A collaborative randomised phase III trial:
The timing of intervention with androgen deprivation in prostate cancer patients with a rising PSA (TOAD)

Version 3 – 1 October 2009

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We gratefully acknowledge the support of Mayne Pharma, makers of Eligard™ who have contributed an educational grant towards data management.
FOREWORD

This document is intended to describe a collaborative study supported by the Cancer Council Victoria, the Trans Tasman Radiation Oncology Group and the Urological Society of Australasia. The document provides information about the study and procedures for entering patients onto the trial. It is not intended that the protocol be used as a guide for the treatment of other patients.

The involved groups will not accept any data for analysis unless the local Human Research 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 central office at the Cancer Council Victoria, to confirm the details of the protocol in their possession.
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Overview

The hypothesis to be tested is that early intervention with androgen deprivation therapy (ADT) in patients with prostate cancer suffering a PSA relapse (Study 1), or considered unsuitable for curative treatment (Study 2), improves overall survival while maintaining an acceptable quality of life, when compared to delayed intervention. The primary endpoint of the trial will be overall survival. An interim review is planned after 300 patients have been recruited to evaluate the feasibility of achieving the trial objectives. At this point the following will be ascertained:

a) the achievable recruitment rate nationally to the study
b) the minimum and median time to intervention in patients randomised to delayed intervention
c) the reasons for patient refusal to participate
d) the proportion of randomised patients who deviate from their allocated treatment arm.

Study schema – Study 1

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Stratification</th>
<th>Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenocarcinoma of the prostate</td>
<td>Arm A ➔ Treatment delay (Control arm)</td>
<td>OS, CSS</td>
</tr>
<tr>
<td></td>
<td>PSA only relapse after curative treatment</td>
<td>Arm B ➔ Immediate ADT</td>
<td>DFS</td>
</tr>
<tr>
<td></td>
<td>≤ 12 months neo-adjuvant ADT (≥ 12 months prior to randomisation)</td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morbidity of Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
</tr>
</tbody>
</table>

Study schema – Study 2

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Stratification</th>
<th>Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenocarcinoma of the prostate</td>
<td>Arm A ➔ Treatment delay (Control arm)</td>
<td>OS, CSS</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic disease at diagnosis, either localized or metastatic</td>
<td>Arm B ➔ Immediate ADT</td>
<td>DFS</td>
</tr>
<tr>
<td></td>
<td>Not suitable for curative treatment</td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>No prior ADT</td>
<td></td>
<td>Morbidity of Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
</tr>
</tbody>
</table>
ELIGIBILITY SUMMARY

Inclusion criteria

Both study groups

1. Histologically confirmed adenocarcinoma of the prostate.
2. Accessible for follow-up.
3. Informed consent to be randomised to immediate or delayed androgen deprivation.

Study 1

1. PSA biochemical relapse definitions:
   (i) Post definitive radiotherapy – a PSA value of ≥ 2ng/ml above the nadir.
   (ii) Post prostatectomy ± adjuvant radiotherapy – a PSA value of ≥ 0.2 ng/ml above the nadir.
   (iii) Post prostatectomy + salvage radiotherapy – a PSA value that
         a) reaches ≥0.2 ng/ml after salvage radiotherapy where the nadir post salvage radiotherapy is lower than this; or,
         b) fails to reach a nadir lower than ≥0.2 ng/ml after salvage radiotherapy, (this
            includes both a PSA level that fails to fall at all after salvage RT, and a PSA level which fails to reach ≤0.2 ng/ml).
   (NB For patients who have previously received neo-adjuvant or adjuvant androgen deprivation, a rise in PSA associated with testosterone recovery is not counted as relapse. It is recommended that follow-up of patients after cessation of androgen deprivation should include assay of serum testosterone levels in parallel with PSA measurements to facilitate interpretation of PSA rises. In patients potentially eligible for trial entry who have not had testosterone measurements, investigators will be advised to use the median time to recovery of testosterone levels documented in the IAB study [21], ie 9 months to determine the true date of PSA nadir.)
2. No evidence of metastatic disease on staging investigations (bone scan, abdomino-pelvic CT scan)
3. Prior androgen deprivation limited to a maximum of twelve months neo-adjuvant/concurrent treatment, completed at least 12 months prior to study entry

Study 2

1. Not suitable for radical treatment at primary diagnosis.
2. Decision not to treat curatively.
3. No symptoms due to local or metastatic disease requiring radiation or immediate hormone therapy.
4. No prior androgen deprivation therapy.

Exclusion criteria

1. Significant co-morbidity limiting life expectancy to less than 5 years.
2. Patients with symptomatic disease requiring therapy.
3. Previous androgen deprivation for longer than 12 months (Study 1).
4. Diagnosis of PSA relapse or incurable disease more than twelve months prior to randomisation.
5. Patients entered into TROG studies 96.01 or RADAR with the exception of patients on RADAR if they have withdrawn from treatment.
6. Patients with a PSA doubling time of less than 3 months (Study 1).

TREATMENT SUMMARY

Patients will be randomised to receive androgen deprivation therapy either immediately (experimental arm) or delayed (control arm) at least until a trigger point for treatment is exceeded. Any currently available means of androgen deprivation may be used, both for type of drug or castration, and for scheduling, either continuous or intermittent. Clinicians should state their schedule preference prior to randomisation to allow for stratification.
Treatment schema

For both Study 1 and Study 2 patients – specify continuous or intermittent ADT before randomisation

Randomisation

Arm A
Delayed ADT

Arm B
Immediate ADT

Day 1

Continuous ADT
Intermittent ADT

Continuous ADT
Intermittent ADT

Proposal

To undertake a combined collaborative randomised study, examining the optimal timing of intervention with androgen deprivation, in men:

Study 1) with a rising PSA after definitive radical treatment (prostatectomy and/or radiotherapy)

or

Study 2) who are not suitable for curative treatment.

1 BACKGROUND INFORMATION

1.1 The significance of PSA availability

The increasingly widespread availability of PSA assay over the last decade has provided a simple means of monitoring the progress of patients with prostate cancer, either after curative treatment or for those who prefer delayed intervention. It has led to the identification, however, of a group of asymptomatic and otherwise apparently healthy men whose PSA nevertheless suggests the presence of active disease. The general presumption is that this will lead to overt clinical failure or progression in many patients, albeit possibly over a period of a number of years [1]. This in turn raises a number of questions:

1) Do all patients with asymptomatic disease require treatment?
2) What factors predict for progression and clinical relapse?
3) At what level of PSA should intervention be recommended (recognising that there are a number of possible clinical scenarios)?
4) Does early intervention affect overall survival?
5) What are the effects of early as opposed to late androgen deprivation in terms of morbidity and quality of life?

There is little available evidence to answer these questions and to support rational decision-making for these patients. It is well recognised that for the symptomatic patient with advanced disease, androgen deprivation is an effective and appropriate form of treatment, and is easily justified as the relief of symptoms along with improved quantity and quality of life outweigh the risks and side effects of androgen deprivation.

Day 1

ADT start date according Section 6.2; strongly recommend not before 2 years
However, in the asymptomatic man the side effects of long-term androgen deprivation need to be carefully weighed against the potential benefit to the patient, particularly where the interval to disease progression may be measured in years.

1.2 Timing of intervention

One study (MRC-UK 1997 [2]) has addressed the timing of intervention, but in the pre-PSA era, and for patients with advanced disease. In this study, nearly a thousand patients with locally advanced or established metastatic disease were randomised to receive immediate androgen deprivation or deferment of treatment until judged clinically necessary. For nearly all end-points examined the men receiving immediate treatment fared better than those for whom treatment was delayed. There are however a number of concerns regarding the applicability of the study to current practice. Very few of the patients completed full staging, with bone scan assessment rarely being used. A number of the deferred group died of prostate cancer without ever starting androgen deprivation, suggesting far from optimal treatment for this group. Although initially an improvement in overall survival was suggested with early treatment, an update [3] indicates this not to be the case for patients for non-metastatic disease, suggesting an adverse effect of prolonged androgen deprivation on mortality from other causes. There is no evidence regarding the need for even earlier intervention in the man with biochemical relapse only, rather than clinically or radiologically defined metastatic disease. However the inference from these results is that progression-free survival may be prolonged. Quality of life and health economic issues were not addressed in this study; a small non-randomised report suggests that quality of life may in fact be inferior in men with immediate intervention [4]. There are also justifiable concerns that androgen deprivation may have significant long-term side effects (such as osteoporosis – [5,6] - and changes in cognitive function [7]) that may counteract potential survival benefits associated with its early introduction.

