33%	>99
			50%	>99
Local Progression	5 (2012)	5 yrs = 4.0; 6 yrs = 5.0; 7 yrs = 5.0	25%	19
			33%	30
			50%	66
	6.5 (2014)	6.5 yrs = 5.0; 7.5 yrs = 5.5; 8.5 yrs = 6.0	25%	21
			33%	35
			50%	74
Distant Progression	5 (2012)	5 yrs = 13; 6 yrs = 16; 7 yrs = 17	25%	51
			33%	79
			50%	>99
	6.5 (2014)	6.5 yrs = 16; 7.5 yrs = 18; 8.5 yrs = 20	25%	59
			33%	86
			50%	>99
Bone Progression	5 (2012)	5 yrs = 9; 6 yrs = 10; 7 yrs = 12	25%	35
			33%	59
			50%	95
	6.5 (2014)	6.5 yrs = 11; 7.5 yrs = 12; 8.5 yrs = 14	25%	42
			33%	69
			50%	98

20 TECHNICAL APPENDICES

Appendix 20.1 - Technical requirements to proceed to 3DCRT dose escalation
Appendix 20.2 - DVH data
Appendix 20.3 - Data Collection
Appendix 20.4 - Data Extraction – Percentage Isodose Encompassing Rectum
Appendix 20.5 - Rectal Filling Protocol

20.1 3DCRT Technical Requirements

To demonstrate that patients can be safely treated with conformal therapy according to this protocol, participating institutions are required to satisfy the TACT as follows:

Set-up accuracy

(1) Before entering any patient into the conformal radiotherapy part of this trial, a departmental report must be submitted indicating the typical level of geometrical variation of planned isocentre to actual isocentre using the immobilisation technique to be used in this trial. Data will be representative of at least 10 patients with (AP and lateral) images acquired daily (minimum of 20 is considered acceptable) during the entire course of treatment. Portal images should be taken within the prescribed monitor units, not additional. Any immobilisation study should be able to determine the mean (ie systematic error) and variance (ie random error) of set-up errors. Software to perform this data analysis is available free of charge on http://radar.genepi.org.au/home. The decision rules applied to move the patient during the course of treatment due to systematic errors shall be described. Films or images will be compared with DRRs to detect systematic differences between treatment planning position and treatment position.

(2) 'Planned isocentre' will be defined as the field centre represented by the DRR. In exceptional circumstances where an institution does not have the facility to compare port films with the DRR it will be necessary for that institution to satisfy the Technical Committee that the simulation films are a reasonable substitute and that systematic errors between simulation and treatment planning position (position during the planning CT) are negligible.

(3) Each institution must satisfy the Technical Committee that random and systematic errors meet the following requirements before progressing to the next level of dose escalation:

- For a dose prescription of 66Gy, 90% of treatment isocentres must coincide with the planned isocentre within 10mm along each of the orthogonal axes.
- For a dose prescription of 70Gy and 74Gy, 90% of treatment isocentres must coincide with the planned isocentre within 5mm along each of the orthogonal axes.
- For a dose prescription of 78Gy, 90% of treatment isocentres must coincide with the planned isocentre within 3mm along each of the orthogonal axes.

In addition to providing details of the set-up accuracy study described above, centres will be required to submit details of their set up accuracy and decision rules for movement of the patient during the course of treatment as described in section 6.2.4.4.

It may be necessary to exclude some patients from the conformal radiotherapy part of this trial on the basis of difficulty in accurate set-up. Each centre will decide which patients are ineligible, but exclusion criteria may include:

- obesity
- physical impairment
- port films after 1 week indicate random set-up error of greater than 5 mm.

Patients who commence treatment under this protocol may continue treatment up to a maximum dose of 66Gy without the reduced volume component (see section 6.2.4.1). Treatment to a higher dose will be at the discretion of the responsible physician.

In vivo dosimetry

- In vivo dose measurements are encouraged and mandatory for at least 10% of patients receiving a dose prescription of 78Gy
    - In vivo dose measurements should be taken on all 'accessible' treatment fields for the first fraction of at least 10% of patients for verification of calculations and set-up. Where the patient skin surface is in contact with the couch, it may not be possible to accurately position the in vivo dosimeter and the entry point for this field will be considered 'inaccessible'. A minimum of an entrance dose measurement shall be made, though measurement of exit dose is also encouraged. In vivo measurements will be within 5% of predicted (calculated) doses.

Intercomparison Phantom Study

All centres will participate in a phantom study under the guidelines of the dosimetry protocol. This will incorporate imaging, treatment planning, setup confirmation and treatment reporting as per protocol requirements, centres will be expected to demonstrate that they are able to treat patients following the trial guidelines. In addition centres will demonstrate that accelerator output can be delivered under reference conditions (Level I) to within ± 2% (± 3% including measurement error for independent Level I measurement), deliver planned doses to the ICRU reference point to within ± 3 % (± 5% including measurement error for intercomparison study using an ionisation chamber), and to within ± 5 % (± 10% including measurement error for intercomparison using thermoluminescent dosimetry) within the 50 % isodose shell surrounding the prostate volume (PTV).

The complete dosimetric data including digital export from the centre's treatment planning system shall be used as an indication of uniformity of dose delivery for trial patients.

Spot Checks

Contouring of target volumes and critical structures will be reviewed by a clinical review team on an ad-hoc basis. Treatment planning data will be submitted in electronic format (see section 20.2 for details).

Progress Reports

In addition to the Spot Checks, after treating a minimum of 10 patients at any dose level, centres will seek approval from the TACT before proceeding to the next dose level.

Verification of IMRT Techniques

Requirements for IMRT techniques will be considered as appropriate as the trial progresses.