1.3 Survival after PSA relapse

It is difficult to deduce from the literature what degree of benefit might be seen in terms of overall and cause-specific survival at 5 or 10 years with early intervention after PSA relapse. Pound et al [1] from Johns Hopkins followed men with PSA relapse after prostatectomy without intervention and reported a mean actuarial time to metastasis of 8 years, and a mean actuarial time from metastasis to death of 5 years, suggesting a very long natural history. However, they have updated their results [8], shown together with the Mayo Clinic experience [9] in Table 1.

<table>
<thead>
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<th>Table 1</th>
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<tr>
<td><strong>5 yr Rates</strong></td>
</tr>
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<td>Johns Hopkins</td>
</tr>
<tr>
<td>Mayo Clinic</td>
</tr>
<tr>
<td><strong>10 yr Rates</strong></td>
</tr>
<tr>
<td>Johns Hopkins</td>
</tr>
<tr>
<td>Mayo Clinic</td>
</tr>
</tbody>
</table>

Combining these data-sets, at 10 years from surgery, of those with a PSA relapse after radical prostatectomy about 35% have metastases and 20%
have died of prostate cancer. The Cleveland Clinic [10] report a 5 year PSA failure rate of 41% after radical surgery, relative to a clinical failure rate of 16%. The median time for progression to overt clinical failure in these patients was 19 months. In a randomised study [11] evaluating the effect of early versus delayed androgen deprivation in node-positive patients after radical prostatectomy, the median delay in introducing therapy was 20 months.

After radiotherapy, the figures range more widely, depend on the extent of disease at presentation. Pollack [12] report 5 year overall survival rates of 90% after radiotherapy, with freedom from failure in 69%. For locally advanced disease, the RTOG 86-10 study [13] achieved the results shown in Table 2 at 8 years.

<table>
<thead>
<tr>
<th></th>
<th>RT alone</th>
<th>RT + 4 months Androgen deprivation</th>
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<tbody>
<tr>
<td>Biochemical failure</td>
<td>90%</td>
<td>76%</td>
</tr>
<tr>
<td>Metastasis</td>
<td>45%</td>
<td>34%</td>
</tr>
<tr>
<td>Cause Specific death</td>
<td>31%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Therefore with relapse after radiotherapy, about half the PSA relapers have developed metastasis and 2/3 of these have died (one third of relapers were dead by 8 years from primary treatment). Examination of the published survival curves from these studies suggests that the median time to PSA relapse is of the order of 20-24 months. Clinical failure has a median lag of about 20 months from PSA relapse, and death a further 30-36 months. The median time to death in those suffering PSA relapse is therefore estimated at about 5 years from the time of PSA relapse.

In none of these studies is it stated in detail how the relapses are managed, it may be assumed that both immediate and delayed strategies were employed, and that these may be ‘average’ figures. It is evident that a proportion of patients require treatment within two years but that overt clinical failure may take a number of years to be manifest. When is the appropriate time to intervene and in which patients is not known.

Two recent publications examine survival and treatment intervention in patients electing to undertake a watchful waiting policy, (although none are available regarding intervention in men deemed unsuitable for attempted cure). In general these patients are older, and have better cancer-related prognostic factors than men who undergo active treatment initially. Koppie [14], in an analysis from the CaPSURE database including all stages of disease, found an intervention rate of 52% by 5 years. A study from Boston [15] found a similar rate of 46%, with overall 5- and 7-year survival rates of 77% and 63%; the likelihood of being alive and free from treatment was 43% and 26% respectively. There is no information regarding progression and survival rates in untreated men considered unsuitable for radical treatment.

A survey [16] was recently undertaken in Australia of the current management policies of three groups of specialists (Urologic Surgeons, Radiation Oncologists and Medical Oncologists) for these two groups of patients. The survey, comprising four brief clinical scenarios, was sent electronically with an on-line address for reply. The scenarios were a rising post-prostatectomy PSA (Case 1), PSA rising rapidly (Case 2) after
radical radiotherapy or more slowly (Case 3), and a man not suitable for curative treatment (Case 4). The summary results are displayed in Table 3; the numbers represent the number of respondents recommending the different management approaches listed.

The wide range of opinion regarding appropriate management in each scenario can clearly be seen, with no consensus of approach. Where specialists opted to delay intervention until a certain PSA level was reached, there was an equally wide range of PSA action levels for each scenario (data not shown). Factors predicting subsequent clinical behaviour after biochemical relapse following surgery include the Gleason score of the primary disease, the interval since primary treatment and the PSA doubling time [1].

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>58</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Immediate AD*</td>
<td>5</td>
<td>31</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>AD for PSA rise</td>
<td>26</td>
<td>40</td>
<td>46</td>
<td>9</td>
</tr>
<tr>
<td>AD for symptoms</td>
<td>7</td>
<td>17</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>9</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

* AD = androgen deprivation

After radiotherapy, PSA doubling times of less than 8 months have been reported as predicting distant metastasis rather than local failure [17], and similar findings are emerging from the TROG study 96.01 (Denham, personal communication). Although more practitioners in our survey recommended immediate intervention with a more rapid PSA doubling time, there was still a large variation in clinical practice, reflecting continued uncertainty regarding optimal management.

It is therefore proposed to evaluate immediate versus delayed androgen deprivation in the above two situations: A) in men with a rising PSA after definitive radical treatment, and B) in men not treated at diagnosis in a curative fashion.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives of the trial

The principal objective of the trial is to test the hypothesis that early intervention with androgen deprivation in the presence of a rising PSA improves survival with acceptable morbidity, compared with delayed intervention.

2.2 Objectives of the interim review

The objective of the interim review is to ensure that the framework of the main study is appropriate, based on determination of the following elements:

a) the achievable recruitment rate nationally to the study
b) the minimum and median time to intervention in patients randomised to delayed intervention
c) the reasons for patient refusal to participate
d) the proportion of randomised patients who deviate from their allocated treatment arm.

2.3 End points of the trial

2.3.1 Primary
Death from any cause.

2.3.2 Secondary
a) Cancer specific survival
b) Clinical progression
c) Time to first androgen independence
d) Complication rate incidence and timing (eg cord compression, pathological fracture)
e) Treatment-related morbidity (including cognitive, osteoporosis)
f) Quality of life
g) Prognostic factors for progression (delayed group)

3 TRIAL DESIGN

3.1 Trial description
This is a multi-centre Phase III randomised controlled trial.

3.2 Study Groups
After written informed consent is obtained, men will be randomised to either immediate androgen deprivation, or delayed treatment.

Patients will be entered in one or other of the two study groups:
Study 1 – PSA only relapse after curative treatment, or
Study 2 – not suitable for curative treatment, no prior ADT.

3.3 Stratification
Stratification will be by:
1. Type of prior therapy (Study 1 - radical prostatectomy and/or radiotherapy)
2. Study 1: Relapse-free interval (interval from the date of surgery or the end of radiotherapy to diagnosis of relapse: less than 2 years vs 2 years or more)
   Study 2: Localised or metastatic disease
3. Planned intermittent or continuous androgen deprivation
4. Treatment centre
5. Study 1: PSA doubling time of \( \geq \) or < 10 months (reference POUND data)

3.4 Prognostic factor analysis
Several factors may interact to influence outcome, but the evidence to support their use as stratification factors is variable. These possible factors include
- Time to PSA nadir after radical treatment
- Duration of intervention delay (eg less than two years, two to four years, more than four years).
- Pre-treatment PSA doubling time
- Interval since diagnosis of relapse (Study 1) or diagnosis (Study 2)
- Use of neo-adjuvant androgen deprivation (Study 1).
- Use of other agents eg bisphosphonates.

These are identified prospectively to allow examination of possible interactions at the time of analysis.
4 PATIENT ELIGIBILITY

4.1 Inclusion criteria

4.1.1 Both study groups

1. Histologically confirmed adenocarcinoma of the prostate.
2. Accessible for follow-up.
3. Informed consent to be randomised to immediate or delayed androgen deprivation.
4. See Sections 6.2, 7.1.3 and 9.2 for further information regarding PSA analysis at relapse diagnosis or intervention.

4.1.2 Study 1

1. PSA biochemical relapse definitions:
   (i) Post definitive radiotherapy – a PSA value of ≥ 2ng/ml above the nadir.
   (ii) Post prostatectomy ± adjuvant radiotherapy – a PSA value of ≥ 0.2 ng/ml above the nadir
   (iii) Post prostatectomy + salvage radiotherapy – a PSA value that
      a) reaches ≥0.2 ng/ml after salvage radiotherapy where the nadir post
         salvage radiotherapy is lower than this; or,
      b) fails to reach a nadir lower than ≥0.2 ng/ml after salvage radiotherapy,
         (this includes both a PSA level that fails to fall at all after salvage RT, and
         a PSA level which fails to reach ≤0.2 ng/ml).
      (NB For patients who have previously received neo-adjuvant or adjuvant androgen deprivation, a rise in PSA associated with testosterone recovery is not counted as relapse. It is recommended that follow-up of patients after cessation of androgen deprivation should include assay of serum testosterone levels in parallel with PSA measurements to facilitate interpretation of PSA rises. In patients potentially eligible for trial entry who have not had testosterone measurements, investigators will be advised to use the median time to recovery of testosterone levels documented in the IAB study [21], ie 9 months to determine the true date of PSA nadir.)
2. No evidence of metastatic disease on staging investigations (bone scan, abdomino-pelvic CT scan).
3. Prior androgen deprivation limited to a maximum of twelve months neo-adjuvant/concurrent treatment, completed at least 12 months prior to study entry.

4.1.3 Study 2

1. Not suitable for radical treatment at primary diagnosis.
2. Decision not to treat curatively.
3. No symptoms due to local or metastatic disease requiring radiation or immediate hormone therapy.
4. No prior androgen deprivation therapy.

4.2 Exclusion criteria

1. Significant co-morbidity limiting life expectancy to less than 5 years.
2. Patients with symptomatic disease requiring therapy.
3. Previous androgen deprivation for longer than 12 months (Study 1).
4. Diagnosis of PSA relapse or incurable disease more than twelve months prior to randomisation.
5. Patients entered into TROG studies 96.01 or RADAR with the exception of patients on RADAR if they have withdrawn from treatment.
6. Patients with a PSA doubling time of less than 3 months (Study 1).

4.3 Subject/patient participation

A patient’s participation in the trial is voluntary. A participant is free to withdraw at any time, and will still receive appropriate treatment for their condition, as is the case if the patient does not consent to enter the trial.
5 RANDOMISATION PROCEDURE

5.1 Pre-Randomisation
Before you randomise please ensure that the patient is eligible for the trial (CRF 1 Eligibility Checklist and CRF 2 or 3 Baseline Assessment must have been completed), the patient has read and understood the Participant Information Sheet/Consent Form and the patient has given written informed consent.

5.2 Randomisation Procedure
Please complete CRF 1 or 2 Eligibility, Baseline and Randomisation Forms, QoL and attached deidentified CT and bone scan reports to register the patient. Fax these forms to the Cancer Council Victoria Clinical Trials Office (+61(0)3 9635 5410). The randomisation details will be entered into the database and treatment is allocated using a database embedded dynamically balanced randomisation method. The participant is allocated a randomisation number and a treatment arm. A confirmation form and treatment schedule with number and treatment arm will be faxed or emailed back to the participating site as soon as possible. Please notify the Clinical Trials Office if your randomisation is urgent and ensure your contact details are provided on CRF 1 or 2.

Tel: +613 9635 5480 or +613 9635 5179
Fax: +613 9635 5410
Office hours are from 8.30-17.30 Australian EST, Monday to Friday

5.3 Confidentiality
Patient/subject confidentiality must be maintained at all times. A randomisation number/subject code will be assigned at registration and must be used throughout the trial. The trial will be conducted in accordance with the Privacy Act 1988 (Australia) and relevant country (New Zealand) or state privacy legislation.

6 PATIENT TREATMENT

6.1 Androgen deprivation treatment
Patients will be randomised to receive androgen deprivation therapy either immediately (experimental arm) or delayed (control arm) for at least two years or until evidence of significant disease progression (see 6.2). Participants randomised to the immediate androgen intervention arm must start their treatment within 8 weeks.

The type of androgen deprivation is at the investigators’ discretion, including the choice of agent(s) used (provided it is recognised therapy), and whether it is used continuously or intermittently. Either bilateral orchidectomy or an LHRH agonist should be used, with or without oral anti-androgen therapy. The schedule used for intermittent therapy should be that employed in the Australian GUOG IAB study: the response to androgen deprivation should be assessed after nine months of treatment; if the PSA is < 4ng/ml the patient may stop treatment and be followed at 3-monthly intervals. Treatment should be restarted when the PSA exceeds 20 ng/ml or a level higher than that at study entry (whichever is lower), or when there is clinical progression.

Ideally an investigator would follow the same treatment protocol for patients in both the immediate and delayed arms, however this may remove the flexibility of patient choice. The Protocol Writing Group do not
consider there to be fundamental differences between the different types of androgen deprivation employed, but the study design will stratify for the two approaches of continuous and intermittent therapy. Clinicians should state their schedule preference prior to randomisation to allow for stratification.

It is also recognised that some of the relapsing patients may have had neo-adjuvant androgen deprivation; this factor has been identified prospectively to allow later sub-group analysis.

6.2 Intervention timing
Treatment of patients in both studies is palliative. As the treatments themselves have side effects, the rationale should be to introduce treatment for symptoms or when the onset of symptoms is judged to be imminent. Hence the immediate treatment arm is regarded as the experimental arm, as we do not know that survival is improved.

It is strongly recommended that intervention in the delayed arm should not occur before two years, unless one of the following clinical criteria is met. It is not mandatory to start treatment if a criterion is exceeded.

PSA doubling time calculation will be based on at least two readings taken between 1 and 12 months apart, and preferably with three readings during this timeframe. See also Sections 7.1.3 and 9.2.

Study 1:
• A PSA doubling time of less than 12 months with a PSA of 10 ng/ml or more. Investigators are free to delay intervention to higher PSA levels
• A PSA doubling time of 6 months or less
• Development of metastases or symptoms

Study 2:
• Development of symptoms
• Increase of PSA to at least 60 ng/ml
• PSA doubling time of 6 months or less

NB The presence of low volume metastatic disease in a well patient is not considered an automatic trigger for androgen deprivation.

6.3 Intervention scheduling
Clinicians will be asked to declare their planned method and scheduling (continuous or intermittent) of androgen deprivation prior to randomisation of each patient, to allow for stratification. They will also be asked to declare prior to randomisation whether or not bisphosphonate use is planned.

6.4 Withdrawal from trial participation
A patient may withdraw from participation in the trial at any time without providing a reason. Patients who do not commence treatment at their randomised time will not be withdrawn from the trial, but will be recorded as protocol violations. They will be analysed by intention to treat.

7 PATIENT ASSESSMENTS
7.1 Pre-randomisation assessments

7.1.1 History and physical examination
- To exclude the presence of symptoms or signs related to prostate cancer activity that would require active management
- To document current medications
- To document the clinical disease stage
- To document pre-existing co-morbidities

7.1.2 Imaging (within two months of randomisation)
- In Study 1: CT scan of abdomen and pelvis, and bone scan to exclude overt recurrence
- Sites are asked to fax through de-identified CT and bone scan reports for Study 1 patients at the time of randomisation for quality assurance purposes.
- In Study 2: CT scan of abdomen and pelvis, and bone scan to document disease stage

7.1.3 Laboratory studies
- Study 1: post-prostatectomy (± adjuvant radiotherapy) – at least two PSA assays, at least a month apart, demonstrating a PSA rise to >2ng/ml (either after prostatectomy, or after salvage radiotherapy); the last PSA should be no more than 12 months prior to randomisation.
- Study 1: post-radiotherapy - at least two PSA assays, taken at least one month and preferably three months apart, demonstrating a rise of 2ng/ml above the absolute nadir level meaning biochemical failure according to the Phoenix definition [18, 22]; the last PSA should be no more than 12 months prior to randomisation. See also Section 4.1.2.
- Study 2: at least two PSA assays, at least a month apart, demonstrating an abnormal result; the last PSA should be no more than 12 months prior to randomisation.
- Testosterone at baseline, after 6 months androgen deprivation and at the development of hormone refractory disease [see 8.1 (e).]
- All other tests as clinically indicated

7.1.4 Quality of life (within one month of randomisation but after the consent form has been signed)
- Will be conducted using the EORTC QLQ-C30 and prostate module. This consists of a 55-item questionnaire that takes most patients less than 7 minutes to complete. Physical, emotional, social functional domains and specific items related to prostatic carcinoma are included. Patients are asked to relate their answers to their experience during the previous week.
- To avoid bias, it is vital that HQoL assessment be completed by the patient prior to seeing the Clinician. This is easily achieved in the waiting room prior to the Doctor’s appointment. It is important that the Clinician checks that all questions have been answered.
- Completion of baseline HQOL questionnaire is a requirement of registration.
7.2 Assessments during follow-up

7.2.1 Clinical assessments
   a) Patients will be reviewed six-monthly while on protocol, or more frequently, according to clinical need
   b) Clinical examination should be focused to detect or monitor signs of progressive disease, illness complications and treatment related adverse events.