20.2 Submission of planning data in electronic format for 3DCRT patients.

- Treatment planning data will be submitted for the purpose of verifying protocol compliance
- Treatment planning data shall be submitted in RTOG or DICOM RT format to the technical committee for review prior to commencement of the radiotherapy component of the trial. Instructions for performing this process for each of the commonly used planning computers are available on the website: **http://www.genepi.waimr.uwa.edu.au/radar**
- The treatment plan shall be computed with the following specifications:
    - Dose matrix will have a minimum grid spacing of 2.5mm x 2.5mm.
    - Data to be presented in “absolute dose”. Export in relative dose mode is not fully supported by some commercial systems
    - All exported data should be contained in a single directory for each patient.
    - The sampling resolution for the dose volume histogram data shall be 0.1cm for contoured structures, 0.2cm for all other tissue. The recommended bin width is 10cGy.

- To assist with treatment plan verification, the following will be provided:
    - Form 2B (which can be downloaded from the website **http://www.genepi.waimr.uwa.edu.au/radar**): Details included in this form include:
        - Details of planning system
        - Dose prescription point
        - Prescribed dose
        - DVH parameters for the rectum and left femoral head
        - Conformity indices for each phase of treatment
        - Details of linear accelerator
        - The maximum dose to the posterior rectal wall (see Appendix 20.4
    - A screen dump of the DVH of the target volume and critical structures if requested by TACT. This may be in the form of a jpeg image or hardcopy
    - A screen dump of the axial central-axis & mid-sagittal with isodoses; max, 100%, 95%, 90%, 70%, 50%, 20% if requested by TACT.

20.3 Data Collection

TACT: The RADAR Trial Technical Advisory Committee (TACT) comprises a group of radiation therapists and physicists responsible for collecting, collating, advising and producing reports of the 3DCRT component of the trial. TACT is also conducting both an electronic and technical compliance review. Address details for TACT:

TACT
c/- Department of Radiation Oncology
Sir Charles Gairdner Hospital
Hospital Avenue
Nedlands, WA 6009
Australia

Planning/Treatment Information to be Collected for each Patient

For all patients the following information shall be collated by the trial centre data manager together with other patient data. The relevant technical data will be forwarded from the trial centre data manager to the TACT:

- For each treatment stage:

  · All treatment characteristics will be documented (ie beam configurations, beam energies, field sizes, field-shaping and modification configurations)

  · Patient T stage, Gleason score and initial PSA

The following forms (that may be downloaded from the website: http://www.genepi.waimr.uwa.edu.au/radar) shall be submitted to TACT:

- Form 1: For each centre to document the following information
  - Contact details
  - Details of the set-up accuracy study (see Section 20.1)
  - Details of bladder and rectal filling protocols
  - In-vivo dosimetry capability
  - DRR capability

- Form 2b: For each patient – this will accompany the electronic treatment plan. See Section 20.2 for further details.

- Form 3: For each patient at the completion of radiotherapy treatment to:
  - Verify treatment was delivered as planned.
  - Document set-up accuracy for that patient
  - Document in-vivo dosimetry results

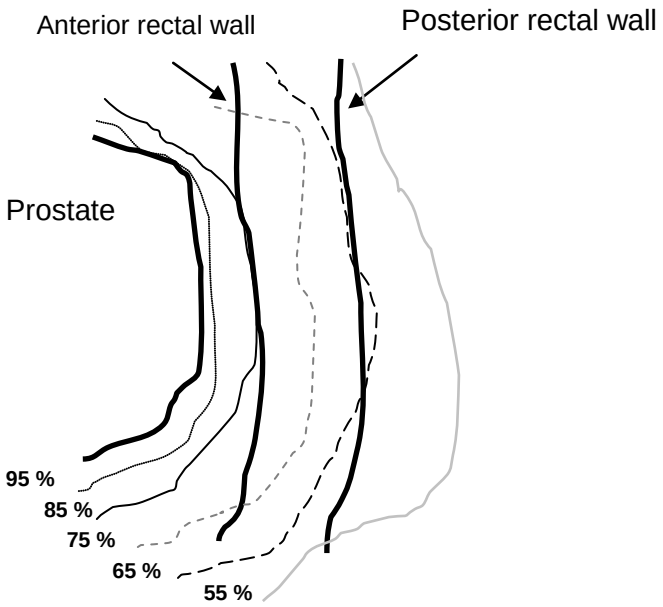
For patients treated with a combination of external beam and HDR, the data for the external beam component will be collected as described above. The following will be collected for the brachytherapy component:

- Dimensions of the prostate measured from the treatment planning CT or MRI
- Mean urethral dose measured at each CT or MRI transverse slice.
- The maximum urethral dose along the length of the urethra

- Mean anterior rectal wall dose measured at the anterior rectal wall surface at each CT or MRI transverse slice
- The maximum anterior rectal wall dose measured at the anterior rectal wall surface
- Volume of target receiving 150% and 200% of the prescribed dose
- The dose rate for each fractional dose delivered will be defined as ‘HDR’ or ‘PDR’
- Details to be provided on TACT Form 4 that may be downloaded from **http://www.genepi.waimr.uwa.edu.au/radar**

20.4 Data Extraction ~ Percentage Isodose Encompassing Rectum

There are two principle methods for determining the percentage isodose which just encompasses the posterior wall of the rectum. It should be noted that this information cannot be obtained from the DVH data for the rectum. The diagram below shows an example where, in this sagittal slice, the 65 % isodose encompasses the rectum. If in all sagittal slices, no greater isodose then 65 % crosses both sides (anterior and posterior) of the rectum, then 65 % is reported.



The two procedures for determining this value are:

(i) In a sagittal view with the rectal structure visible, determine on each slice the percentage isodose that just encompasses the posterior rectal wall. The reported value is the maximum isodose determined in this way.

(ii) In a 3D view with the rectal structure visible, decrease the dose value used to generate a dose ‘cloud’ (dose iso-surface) until the iso-surface just protrudes through the posterior rectal wall.

20.5 Rectal Filling Protocol

The following protocol may be used to assist the patient in maintaining consistent filling of the bladder and rectum from simulation through the duration of treatment. The effectiveness of any protocol should be verified at the treating centre before adopting into routine clinical use.