7.2.2 Biochemical assessments
   a) Serum PSA will be measured routinely at three monthly intervals for the first two years, 6 monthly to 5 years and thereafter at the investigator’s discretion. However, the Investigator can elect to perform the test more frequently if there is a clinical concern.
   b) Testosterone after 6 months on androgen deprivation, and when hormone refractory disease is diagnosed (see 8.1 (e).)
   c) Other laboratory indices as clinically indicated.

7.2.3 Imaging
   a) CT scans, bone scans and other imaging will be carried out only as clinically indicated.
   b) Patients with clinical evidence suggesting fracture(s) or other complications should have appropriate imaging when the fracture occurs or at next follow up.

7.2.4 Quality of Life assessment
   a) Patients will complete the EORTC QLQ 30 and PR 25 questionnaires at baseline, six monthly for two years and then annually up to 5 years.
   b) Assessment points and their aims are:
      • Baseline: baseline or “normal” state
      • Initial treatment effect, Months 6, 12, 18, 24: to assess impact of initial testosterone suppression on activities of daily living. To identify adverse effects on QoL if treatment is delayed.
      • Late assessments, months 36, 48, 60. Employ AUC statistical techniques to identify cumulative effects of long term testosterone suppression and to assess QoL impacts of differing levels of disease activity between each arm.

7.3 Patients refusing randomisation
   It is highly desirable that a screening log be kept of patients declining participation to allow determination in future of the extent of selection in the study group. If a patient volunteers a reason for refusing to participate in the trial this will be recorded on CRF 0–Non-randomisation form. No identifying data will be recorded. The form will be returned to the Trial Coordinating Centre for collation in order to ascertain whether the population of patients offered trial entry but refusing is similar to the trial population.

8 CRITERIA FOR ASSESSING OUTCOMES
   All events are measured from the date of randomisation, unless otherwise stated.

8.1 Criteria for the main trial
a) Interval to death from any cause
b) Interval to death from prostate cancer
c) Interval to initiation of androgen deprivation in the control arm
d) Prognostic factors for progression in the control arm
e) Interval to the development of hormone-refractory disease (defined as the date of first PSA rise while on androgen deprivation).
f) Occurrence of adverse events – disease or treatment related complications
g) Quality of life

8.2 Criteria for the interim review
a) Cumulative monthly patient accrual when 300 patients have been accrued; an accrual rate of 150 patients per year is planned.
b) Proportion of patients per investigator consenting to be randomised
c) The reasons for refusing trial entry
d) The proportion of patients deviating from the allocated treatment arm.
e) The proportion of patients in the delayed arm starting treatment before two years.

9 DATA COLLECTION

9.1 Completing case report forms (CRFs)
Investigators and/or data managers should complete the case report forms (CRFs) at the time of patient assessment/s. When received at the Trial Centre, the forms will be checked for legibility, accuracy, and completeness. The Central Trial Coordinator will follow up with the relevant institution on any deficiencies noted. The quality of data will be audited during the trial, as high standards are considered essential for the success of the trial.

The completed CRFs and QOL questionnaires should be faxed or mailed to:

Clinical Trials Office
The Cancer Council Victoria
1 Rathdowne Street
Carlton Victoria 3053 Australia
Fax: +61 (0)3 9635 5410

If you are regular mailing pages to the CTO, please send the original page and retain a photocopy of the completed CRF and QoL forms. Pages will be receipted by the CTO via fax or email. Please keep a log of all pages sent.

9.2 Baseline data collection

- Study 1 or 2
- Date of randomisation
- Primary treatment (and date started)
- Primary stage, Gleason grade
- PSA, PSA doubling time*, testosterone
- Adverse Events/Complications not related to study treatment but present at baseline, eg decreased libido

NB. A useful tool for calculating PSA doubling time can be found at the Memorial Sloan-Kettering Cancer Centre website:
http://www.mskcc.org/applications/nomograms/prostate/PsaDoublingTime.aspx

Baseline data collection (cont)

- Chest/abdominal pelvic CT scan (must be NED for Study 1).
- Whole body scan (must be NED for Study 1).
- Adverse Events/Complications not related to study treatment but present at baseline, eg decreased libido
Quality of life
Proposed type and schedule of androgen deprivation
Planned bisphosphonate use

*The Trial Centre statistician will confirm the PSA doubling time. At least two measurements must be supplied, taken no less than a month and no more than 12 months apart, with the latest no earlier than a month prior to randomisation. Optimal calculation of PSA doubling time would require three or more readings taken no more frequently than monthly.

PSA doubling time calculation [19]:
\[
dt = \frac{\log(2) \times T}{\log[\text{latest PSA}] - \log[\text{initial PSA}]} \quad \text{where } T = \text{interval between PSA measurements}
\]

9.3 **Follow up data collection**

CRFs will be completed at each six monthly assessment. Follow up data to be collected are:
- Date of initiation and type of androgen deprivation – immediate and delayed treatment arms
- Use of other agents eg bisphosphonates, radiotherapy, strontium
- Delayed group only: reason for initiation
- Date of clinically evident progression
- PSA
- Testosterone after 6 months on androgen deprivation and at the time of developing hormone refractory disease
- Date of change of therapy and reason
- Date of death
- Cause of death
- Complications (illness related)
- Adverse events (treatment related)
- Quality of life

10 **ADVERSE EVENTS**

10.1 **Adverse Events (AEs)**

An AE is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. All adverse events, while on study treatment, should be categorised, named, graded and attributed according to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [20]. A truncated version of expected AEs is provided in Appendix 7.

10.2 **Serious Adverse Events (SAEs)**

An SAE is defined as any untoward medical occurrence that:
1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity
5. Includes development of a new cancer.

The clinician is responsible for monitoring the safety of patients participating in this study and reporting any SAEs.

SAEs are required to be reported whether or not considered related to the treatment under investigation. SAEs should be reported to the Central Study Coordinator within 24 hours or as soon as practicable of detection by completing the study SAE form. All SAE forms should be signed by the clinician.

Fax: +61 (0)3 9635 5410        Tel: +61 (0)3 9635 5480

If all details are not available at the time of the initial SAE report, a completed report must be sent within the next 10 days. If the SAE is not resolved (ie. is ‘on-going’) at the time of the initial report, the Central Study Coordinator will require an SAE update when the date of event resolution (or death) is known.

This includes SAEs that occur anytime while the patient is on protocol treatment or within 30 days of completion of protocol treatment. Development of new cancers at any time during the follow-up period should be reported.

The clinician is responsible for ensuring their institutional Ethics Committee are notified of SAEs in accordance with local requirements. The Central Study Coordinator will forward all copies of SAE reports to the TROG Central Operations Office.

11 STATISTICS

11.1 Background

There are approximately 10,000 new diagnoses of prostate cancer annually in Australia, with 2600 deaths. In 1999 in Victoria, there were 2684 cases of prostate cancer diagnosed and 680 deaths from the disease. There were 373 radical prostatectomies recorded, and 471 patients in the public sector received radical radiotherapy. (Data Sources: Cancer Council Victoria, and the public sector Radiation Oncology departments; data were not available for the private RO sector).

Using conservative estimates of PSA relapse rates of 20% for radical prostatectomy and 30% for radical radiotherapy, based on the published data discussed previously, and extrapolating to the national population, just over 1000 PSA relapses would occur annually. A recruitment rate of 20% would accrue 200 cases per year to Study 1. There are no reliable figures available for the numbers of Study 2 patients, but a reasonable proportion of those diagnosed but not receiving radical treatment would be in this category, and recruitment of similar numbers is thought to be feasible. International collaboration will be considered should accrual rates appear low.

11.2 Control arm

For both Study 1 and Study 2 the control arm is considered to be the arm with intervention delayed, that is treatment at the time of developing symptoms or disease progression. The experimental arm is the early intervention arm.
11.3 Interim review

Given the paucity of information on the likely change in overall survival it is difficult to calculate with certainty the required patient numbers in each group to ensure an adequately powered trial or to judge its feasibility. It is therefore proposed to hold an interim review after 300 patients have been recruited across both groups. This will provide necessary information regarding a number of factors:

a) the achievable recruitment rate nationally to the study, which will determine the total number to be accrued to adequately power the study.

b) the minimum and median time to intervention in patients randomised to delayed intervention

c) the reasons for patient refusal to participate

d) the proportion of randomised patients who deviate from their allocated treatment arm.

11.4 Sample size determination

The strategy to be adopted is to determine the size of the difference in survival that can be detected according to the accrual rate. The following assumes exponential survival, an accrual period of 5 years and a follow-up period of 3 years, 80% power, type I (alpha) level of 5% and a 2-sided statistical test.

<table>
<thead>
<tr>
<th>Accrual rate per year</th>
<th>N</th>
<th>Deaths required</th>
<th>Hazard ratio detectable</th>
<th>Control 5-year OS rate</th>
<th>Test 5-year OS rate</th>
<th>Difference in 5-year OS rates</th>
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<td>75%</td>
<td>88.5%</td>
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</tr>
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</table>

Depending on accrual, we aim to recruit 750 patients over 5 years, which would provide the power to detect a 10% improvement in overall survival. The final sample size will be determined at the interim review, depending on the accrual rate to date.

11.5 Analytical methods

11.5.1 Primary analyses

The primary analyses will be performed according to the intention-to-treat policy; that is all patients will be included and analysed according to the arm to which they were randomly assigned, regardless of compliance with entry criteria or treatment compliance.

Baseline characteristics by treatment arm will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables, including type of prior therapy, intermittent or continuous policy and PSA characteristics. Summary tables by
treatment arm giving numbers of patients by completion of assessments, treatment compliance, dropouts and randomisation errors will be prepared.

The Kaplan-Meier (product limit) method will be used to estimate overall survival and late toxicity curves and rates. The competing risks methodology will be used to analyse progression and cancer-specific deaths.

A close-out date will be determined at the time of final analysis as the earliest date of last contact of all patients alive and not lost to follow-up. All follow-up beyond this date will be ignored for the purposes of analysis in order to minimize bias arising from the possible earlier reporting of follow-up for patients who experience an event.

Ninety-five percent confidence intervals for differences between arms for all important endpoints will be calculated. All $p$-values will be two-sided.

11.5.2 Analyses of Primary Objective

The primary analysis comparing early versus delayed ADT intervention will be performed using an unadjusted 2-sided log rank test at the 5% (alpha) level of significance. Secondary analyses will compare treatment arms adjusting for other variables (including those of the stratification criteria), prior therapy (Study 1), and intermittent/continuous policy, using the Cox regression model. It is recognised that there may be an interaction between the treatment arm allocation and risk group, although the statistical calculation assumes that the relative risk reductions in both groups are equal. The possible effects of the possible prognostic factors identified in Section 3.4 will also be examined, using the values above and below the median.

11.5.3 Analyses of Secondary Objectives

Cancer-specific survival rates will be estimated as part of a competing risks analysis in which cancer-related death and death due to other causes are the competing events. The competing risks methodology will also be used to analyse progression where death without prior progression will be a competing event. Comparison of treatment arms and allowance for other factors will be undertaken using Cox regression.

Mean change in quality of life (QOL) scores, global and component, 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 two years, adjusted for baseline QOL score, for patients alive at two years, using multiple regression. Late toxicity rates will be compared using log rank and Cox regression methods.

12 EARLY CLOSURE CRITERIA

The study will close before completion if any of the following criteria are fulfilled:

(a) accrual in the first two years is less than 100 patients
(b) if the Trial Management Committee or Independent Data Monitoring Committee determine there has been an unacceptably high incidence of SAEs

(c) if the Trial Management Committee or Independent Data Monitoring Committee determine there has been an unacceptably high incidence of patient non-compliance

(d) if evidence becomes available, during the accrual phase of this trial, which clearly demonstrates that one or other treatment for this group of patients is clearly superior, and/or that the objectives of this trial are no longer valid.

13 INVESTIGATOR RESPONSIBILITIES

The study will be performed in accordance with the CPMP/ICH Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) in Australia.

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.

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 Trial Centre, making it clear which version of the protocol was submitted for review, and the Investigator should chair a local 'start up' meeting involving all parties involved in the care of patients participating in this study.

The investigator is required to ensure compliance with all aspects of this protocol. It is the responsibility of the Investigator to maintain adequate and accurate case report forms (CRFs). 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 reason for the correction, initials, and date.

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

14 ETHICAL CONSIDERATIONS

The final approved protocol, the “trial information for patients” document and the institution consent form must be reviewed and approved by a properly constituted Human Research Ethics Committee (HREC). All written HREC decisions concerning the conduct of the trial will be copied to the Trial Coordinating Centre. The Site Investigator will agree to make the required progress reports to the HREC, as well as report any SAEs as soon as possible. The Ethics of the trial are governed in Australia by the World Medical Association Declaration of Helsinki and the NHMRC National Statement on Ethical Conduct in Research Involving Humans.

15 DATA MONITORING AND QUALITY ASSURANCE

15.1 Independent Data Monitoring Committee

An independent data monitoring committee has been constituted (see appendix 6) to undertake and evaluate interim analyses of the outcome data; early stopping rules will be defined in case of one arm appearing clearly superior to the other in outcome.

15.2 Quality assurance

The Coordinating Trial Centre will request copies of relevant documents (such as signed consent forms and pathology reports) necessary to
conduct eligibility verification checks. The case report forms (CRFs) will capture sufficient data to enable ongoing assessment of potential study violations. Results will be reported to the TMC at least 6 monthly.

All patient treatment records including medical histories, radiological imaging, laboratory tests and drug administration charts must be considered ‘source data’ and should be available for monitoring/audit if required and retained for at least 15 years after completion of the trial in accordance with Good Clinical Research Guidelines.

A site source data verification audit is planned for each site at a single point to check that data completed on the case report forms conforms with that in the medical records, especially drug administration. Further audits will be dependent on the results of the initial audit.

15.3 Access to data for collaborating groups

The Cancer Council Victoria will be responsible for analysing the data, but will accord collaborating organisations the right to have their own statisticians review and analyse the data independently.

16 FINANCE AND INSURANCE

16.1 Finance

The trial has received direct financial support in the form of an un-tied donation to the Cancer Council Victoria from Mayne Pharma. Neither participants/patients nor Site Investigators will receive any payment for participating in the trial. A capitation fee in support of data management may be payable, depending on the level of peer-reviewed grant funding being awarded.

16.2 Insurance

The trial has no commercial sponsor. Indemnity suitable for the risk of participating in clinical trials, must be provided by the investigator’s institution or by private urologists’ medical defence organisation.

17 PUBLICATION POLICY

Authorship of any publication arising from this work will generally be defined according to the agreement of the International Committee of Medical Journal Editors), published in Annals of Internal Medicine, Vol 126, No.1, p.36-47, 1 January 1997. Individual investigators are at liberty to present results relating to their own patients, but must not publish trial data without the agreement and participation of the principal investigators, with or without other members of the trial management committee.

References


### Appendices

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<td>Independent data monitoring committee</td>
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<td>Appendix 7</td>
<td>Abridged Common Terminology Criteria for Treatment Related Adverse Events v3.0</td>
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Appendix 1 Related studies

1. NCI-C PR-7: Phase III Randomized Study of Intermittent Versus Continuous Androgen Suppression in Patients With Prostate Specific Antigen Progression in the Clinical Absence of Distant Metastases After Prior Radiotherapy for Prostate Cancer.
   Currently open to accrual.
   Investigating continuous or intermittent androgen ablation in PSA relapse after radical radiotherapy

2. EORTC 30846 Phase III trial of endocrine treatment versus delayed endocrine treatment for patients with pN1-3M0 carcinoma of the prostate.
   This trial randomised 320 patients with positive nodes at prostatectomy to immediate or delayed androgen ablation, between 1986-1998, and is now closed to accrual.

3. EORTC 30891 Phase III study comparing early versus delayed orchidectomy, or early versus delayed treatment with a depot LHRH analogue (Buserelin) respectively, in patients with asymptomatic non metastatic prostate cancer T0-4 N0-2 M0.
   This trial randomised 900 patients with any stage of asymptomatic primary disease to immediate or delayed androgen ablation, between 1990-1999 and is now closed to accrual.

None of these three studies examines the timing of androgen ablation in the patient groups proposed in this protocol.
Appendix 2a   Participant Information and Consent Form – Study 1

Project title: Study of the timing of intervention with androgen deprivation in prostate cancer patients with a PSA relapse after curative treatment.

A signed copy of this form must be provided to the patient prior to study entry

Introduction
We invite you to take part in this research project for men with prostate cancer. This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part. Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the Statement.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give consent to participate in the research project. You will be given a copy of both the Consent Form and this Plain Language Statement to keep as a record.

Purpose
This is a clinical trial for patients with prostate cancer. The aim of the project is to provide information about the best timing to start treatment in men who have a rising PSA (prostate specific antigen) blood test, after having had treatment with the aim of curing their prostate cancer. In some men, the surgery or radiotherapy given initially in the attempt to cure the cancer is not successful. One of the earliest ways of detecting recurrence of the cancer in these men is with the PSA blood test, which can detect activity of the cancer months or years before other tests, and usually long before any symptoms appear. Before this study has been discussed with you, you will have had scans to see if any other sign of active cancer can be detected. Your scans have been negative, so you have evidence of prostate cancer activity as shown by the PSA, but no other sign of the disease.