Bladder and bowel preparation
Patient information for prostate external beam radiotherapy

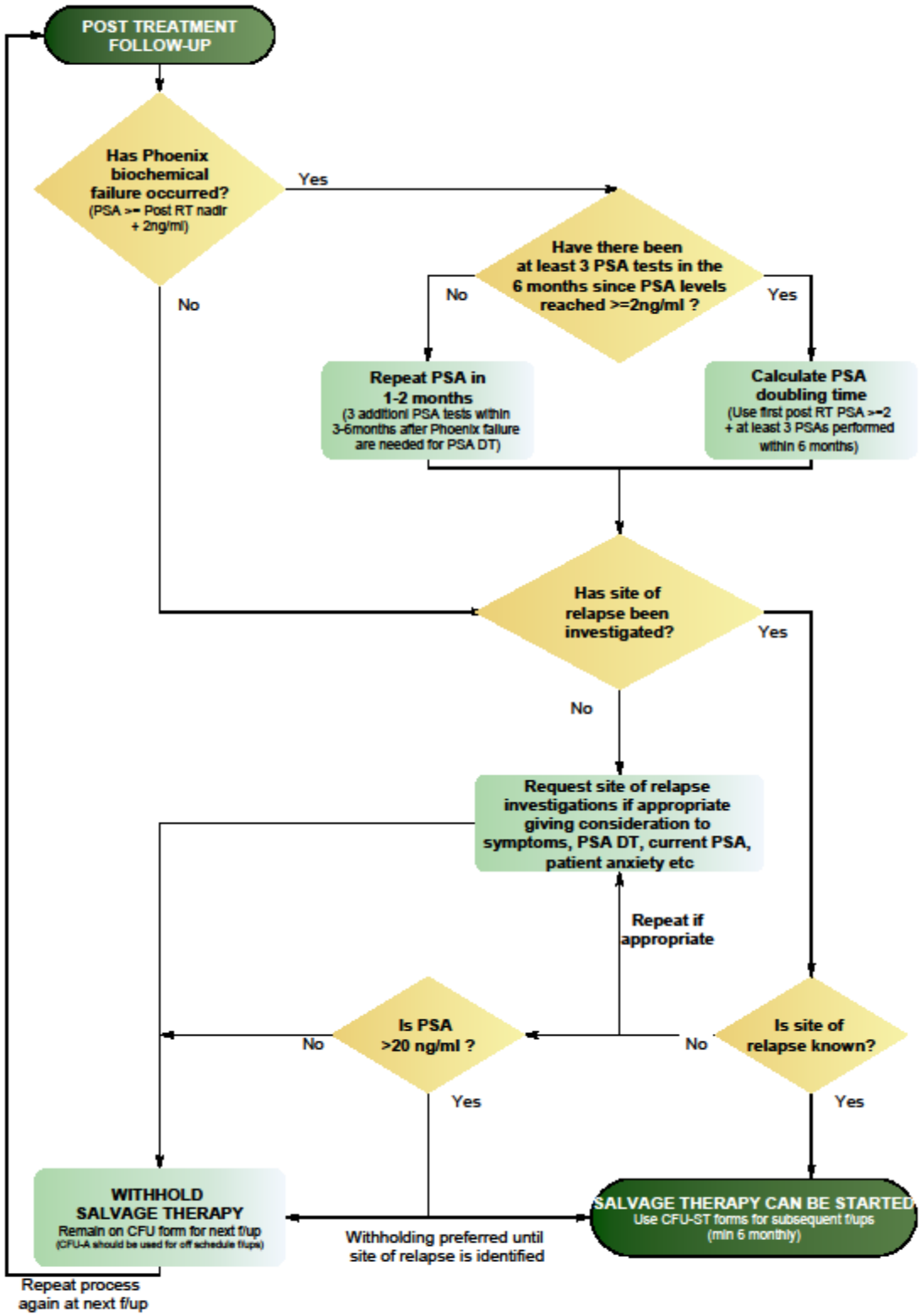
Your treatment planning involves having a CT scan of your pelvis. We take a number of measurements during planning which are then checked daily as your go through treatment. We like your position during treatment to be as close as possible to your position during planning, and that includes your bladder and bowel.