We know that treatment with hormone therapy – removing the male hormone testosterone – is helpful in controlling advanced disease causing symptoms, although it is not a cure. This is called ‘androgen deprivation’, testosterone being an androgen hormone. The cancer cells are deprived of a source of energy, keeping them under control for a while, but eventually they tend to start growing again in spite of the treatment. We know that using androgen deprivation usually causes the PSA level in men to fall, including men in your situation who have no other signs of active cancer. What we do not know is whether using androgen deprivation immediately the PSA starts to rise will prolong life more than waiting to start treatment until there are other signs that the disease is progressing.

It would be simple to start everyone on treatment with androgen deprivation if there were no side effects with the treatment. However, there are a number of side effects that may interfere with day-to-day living. These include (but are not limited to): hot flushes, tiredness, anaemia, and loss of muscle mass and bone density. There may be weight gain, and nipple tenderness or swelling. Some men notice changes in mental function, or shortness of breath. Most also find that sex drive and erectile function, if normal before starting treatment, cease. Quality of life may be affected. If androgen deprivation therapy is ceased, some of the side effects (such as loss of sex drive, loss of muscle bulk or bone mineral density) may be halted or reversed. Generally the standard approach would be to delay introducing treatment until the disease progresses.
So the purpose of the study is to see whether immediate treatment is better or worse than delayed treatment in terms of prolonging lifespan, balanced against the effects on the quality of life.

**Treatment program**

The structure of the study allocates men randomly to either start androgen deprivation as soon as a significant rise in PSA is detected, or to delay starting treatment for a period of time (usually at least a year) until the PSA has been shown to rise further or faster, or symptoms develop. By ‘randomly’ we mean that the timing of treatment is decided at a central office through a method similar to flipping a coin; neither you nor your doctor will decide whether to start immediately or after a delay. This method is important to use to prevent the results being biased up front to one approach or the other. Whichever timing is allocated, you will be carefully monitored for any sign of activity and for the side effects of treatment. For men who are assigned to the delayed arm, the decision about the timing to start treatment will be taken by your treating physician in consultation with you, based on the results of monitoring your progress.

To achieve a clear answer about the best timing to introduce treatment in this setting, we may need to include as many as two thousand men in the study. We are inviting you to join in the first phase of the study, which will recruit a total of 300 men. From this preliminary work we will be able to get a clearer idea of the usual timing of hormone treatment in the delayed group of men, which will help us decide the exact number of men the full study will need to include.

**Trial procedures**

Much of your care will be the same whether you choose to join the trial or not. We will undertake (if not already done) scans and blood tests before entering you into the trial, and ask you to complete a questionnaire about your quality of life. You will have repeat PSA tests initially every three months then 6 monthly after 2 years, and be reviewed in clinic at least every six months. The quality of life questionnaire will be repeated each 6 months for two years, and then annually for 3 more years. Other tests will depend on your clinical progress.

We plan to recruit men to the trial over a five year period, and then follow for a further three years. The maximum time you would therefore be followed on study would be eight years, depending on when you join after the opening of the study.

**Possible outcomes**

We cannot assure you that you will gain benefit from entering the study. We hope that the results of the study will benefit other men in the future. The treatment that you will receive in the study will not be different from the treatment given if you choose not to enter the study; only the timing of when it is started may vary.

We will be happy to make the results of the study available to you when they are published.

**Possible Risks**

There are possible risks in participating in the study, but these are no greater than if you do not participate. There are risks in starting treatment early, because you will be exposed to the potential side effects (as described above) for a longer period of time than if the treatment is delayed. However, if you start treatment later, it is possible that the treatment may be less effective. We do not know which is more likely, which is why we are conducting the study.

**Patients rights**

a) You may ask information regarding this trial, and you can expect clear and understandable answers in return.
b) Participation in this study is voluntary, and you are not obliged to participate if you do not wish to do so. You may withdraw from this study at any time without jeopardising further treatment at this hospital. Your doctor may withdraw you from the trial at any time if s/he feels that continuing would involve a serious risk to you. If you decide to withdraw from this study, you should notify……..name and telephone number.

c) During the research project, if any new information about the risks and benefits becomes available that could influence your decision to continue in this study should become known, you will be given this new information.

d) Any information obtained in connection with this project and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. If you give us permission by signing the Consent Form, we plan to publish the results in reports to funding bodies and in scholarly journals. You will not be identified in any of these reports or subsequent publications, as all references to personal information will be deleted.

Please note that by consenting to your participation in this trial, you also consent to the release of your medical records to authorities such as the Human Research Ethics Committees and to coordinating trial centre personnel, with the understanding that these records will only be used in connection with carrying out our obligations relating to this study.

The data we collect will be stored in a locked cabinet in a secure office, and access will only be permitted to those who have direct involvement in the trial.

e) Your participation will not influence the fees (if any) you pay for treatment.

f) This study will be conducted in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans (June 1999), developed to protect the interests of research participants. The Human Research Ethics Committee of The Cancer Council Victoria has approved this project, so that it meets ethical standards, and ensures the confidentiality of participants. If you have any concerns or complaints about the project, these should be directed to [insert name and contact details for Institutional HREC or state Cancer Council HREC or independent HREC].

Whom to call

The doctor you should contact should any medical problems arise is Dr [insert site investigator’s name] The telephone number is [insert best telephone number].

If you have any general questions about the study, or would like any additional information before deciding to participate, please contact the Principal Investigator: Prof Gillian Duchesne, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria, 3002. Telephone: (03) 9656 1111.
Project title: Study of the timing of intervention with androgen deprivation in prostate cancer patients with a PSA relapse after curative treatment – Study 1.

Dr ………………………………… has discussed this study with me. I have had the opportunity to ask questions and received answers that are satisfactory. I can withdraw from this study at any time without prejudicing my management. I consent to the publishing of results provided my identity is not revealed. I have read and kept a copy of the attached Patient Information Sheet and understand the purposes, risks and methods of this study. I agree to participate. I also give permission for medical practitioners, other health professionals, hospitals or laboratories outside this hospital to release information to ...................... Institute concerning my disease or treatment that is needed for this study and understand that such information will remain confidential.

PATIENT’S NAME ______________________________________________

Please print

PATIENT’S SIGNATURE _____________________________DATE_______

WITNESS’ NAME ______________________________________________

Please print

WITNESS’ SIGNATURE _____________________________DATE_______

I confirm that I have explained the study’s purpose, nature and risks. I confirm that he has read and kept a copy of the Patient Information Sheet and agrees to participate.

PHYSICIAN’S NAME ____________________________________________

Please print

PHYSICIAN’S SIGNATURE ___________________________DATE_______
Appendix 2b  Participant Information and Consent Form – Study 2

Project title: Study of the timing of intervention with androgen deprivation in prostate cancer patients not undergoing curative treatment

A signed copy of this form must be provided to the patient prior to study entry

Introduction

We invite you to take part in this research project for men with prostate cancer.

This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part. Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the Statement.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give consent to participate in the research project. You will be given a copy of both the Consent Form and this Plain Language Statement to keep as a record.

Purpose

This is a clinical trial for patients with prostate cancer. The aim of the project is to provide information about the best timing to start treatment in men such as yourself with a recent diagnosis of prostate cancer. Many men have cancer that is not considered curable, or may have other serious medical conditions that may overtake the risk of the cancer progressing. In this situation it may be months or years before the cancer causes any symptoms that require treatment.

We know that treatment with hormone therapy – removing the male hormone testosterone – is helpful in controlling advanced disease causing symptoms, although it is not a cure. This is called ‘androgen deprivation’, testosterone being an androgen hormone. The cancer cells are deprived of a source of energy, keeping them under control for a while, but eventually they tend to start growing again in spite of the treatment. We know that using androgen deprivation usually causes the cancer to shrink and the PSA (prostate specific antigen) blood test to fall. What we do not know is whether it is helpful to start treatment straight away before symptoms develop, or to wait until the cancer shows signs of progression.

It would be simple to start everyone on treatment with androgen deprivation if there were no side effects with the treatment. However, there are a number of side effects that may interfere with day-to-day living. These include (but are not limited to): hot flushes, tiredness, anaemia, and loss of muscle mass and bone density. There may be weight gain, and nipple tenderness or swelling. Some men notice changes in mental function, or shortness of breath. Most also find that sex drive and erectile function, if normal before starting treatment, cease. Quality of life may be affected. If androgen deprivation therapy is ceased, some of the side effects (such as loss of sex drive, loss of muscle bulk or bone mineral density) may be halted or reversed. Generally the standard approach would be to delay introducing treatment until the disease progresses.

So the purpose of the study is to see whether immediate treatment is better or worse than delayed treatment in terms of prolonging lifespan, balanced against the effects on the quality of life.