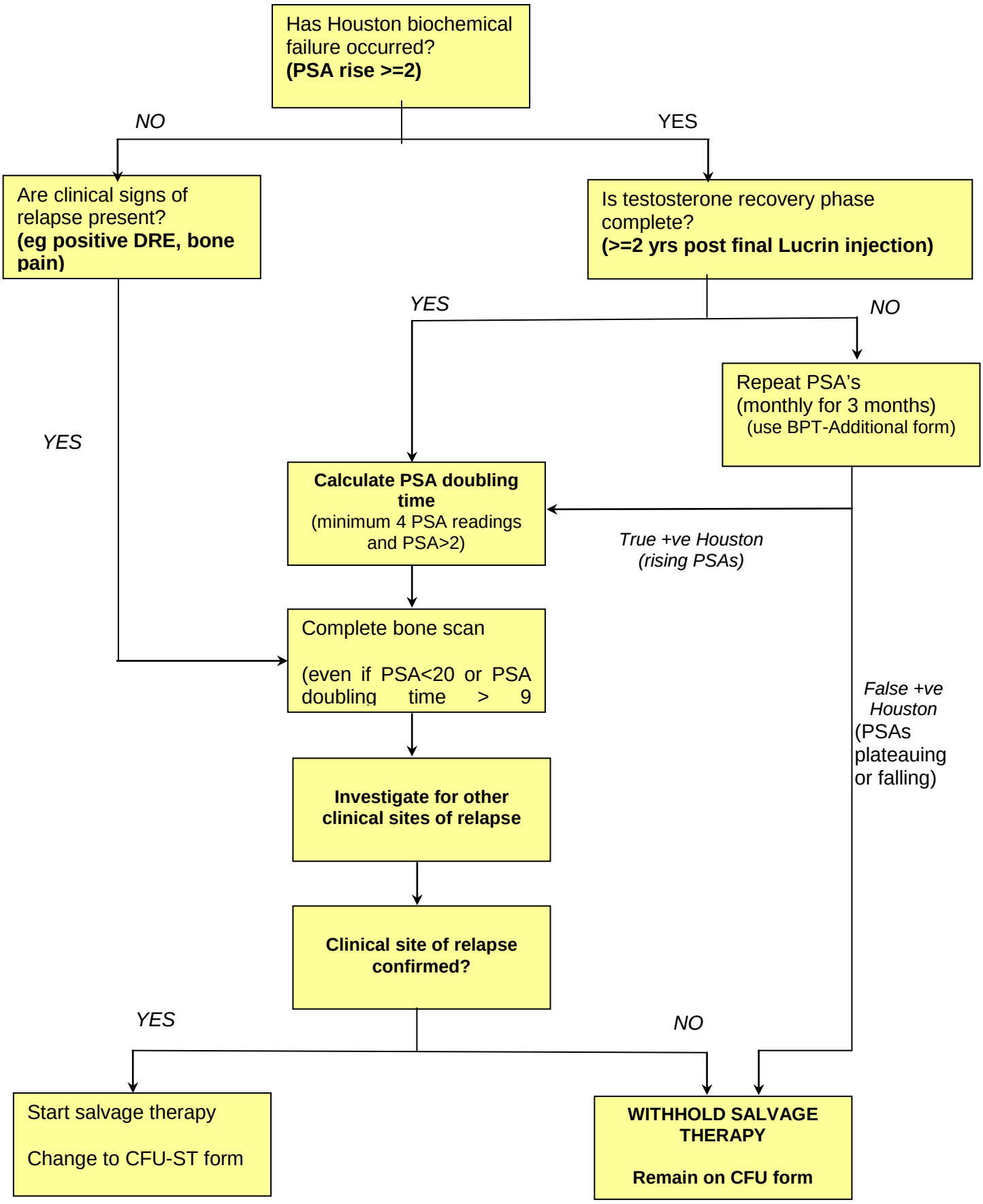
It is helpful to have the bladder *comfortably* full (not bursting) on each occasion; you may wish to empty your bladder about an hour before treatment and then drink 3 glasses of water. If you need to pass water while you are waiting for your planning or before treatment, please inform the staff. You will be required to drink more fluid again. You will be able to relieve yourself once the treatment for the day has been delivered.

We like the bowel to be empty if possible: if your bowels are not regular we recommend you start taking Fybogel (from any Pharmacy) about three days before your scan, and then again before your start of treatment date. If the bowels start to become loose during radiotherapy, you may stop the Fybogel. Many people do not need a laxative if their bowel habit is regular.

21 RELAPSE GUIDELINES

21.1 RADAR Relapse Flowchart




Has Houston biochemical failure occurred?
(PSA rise >=2)
NO
YES
Are clinical signs of relapse present?
(eg positive DRE, bone pain)
Is testosterone recovery phase complete?
(>=2 yrs post final Lucrin injection)
YES
NO
Repeat PSA's
(monthly for 3 months)
(use BPT-Additional form)
YES
Calculate PSA doubling time
(minimum 4 PSA readings and PSA>2)
True +ve Houston (rising PSAs)
Complete bone scan
(even if PSA<20 or PSA doubling time > 9
False +ve Houston
(PSAs plateauing or falling)
Investigate for other clinical sites of relapse
Clinical site of relapse confirmed?
YES
NO
Start salvage therapy
Change to CFU-ST form
WITHHOLD SALVAGE THERAPY
Remain on CFU form

21.2 Relapse Diagnosis Guidelines

Relapses are beginning to occur in the RADAR trial. After only 10 relapses it is clear that a revised set of relapse diagnosis guidelines is necessary.

Of the 10 patients with biochemical failure:

- 5 are being followed to determine relapse site (as per protocol)
- 2 have had relapse site diagnosed before salvage therapy (as per protocol)
- 3 have received salvage therapy before relapse site has been diagnosed (2 without any investigation).

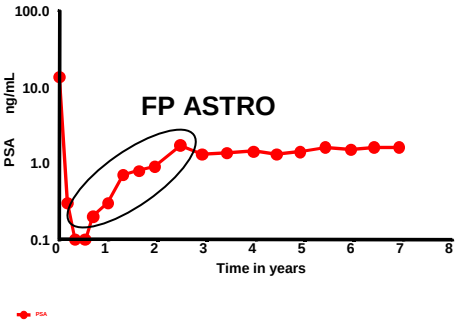
At present therefore the salvage therapy before relapse site diagnosis rate is 30%. It will be necessary to get this rate down to below 10% if we are to have *any* chance of determining whether additional leuprolide (Lucrin®) for 12 months or 18 months zoledronate (Zometa®) reduces the appearance of metastases (and, in particular, bone metastases).

Fortunately, some very useful data from the 96.01 trial have emerged to help us to improve our relapse site diagnosis rate:

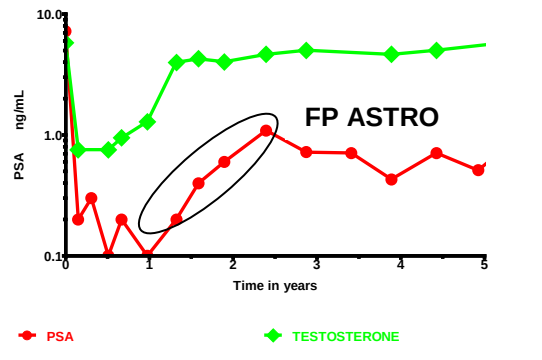
1- **<u>Reduction of false positive biochemical failure diagnoses</u>**

PSA "rebounds" and "rises to plateau" occurred in at least 60% of patients treated with neo-adjuvant androgen deprivation (AD) on the 96.01 trial. These rises frequently coincide with recovery in testosterone levels and are responsible for 46 false +ve (FP) ASTRO fails (see patients A and B below) and 10 FP Phoenix fails.

Patient A

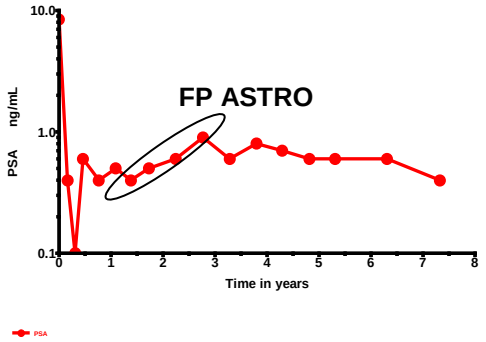


Patient B

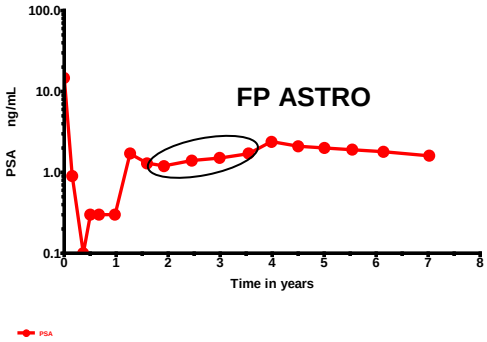


Further FP ASTRO fails also occurred during very small temporary rises in PSA during the plateau phase in 11 cases. Two examples from the 96.01 trial (patients C and D) appear below:

Patient C



Patient D



The inadequacy of the ASTRO definition in patients treated by neo-adjuvant androgen deprivation led us to become the first to report biochemical failure in a randomised controlled trial using the Houston definition.

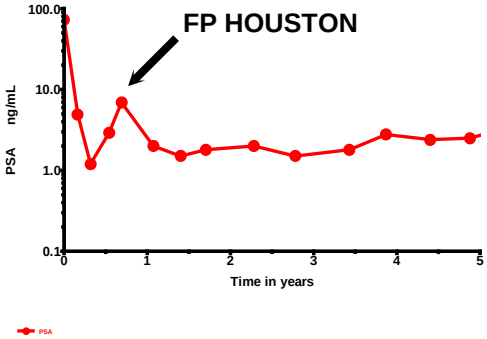
In the RADAR trial we are therefore abandoning the use of the ASTRO definition in favour of the Phoenix definition.

GUIDELINE 1:

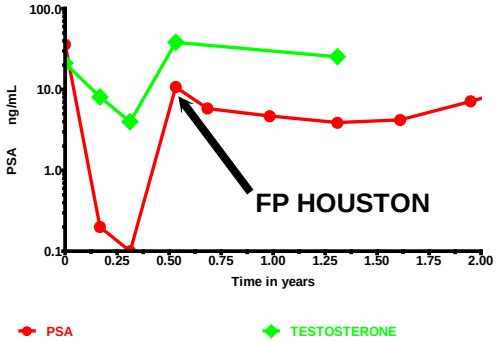
The Phoenix method of diagnosing biochemical failure is now used *exclusively* in the RADAR trial. Failure is diagnosed (*and* its timing occurs) when the PSA rises 2ng/ml or more above the post radiotherapy nadir value.

However, it is important to note that FP *Phoenix* fails are possible in the first couple of years following cessation of AD. In the 96.01 trial we found that there were a handful of "rebounds" that exceeded 5ngs/ml and then settled to a lower plateau for several years without intervention (e.g., patients E and F).

Patient E

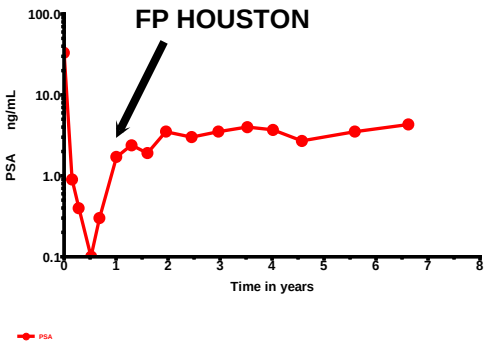


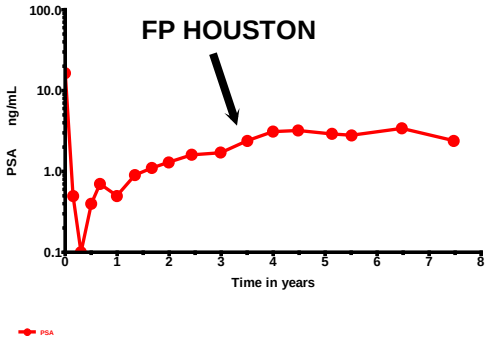
Patient F



Regardless of whether a rebound occurred, we also found that PSA rose slowly to a plateau (as in patients A and B) in approximately 60% of cases. This plateau is due to the recovery of PSA secretion by residual normal prostatic tissue that has survived treatment. While the median plateau level was only 0.45 for patients treated with AD, the range was 0.1 to 2.6ngs/ml and Phoenix fails occurred in 10 of these patients (as in patients G and H).

Patient G





Patient H

To avoid false positive Phoenix fail calls, it is necessary to recognise that PSA rises of 2ngs/ml or more above the post treatment nadir level to a plateau are, while uncommon, not rare. To be sure that a false positive call is not made it is necessary to request additional PSA readings over the next few months. Of course, there is a natural tendency for patients to feel extremely anxious when they see their PSA levels rising in the first couple of years after AD and RT and to press for the early introduction of salvage therapy. However, there are good grounds for urging them to remain calm until it becomes more obvious what is happening by obtaining further PSA readings. During this time it is often desirable to review the patient more frequently than indicated in the protocol. We have therefore produced a separate CRF for these non-protocol visits, because it has become obvious that many centres are in doubt as to the correct CRF to use, and may not use a CRF at all. This of course can mean that valuable relapse site data can be lost.