Treatment program

The structure of the study allocates men randomly to either start androgen deprivation after the diagnosis has been made, or to delay starting treatment for a period of time.
(usually at least a year) until the PSA has been shown to rise further or faster, or symptoms develop. By 'randomly' we mean that the timing of treatment is decided at a central office through a method similar to flipping a coin; neither you nor your doctor will decide whether to start immediately or after a delay. This method is important to use to prevent the results being biased up front to one approach or the other. Whichever timing is allocated, you will be carefully monitored for any sign of activity and for the side effects of treatment. For men who are assigned to the delayed arm, the decision about the timing to start treatment will be taken by your treating physician in consultation with you, based on the results of monitoring your progress.

To achieve a clear answer about the best timing to introduce treatment in this setting, we may need to include as many as two thousand men in the study. We are inviting you to join in the first phase of the study, which will recruit a total of 300 men. From this preliminary work we will be able to get a clearer idea of the usual timing of hormone treatment in the delayed group of men, which will help us decide the exact number of men the full study will need to include.

**Trial procedures**

Much of your care will be the same whether you choose to join the trial or not. We will undertake (if not already done) scans and blood tests before entering you into the trial, and ask you to complete a questionnaire about your quality of life. You will have repeat PSA tests initially every three months, then 6 monthly after 2 years and be reviewed in clinic at least every six months. The quality of life questionnaire will be repeated each 6 months for two years, and then annually for 3 more years. Other tests will depend on your clinical progress.

We plan to recruit men to the trial over a five year period, and then follow for a further three years. The maximum time you would therefore be followed on study would be eight years, depending on when you join after the opening of the study.

**Possible outcomes**

We cannot assure you that you will gain benefit from entering the study. We hope that the results of the study will benefit other men in the future. The treatment that you will receive in the study will not be different from the treatment given if you choose not to enter the study; only the timing of when it is started may vary.

We will be happy to make the results of the study available to you when they are published.

**Possible Risks**

There are possible risks in participating in the study, but these are no greater than if you do not participate. There are risks in starting treatment early, because you will be exposed to the potential side effects (as described above) for a longer period of time than if the treatment is delayed. However, if you start treatment later, it is possible that the treatment may be less effective. We do not know which is more likely, which is why we are conducting the study.

**Patient’s rights**

a) You may ask information regarding this trial, and you can expect clear and understandable answers in return.

b) Participation in this study is voluntary, and you are not obliged to participate if you do not wish to do so. You may withdraw from this study at any time without jeopardising further treatment at this hospital. Your doctor may withdraw you from the trial at any time if s/he feels that continuing would involve a serious risk to you. If you decide to withdraw from this study, you should notify........name and telephone number.

 c) During the research project, if any new information about the risks and benefits becomes available that could influence your decision to continue in this study should become known, you will be given this new information.
d) Any information obtained in connection with this project and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. If you give us permission by signing the Consent Form, we plan to publish the results in reports to funding bodies and in scholarly journals. You will not be identified in any of these reports or subsequent publications, as all references to personal information will be deleted.

Please note that by consenting to your participation in this trial, you also consent to the release of your medical records to authorities such as the Human Research Ethics Committees and to coordinating trial centre personnel, with the understanding that these records will only be used in connection with carrying out our obligations relating to this study.

The data we collect will be stored in a locked cabinet in a secure office, and access will only be permitted to those who have direct involvement in the trial.

e) Your participation will not influence the fees (if any) you pay for treatment.

f) This study will be conducted in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans (June 1999), developed to protect the interests of research participants. The Human Research Ethics Committee of The Cancer Council Victoria has approved this project, so that it meets ethical standards, and ensures the confidentiality of participants. If you have any concerns or complaints about the project, these should be directed to [insert name and contact details for Institutional HREC or state Cancer Council HREC or independent HREC].

**Whom to call**

The doctor you should contact should any medical problems arise is [insert site investigator’s name] The telephone number is [insert best telephone number].

If you have any general questions about the study, or would like any additional information before deciding to participate, please contact the Principal Investigator: Prof Gillian Duchesne, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria, 3002. Telephone: (03) 9656 1111.
Project title: Study of the timing of intervention with androgen deprivation in prostate cancer patients with a PSA relapse after curative treatment – Study 2.

Dr ………………………………… has discussed this study with me. I have had the opportunity to ask questions and received answers that are satisfactory. I can withdraw from this study at any time without prejudicing my management. I consent to the publishing of results provided my identity is not revealed. I have read and kept a copy of the attached Patient Information Sheet and understand the purposes, risks and methods of this study. I agree to participate. I also give permission for medical practitioners, other health professionals, hospitals or laboratories outside this hospital to release information to …………………. Institute concerning my disease or treatment that is needed for this study and understand that such information will remain confidential.

PATIENT’S NAME ______________________________________________

Please print

PATIENT’S SIGNATURE _____________________________ DATE _______

WITNESS’ NAME ____________________________________________

Please print

WITNESS’ SIGNATURE _____________________________ DATE _______

I confirm that I have explained the study’s purpose, nature and risks. I confirm that he has read and kept a copy of the Patient Information Sheet and agrees to participate.

PHYSICIAN’S NAME ____________________________________________

Please print

PHYSICIAN’S SIGNATURE _____________________________ DATE _______
# Appendix 3  Data Collection / Investigations Schema

<table>
<thead>
<tr>
<th>Investigations and data to be collected</th>
<th>Pre – rand</th>
<th>Months after randomisation</th>
<th>+3 yrs Annual f / up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 6 9 12 15 18 21 24 30 36 42 48 54 60 60+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History / Examination</td>
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<td>X ^</td>
<td>X X X X X X X X X X X X X ^*</td>
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<tr>
<td>- diagnosis date</td>
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<tr>
<td>- initial clinical stage</td>
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<tr>
<td>- current clinical stage</td>
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<td></td>
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<tr>
<td>- initial Gleason score</td>
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<tr>
<td>- neoadjuvant androgen deprivation</td>
<td></td>
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<tr>
<td>yes/no; start/finish dates</td>
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<tr>
<td>- bisphosphonate planned, yes or no</td>
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<tr>
<td>Illness related complications</td>
<td></td>
<td>X</td>
<td>Continuously</td>
</tr>
<tr>
<td>Pre-existing co–morbidities</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse events (type, date, grade)</td>
<td></td>
<td></td>
<td>Continuously</td>
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<tr>
<td>Concomitant medication/s</td>
<td></td>
<td>X</td>
<td>Continuously</td>
</tr>
<tr>
<td>Previous definitive prostate cancer</td>
<td></td>
<td>X</td>
<td>Continuously</td>
</tr>
<tr>
<td>(type, start/finish date)</td>
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<td></td>
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</tr>
<tr>
<td>Study 1 – PSA relapse</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Call date</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum PSA</td>
<td>X ^</td>
<td>X X X X X X X X X X X X X X X^*</td>
<td></td>
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<tr>
<td>PSA doubling time</td>
<td>X ^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>X</td>
<td>After 6 months’ AD and onset of hormone refractory disease</td>
<td></td>
</tr>
<tr>
<td>CT Abdo / Pelvis</td>
<td>X ^</td>
<td></td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Whole body bone scan</td>
<td>X ^</td>
<td></td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Quality of life</td>
<td>X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for refusal to participate</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>if provided voluntarily</td>
<td></td>
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</tr>
<tr>
<td>Arm A delayed intervention – start date/s, stop date/s, type</td>
<td>Record delayed intervention type, start date (start date preferably ≥ two years post randomisation) and start/stop dates for intermittent treatment schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B immediate intervention – start date/s, stop date/s, type</td>
<td>Record immediate intervention type, start date and start/stop dates for intermittent treatment schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival / recurrence</td>
<td></td>
<td></td>
<td>Continuously</td>
</tr>
</tbody>
</table>

X ^ within two months prior to randomisation (please fax de-identified copies with CRF 1); X ^* as clinically indicated; X ^ refer protocol 7.1.3
Appendix 4  Data collection items – case record form (CRF)

1  Registration and randomisation
   Name, date of birth, date of diagnosis, date of randomisation
   Initial clinical stage
   Initial Gleason score
   Previous definitive treatment: type, start date
   Neo-adjuvant androgen deprivation:— Yes/no; start/finish dates; type
   Study 1: PSA at diagnosis; PSA nadir; PSA at relapse call; interval PSA;
   PSA at randomisation
   PSA doubling time at randomisation
   Study 2: PSA at diagnosis; and at randomisation
   Testosterone
   Current clinical stage
   Planned androgen deprivation:— type, schedule
   Pre–existing co–morbidities
   Prostate cancer related complications