GUIDELINE 2:

- **Rising PSA values during testosterone recovery can cause needless anxiety.**
- **Patients should be reassured that PSA rises of up to 10ngs/ml during the testosterone recovery phase (up to 2 years after the last LHRH injection) do *not* necessarily mean relapse. They should be told that further PSA tests are necessary to establish that the PSA has plateaued and that relapse is *not* occurring.**
- **Use the new "non-protocol visit" CRFs to ensure that all important data are recorded.**

2- Improvements in relapse site determination

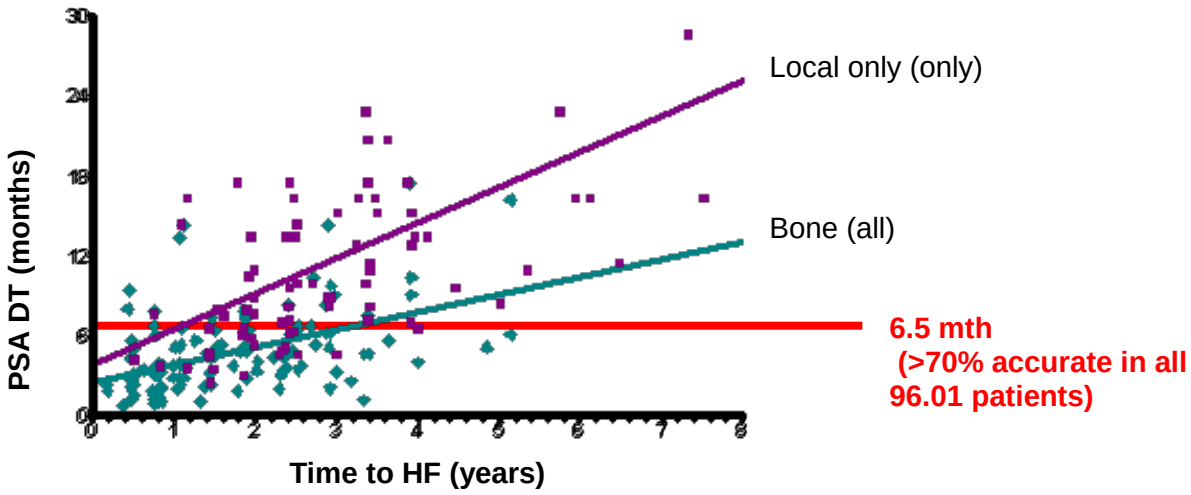
Two valuable pieces of information emerged from the 96.01 data to help in the determination of relapse site. The first is that bone scan positivity can occur at PSA levels well below 20. In fact, one half of all bony failures in the 96.01 trial so far have been diagnosed at PSA levels below 20. While we would still recommend that the PSA be allowed to rise above 20 before attempts to identify relapse site are abandoned, we would urge participant clinicians to remember that bone scans can be diagnostic at levels *below* 20, and to order these *before* ST is instituted in patients who are not willing to let their PSA rise to 20.

GUIDELINE 3:

- **During relapse bone scans can, and often do, become positive at PSA levels below 20ngs/ml. They can also become positive after PSA rises with doubling times of up to 17.5 months (especially if relapse has taken place several years after therapy). 95% of bone failures, however, are associated with PSA doubling times under 9.6 months.**
- **Always request a bone scan before salvage therapy is started.**

The second useful piece of information is that PSA doubling time may be helpful in combination with other markers as a surrogate indicator for site of failure. As the figure below shows a careful and disciplined attention to clinical detail in the 96.01 trial can provide some extremely valuable diagnostic information:

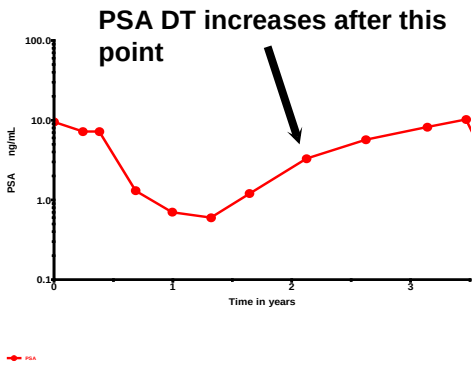
Figure 1



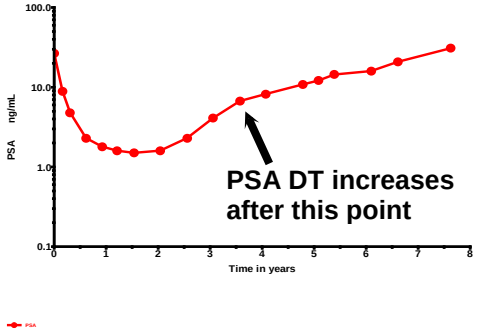
Cutpoints of 7.5 months after RT only and 5 months after AD + RT discriminate between local only and bone metastasis (inclusive) failure with 70% accuracy

However, 96.01 data indicate that care needs to be exercised in calculating the correct doubling time. It is very common for the PSA to rise very rapidly during testosterone recovery. However, after this the rate at which the PSA rises often slows considerably as the relapse process evolves (as patients I, J, K clearly indicate).

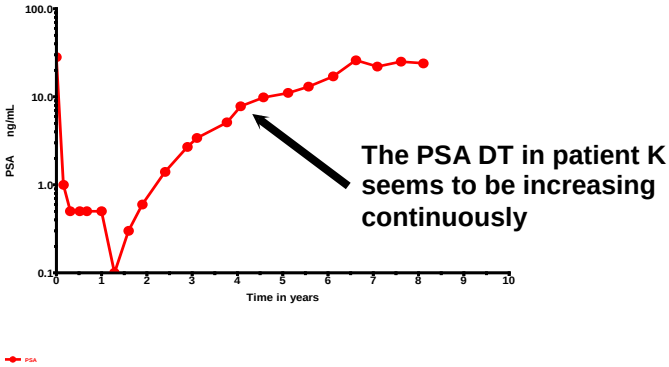
Patient I



Patient J

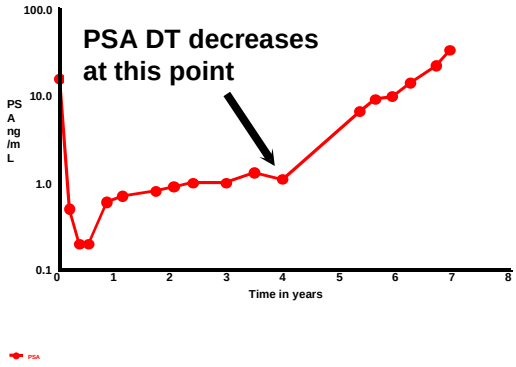


Patient K

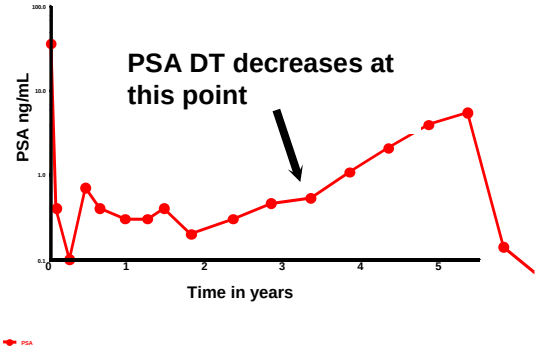


This can also happen in patients treated by RT only who have low nadirs or plateaus. However, in some patients doubling time reduces with time (i.e. the rate of rise increases) as patients L and M show.

Patient L



Patient M



PSA doubling time estimates are unreliable if obtained using PSA readings during the testosterone recovery phase (i.e., within 2 years of therapy). They are also unreliable while PSA levels remain in the plateau range (i.e., while PSA levels remain below 2ngs/ml).

GUIDELINE 4:

PSA doubling time estimates are unreliable if obtained using PSA readings during the testosterone recovery phase (i.e., within 2 years of therapy). They are also unreliable while PSA levels remain in the plateau range (i.e., while PSA levels remain below 2ngs/ml).

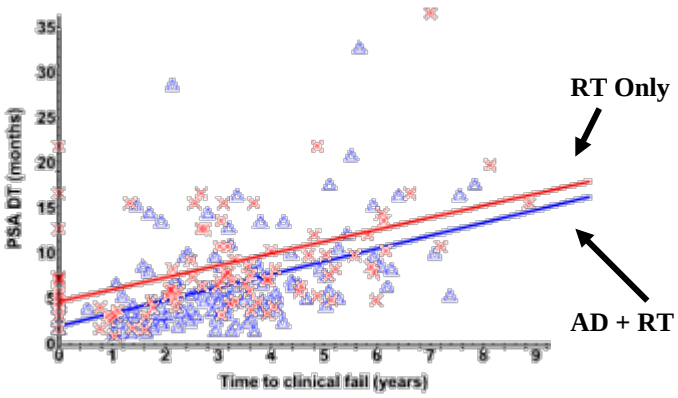
96.01 data indicate that the larger the number of PSA readings the more reliable PSA doubling time estimates will be. However, for PSA doubling time to be of use as a predictor of local or distant failure it needs to be determined before evidence of clinical failure. The RADAR trial has adopted a protocol of calculating a PSA doubling time with PSA data (at least 4 PSA results) collected within the 6 months following Phoenix failure.

GUIDELINE 5:

- **At least 4 readings, each a minimum of one month apart (i.e., over a minimum period of 3 months) are necessary to obtain a reliable estimate for diagnostic purposes.**
- **In the RADAR Trial the Phoenix Failure PSA and at least 3 subsequent PSAs performed within 6 months will be used to derive a PSA doubling time**
- **Patients can be reassured that there are no data presently available to indicate that delays in salvage therapy for a period of 3 months (while PSA doubling time is estimated reliably) is in any way harmful.**

When estimating PSA doubling time, it is helpful to remember that PSA doubling time increases as the length of time between the end of treatment and failure increases. This is true regardless of whether failure is local or distant, or whether neo-adjuvant androgen deprivation has been administered or not (as shown in Figure 2 below).

Figure 2



We would therefore urge that ST *not* be instituted until it becomes possible to determine the *true* rate of rise. Anxious patients can be reassured that *no* evidence at all has emerged from the 96.01 trial that delays in instituting start of ST by just a few months is in any way detrimental. Indeed uncertainty about the optimal moment to intervene is the reason why many of us are happy to participate in the TOAD trial.

Tell me that I am not relapsing please Doctor

Almost invariably patients follow their own PSA trends over time with the utmost interest. After therapy they are usually concerned that their PSA levels are satisfactory and, in particular, do *not* indicate that a relapse is occurring or is likely to occur within the foreseeable future. In response to questions from patients who wish to know how low their PSA should fall to after treatment, it is reasonable to state that levels between 0.1 and 2ngs/ml are acceptable, and that 0.4-0.5ngs/ml would be an average level when 6 months of AD has been administered. Lower values may occur after 18 months AD (we do not know yet).

RADAR Trial Relapse Diagnosis Guidelines

GUIDELINE 1:
The Phoenix method of diagnosing biochemical failure is now used *exclusively* in the RADAR trial. Failure is diagnosed (*and* its timing occurs) when the PSA rises 2ng/ml or more above the post radiotherapy nadir value.

GUIDELINE 2:

- **Rising PSA values during testosterone recovery can cause needless anxiety.**
- **Patients should be reassured that PSA rises of up to 10ngs/ml during the testosterone recovery phase (up to 2 years after the last LHRH injection) do *not* necessarily mean relapse. They should be told that further PSA tests are necessary to establish that the PSA has plateaued and that relapse is *not* occurring.**
- **Use the new "non-protocol visit" CRFs to ensure that all important data are recorded.**

GUIDELINE 3:

- **During relapse bone scans can, and often do, become positive at PSA levels below 20ngs/ml. They can also become positive after PSA rises with doubling times of up to 17.5 months (especially if relapse has taken place several years after therapy). 95% of bone failures, however, are associated with PSA doubling times under 9.6 months.**
- **Always request a bone scan before salvage therapy is started.**

GUIDELINE 4:

PSA doubling time estimates are unreliable if obtained using PSA readings during the testosterone recovery phase (i.e., within 2 years of therapy). They are also unreliable while PSA levels remain in the plateau range (i.e., while PSA levels remain below 2ngs/ml).