2  Refusal to participate
   Data as if to be randomised, excluding name or other ID
   Reason for refusal to participate
      - wanted immediate treatment
      - wanted delayed treatment
      - did not want to be part of a clinical trial
      - preferred clinician to decide
      - other, specify

3  Treatment and clinical assessment – Visits 1 to 10
   Date of clinical assessment
   PSA result
   Start date androgen deprivation treatment
   ADT type and schedule – continuous/intermittent
   Reason for starting treatment
   Current status:
      Alive  Yes/No.  If no: date of death, cause of death
      Biochemical remission  Yes/No  Current PSA:
      Local progression  Yes/No  Symptomatic  Yes/No
      Distant metastasis  Yes/No  Symptomatic  Yes/No
   Prostate cancer related complications  Yes/No, If Yes, date & description
   ADT related complications  Yes/No, If Yes, date & description
   Change of therapy  Yes/No
      If yes, date, description and reason
   Quality of life forms completed – Yes/No

4  Follow up assessment – Visits 11+
   Date of clinical assessment
   PSA result
   Current status:
      Alive  Yes/No.  If no: date of death, cause of death
      Biochemical remission  Yes/No  Current PSA:
      Local progression  Yes/No  Symptomatic  Yes/No
      Distant metastasis  Yes/No  Symptomatic  Yes/No
   ADT related complications  Yes/No, If Yes, date & description
   Prostate cancer related complications  Yes/No, If Yes, date & description
Appendix 5  Quality of life forms

**EORTC QLQ-C30** (version 3)

**EORTC QLQ - PR25**

These PDF files can be requested in either electronic or paper format from:

The Cancer Council Victoria  
Clinical Trials Office  
Phone: (03) 9635 5179 or 9635 5179  
trials@cancervic.org.au
Appendix 6  Independent Data Monitoring Committee (IDMC)

The following have agreed to form the IDMC at the trial's inception:

Professor David Dearnaley, London  davidd@icr.ac.uk
Dr David Machin, Sheffield david@machin-home.freeserve.co.uk
Dr Tom Pickles, Vancouver  tpickles@bccancer.bc.ca
### Appendix 7: Abridged Common Terminology Criteria for Treatment Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGY / IMMUNOLOGY</strong></td>
<td></td>
<td></td>
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<tr>
<td>Allergic reaction / hypersensitivity (including drug fever)</td>
<td>Allergic reaction</td>
<td>Transient flushing or rash; drug fever &lt;38°C (&lt;100.4°F)</td>
<td>Rash; flushing urticaria; dyspnoea; drug fever ≥38°C (≥100.4°F)</td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy–related oedema / angioedema; hypotension</td>
<td>Anaphylaxis</td>
<td>Death</td>
</tr>
<tr>
<td><strong>BLOOD / BONE MARROW</strong></td>
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<tr>
<td>Hemoglobin (Hgb)</td>
<td>WNL</td>
<td>&lt;LLN – 10.0 g/dL</td>
<td>&lt;LLN – 6.2 mmol/L</td>
<td>&lt;LLN – 100 g/L</td>
<td>&lt;8.0 – 6.5 g/dL</td>
<td>&lt;4.9 – 4.0 mmol/L</td>
</tr>
<tr>
<td><strong>CONSTITUTIONAL SYMPTOMS</strong></td>
<td></td>
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<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>Fatigue</td>
<td>Mild fatigue over baseline</td>
<td>Moderate or causing difficulty performing some activities of daily living</td>
<td>Severe fatigue interfering with activities of daily living</td>
<td>Disabling</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight gain</td>
<td>5 – &lt;10% of baseline</td>
<td>10 – &lt;20% of baseline</td>
<td>≥20% of baseline</td>
<td>–</td>
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<tr>
<td><strong>ENDOCRINE</strong></td>
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<tr>
<td>Hot flushes /flushes</td>
<td>Hot flushes</td>
<td>Mild</td>
<td>Moderate</td>
<td>Interfering with activities of daily living</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>METABOLIC / LABORATORY</strong></td>
<td></td>
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<tr>
<td>Alkaline phosphatase</td>
<td>Alkaline phosphatase</td>
<td>&gt;ULN – 2.5 ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 20.0 X ULN</td>
<td>&gt;20.0 X ULN</td>
<td>–</td>
</tr>
<tr>
<td>ALT, SGPT</td>
<td>ALT</td>
<td>&gt;ULN – 2.5 ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 20.0 X ULN</td>
<td>&gt;20.0 X ULN</td>
<td>–</td>
</tr>
<tr>
<td>AST, SGOT</td>
<td>AST</td>
<td>&gt;ULN – 2.5 ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 20.0 X ULN</td>
<td>&gt;20.0 X ULN</td>
<td>–</td>
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<tr>
<td>GGT</td>
<td>GGT</td>
<td>&gt;ULN – 2.5 ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 20.0 X ULN</td>
<td>&gt;20.0 X ULN</td>
<td>–</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL</strong></td>
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<tr>
<td>Fracture</td>
<td>Fracture</td>
<td>Asymptomatic, radiographic findings only (eg, asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc)</td>
<td>Symptomatic but non-displaced; immobilization indicated</td>
<td>Symptomatic and displaced or open wound with bone exposure; operative intervention indicated</td>
<td>Disabling; amputation indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Osteoporosis</td>
<td>Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated</td>
<td>BMD t-score &lt;-2.5; loss of height &lt;2cm; anti-osteoporotic therapy indicated</td>
<td>Fractures; loss of height ≥ 2cm</td>
<td>Disabling</td>
<td>Death</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Short Name</td>
<td>Grade</td>
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<tr>
<td><strong>NEUROLOGY</strong></td>
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<tr>
<td>Cognitive disturbance</td>
<td>Cognitive disturbance</td>
<td>Mild cognitive disability; not interfering with work/school/life</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>performance; specialized educational services/devices not indicated</td>
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<td></td>
<td></td>
<td>Moderate cognitive disability; interfering with work/school/life</td>
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<td></td>
<td></td>
<td>performance but capable of independent living; specialized resources</td>
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<td>on part-time basis indicated</td>
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<td></td>
<td></td>
<td>Severe cognitive disability; significant impairment of work/school/life</td>
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<td></td>
<td></td>
<td>performance</td>
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<tr>
<td></td>
<td></td>
<td>Unable to perform activities of daily living; full-time specialized</td>
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<td>resources or institutionalisation indicated</td>
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<td>Death</td>
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<td>Mood alteration— Select:</td>
<td>Mood alteration: — Select</td>
<td>Mild mood alteration not interfering with function</td>
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<td>— agitation</td>
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<td>Moderate mood alteration interfering with function, but not</td>
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<td>— anxiety</td>
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<td>interfering with ADL; medication indicated</td>
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<td>— depression</td>
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<td>Severe mood alteration interfering with activities of daily living</td>
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<td>— euphoria</td>
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<td>Suicidal ideation; danger to self or others</td>
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<td>Death</td>
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<tr>
<td><strong>RENAL/ GENITOURINARY</strong></td>
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<td>Urinary frequency/ urgency</td>
<td>Urinary frequency</td>
<td>Increase in frequency or nocturia up to 2 x normal; enuresis</td>
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<td>Increase &gt;2 x normal but less than hourly</td>
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<td>≥1 x/hour; urgency; catheter indicated</td>
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<td><strong>SEXUAL/REPRODUCTIVE FX</strong></td>
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<td>Erectile dysfunction</td>
<td>Erectile dysfunction</td>
<td>Decrease in erectile function (frequency/ rigidity of erections)</td>
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<td>but erectile aids not indicated</td>
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<td>Decrease in erectile function (frequency/ rigidity of erections) but</td>
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<td>erectile aids indicated</td>
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<td>Decrease in erectile function (frequency/ rigidity of erections) but</td>
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<td>erectile aids not helpful; penile prosthesis indicated</td>
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<td>Gynaecomastia</td>
<td>Breast enlargement</td>
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<td>Asymptomatic breast enlargement</td>
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<td>Symptomatic breast enlargement; intervention indicated</td>
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<td>Libido</td>
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<td>Decrease in interest but not affecting relationship; intervention not</td>
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<td>Decrease in interest and adversely affecting relationship; intervention</td>
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<td><strong>VASCULAR</strong></td>
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<td>Thrombosis/ thrombus/ embolism</td>
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<td>Deep vein thrombosis or cardiac thrombosis; intervention (eg</td>
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<td>Deep vein thrombosis or cardiac thrombosis; intervention (eg</td>
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<td>Embolic event including pulmonary embolism or life threatening</td>
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<td>thrombus</td>
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<td>Death</td>
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Other Events to be categorized and graded according to the unabridged Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, (publish date 10 June 2003) [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)