GUIDELINE 5:

- **At least 4 readings, each a minimum of one month apart (i.e., over a minimum period of 3 months) are necessary to obtain a reliable estimate for diagnostic purposes.**
- **In the RADAR Trial the Phoenix Failure PSA and at least 3 subsequent PSAs performed within 6 months will be used to derive a PSA doubling time**
- **Patients can be reassured that there are no data presently available to indicate that delays in salvage therapy for a period of 3 months (while PSA doubling time is estimated reliably) is in any way harmful.**

22 RADAR SUB-STUDIES

22.1 Be-Prepared

Bone metastasis Evolution: Prospective Evaluation of P1NP and CgA/NSE measures to Assess bony Relapse of prostate cancer Early in its Development

This is a prospective study of serial P1NP, CgA, NSE and PSA measures.

P1NP: Procollagen 1 amino-terminal propeptide, a marker of bone formation
CgA: Chromogranin A, a marker of neuroendocrine differentiation
NSE: Neurone specific enolase, a marker of neuroendocrine differentiation

The first aim is to determine whether a combination of PSA DT and/or specific changes in P1NP can predict the appearance of bone metastases months earlier than imaging investigations become positive. The second aim is to determine whether a combination of PSA DT and/or specific rises in CgA and/or NSE during relapse predict its response to salvage androgen deprivation.

Aims

a) to derive a surrogate marker (using permutations of PSA DT and PINP values) for the presence of sub-radiological bone metastases and
b) to establish the utility of serial measures of CgA and NSE as markers for androgen independent relapse.

Study population - The study population comprises two cohorts:

(i) Cohort 1: a group of 135 patients at extremely high risk of biochemical failure (BF) and subsequent bone metastases.
(ii) Cohort 2: approximately 35 patients, who are not in the high risk category of Cohort 1, but who nevertheless experience BF.

Timing of marker estimation **-** Patients in Cohort 1 will have blood taken for P1NP CgA and NSE every 6 months after the end of therapy and every 2-3 months when BF (by Phoenix definition) occurs depending on PSA DT. Patients in Cohort 2 will also have these blood indices repeated every 2-3 months depending on PSA DT.

Project timeline **-** The study will commence in 2007 and finish mid-late 2012 during which time approximately 75 patients will have experienced BF and will have had their PSA doubling times estimated accurately.

Analyses **-** At the end of the study period it is anticipated that:

- 85 patients will have had no evidence of biochemical progression or progression at any site (Group A)
- 40 patients will have imaging proof of Bony progression. (Group B)
- 20 will have evidence of relapse at other sites, but not bone. (Group C)
- 18 will have evidence of bony progression and will not have relapse site determined due to the introduction of early AD treatment. (Group D)
- 7 will have evidence of bony progression, but relapse site will not have been diagnosed because the study period has elapsed. (Group E)

Construction of receiver operating characteristics for PSA DT and P1NP alone and in combination will be derived, a) to confirm that each has independent predictive value of the imaging diagnosis of bone metastases, and if so, b) to define permutations of specific cutpoints of both that will define high, low and intermediate probability of imaging investigations for bone metastases becoming diagnostic at least 3 months later.

22.2 Life 10 Years After Prostate Cancer Treatment (Survivorship Substudy)

Background

In spite of its commonness there is little information in the international literature concerning long term survivorship issues in men treated successfully for prostate cancer. The limited information available relates to urinary, bowel and sexual issues and ignores problems caused by hormonal treatment. Without any evidence to the contrary it is commonly believed that long term survivors of prostate cancer lead a much diminished existence. Of the dozen international trials of new treatments for LAPC only two (EORTC 22961 and RADAR) have already published quality of life measures and one other (French Canadian) will do so. Of these only the RADAR trial plans to report long term survivorship issues. The long term (10-15 year) needs of men treated for the cure of LAPC with modern techniques such as radiation dose escalation and temporary adjuvant androgen suppression are therefore poorly understood. These techniques have resulted in major improvements in outcome in the last 15 years. It is therefore unclear whether the dire treatment side effect profiles in 15 year survivors of treatment in the mid 1990s are applicable in men treated after 2000. This uncertainty is of enormous importance, because survival expectations are so much better. For example, the RADAR trial will be reporting very high survival rates in early 2014. Five years after treatment started the prostate cancer specific mortality (PCSM) for all men in the trial is only 3.2%. This suggests that PCSM in one or more of the experimental treatment trial arms of the RADAR trial will be under 10% at 10 years after treatment (in late 2017). This will be in the 0-10% PCSM range reported by the leading US and European radical prostatectomy institutions for earlier tumours (i.e. T1 and 2 intra-capsular tumours). If long term treatment side effects in the RADAR trial for LAPC are similar to or less than those following modern radical prostatectomy, which is the current gold standard for these less dangerous tumours, the use of prostatectomy will require reconsideration. With minimum follow up of 10 years in late 2017, RADAR trial subjects are therefore an excellent, sizeable group of patients in which to study long term survivorship issues.

Summary

In this substudy of the RADAR randomised controlled trial, one-off postal surveys addressing survivorship issues will be sent to men remaining alive and on study 10 years after commencing their prostate cancer treatment. The surveys, which will also be completed by the men's partners/carers, comprise validated questionnaires as well as questionnaires designed by the investigators, and collect data on a broad range of factors including socio-economic, general health, depression, anxiety, resilience, lifestyle satisfaction, relationships, urinary/bowel/sexual side-effects (RADAR men only), and impact of the prostate cancer diagnosis and treatment on their lives.

Aims

1. To establish which factors influence long term survivorship
2. To identify unmet needs in the men and their partners
3. To test the hypotheses that the support that the men's partners provide, plus the psychological resilience of both parties, will have important positive effects on long term survivorship
4. To test the hypothesis that potentially treatable problems such as anxiety and depression are common for many years after primary treatment, particularly in subjects who have relapsed
5. To establish whether a simple 8 point survivorship assessment score designed by the investigators satisfactorily reflects survivorship issues related not just to prostate cancer and its treatment but to issues related to the effects of increasing age including progressive social isolation.

Study population

Men (and their partners/carers) who remain alive and on study 10 years after randomisation. (NB: In 2014 approximately 750 men were still alive and on study.)

Project Timeline

Surveys will be posted out during 2014-2017 and final reporting will be completed in 2018.