A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

Trapeze

Taxane

Radioisotope

Zoledronic acid

Phase II/III Efficacy and Safety Clinical Trial in Hormone Refractory Prostate Cancer

Protocol

Version 11, 17 February 2012

Protocol Number: PR2100

EudraCT Number: 2004-002295-41

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www.hta.ac.uk

NCRN National Cancer Research Network

UNIVERSITY OF BIRMINGHAM

SUMMARY OF AMENDMENTS

Protocol Version No. /Date	Brief description of previous amendments
Trapeze, Phase II Version 4 (01/09/2004) Version 5 (23/03/2005)	• Change to the eligibility criteria to enable patients to enter the study without the need for a confirmation prostate biopsy if they have confirmed bone disease with a PSA value ≥ 100ng/ml. • Change to wording of baseline and post chemotherapy assessment requirements will allow centres to take part in the study without the need to perform clinical procedures if local facilities are not available.
Version 6 (07/06/2005)	• Safety amendment to clarification of zoledronic acid dose procedures to comply with SmPC.
Version 7 (04/05/2007)	• Changes to the inclusion criteria clarified patient eligibility regarding abnormal ALT and AST levels. • The requirement for a confirmed Serum Testosterone blood test was removed from the screening procedures. • A new entry criteria question was added to ensure that at time of study entry all patients were fit enough to receive any of the trial treatments, in the opinion of the investigator. • Clarification of administration sequence of trial treatments.
Trapeze, Phase III Version 8 (24/09/2008)	• The majority of the changes related to the transition from a phase II to a phase III clinical trial, covering trial infrastructure, data collection procedures and statistical considerations. These changes had no direct impact on patient participation or safety, but did increase the maximum number of chemotherapy cycles from 6 to10, according to NICE guidelines for docetaxel chemotherapy.
Version 9 (12/04/2011)	• This amendment concerns a statistical redesign of the phase III trial from a 4 arm comparison to a 2 by 2 factorial design to assess treatment efficacy. • Reduction of target recruitment from 1240 (as per version 8 amendment) to 618 evaluable patients. The trial will close to recruitment at the end of February 2012.
Version 10 (25/05/2011)	• This amendment concerns a correction in section 12.2.3 on timing of analysis. We intend to conduct initial analysis once all patients have at least 1 year's follow-up not 2 years as previously stated.

Version 11 (17/02/2012)	Substantial amendments : • Changing the requirement for both ALT and AST to be tested – only one of them needs to have been performed. • Change of definition for skeletal related event-free interval and pain progression-free interval, and removal of the event of death as a skeletal related event and element of pain progression criteria. Non-substantial amendments : • Clarification of prophylactic anti-emetic for nausea/vomiting due to chemotherapy, and permission to use local protocols that coincide with off-study practice. • Updating of Deputy Clinical Co-ordinators details. • Additional safety information for zoledronic acid administration. • Various typographical corrections and clarifications of existing text.

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RANDOMISATION

CLOSING TO RECRUITMENT AT 5PM ON WED 29 FEBRUARY 2012

Mon-Fri 9.00–5.00

Tel: [redacted] or [redacted]

Fax: [redacted] (24hrs) or [redacted]

CLINICAL QUERIES

Clinical queries during office hours should be directed to the Clinical Co-ordinator,

Professor N James, on Tel: [redacted]

or an appropriate member of the Trial Management Group*.

Out of hours, please call Queen Elizabeth Hospital switchboard on Tel: [redacted] and ask to bleep Professor N James, Clinical Co-ordinator.

CHIEF INVESTIGATOR SIGNATURE PAGE

A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

TRAPEZE

Version 11, 17 February 2012

This Protocol is approved by :

Professor Nicholas James, Chief Investigator

Signature : [redacted]

Date : 1st May 2012

INVESTIGATOR SIGNATURE PAGE

I have thoroughly read and reviewed the study protocol:

A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

TRAPEZE

I have read and understood the requirements and conditions of the study protocol.

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, local regulations and the study protocol and I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control who will be involved in the study.

I agree to use the study material, including medication, only as specified in the protocol.

I understand that changes to the protocol must be made in the form of an amendment, which has to be approved by the relevant Ethics Committee prior to its implementation.

I understand that any violation of the protocol may lead to early termination of the study.

Investigator's Name: ……

Signature: ……

Date: ……

The Principal Investigator must sign this page and return a copy to the Trapeze Study Office.

PROTOCOL SYNOPSIS

TITLE:	A randomised phase II/III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.
STUDY DESIGN:	Randomised Phase II/III clinical trial with 4 different treatment combinations
STUDY OBJECTIVES:	Phase II objective: To compare the four trial arms with respect to feasibility, tolerability and safety Phase III objective: To assess treatments with respect to efficacy within a 2×2 factorial design framework i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use).

STUDY POPULATION SAMPLE SIZE, INCLUSION & EXCLUSION CRITERIA:	The trial aims to recruit a minimum of 618 evaluable adult male patients with Hormone Refractory Prostate Cancer with:
	
	INCLUSION CRITERIA
	• Histologically/cytologically-proven prostate adenocarcinoma OR multiple sclerotic bone metastases with a PSA≥100ng/ml without histological confirmation.
	• Radiological evidence of metastasis.
	• Fit enough to receive trial treatment.
	• Prior hormonal therapy for prostate cancer.
	• For patients who have received prior hormonal drug therapy:
	  • Flutamide, nilutamide, bicalutamide, cyproterone acetate or stilboestrol must have stopped at least four weeks prior to enrolment and progression must have been demonstrated since cessation.
	  • Estramustine must have stopped at least four weeks prior to enrolment and any adverse events must have been resolved and progression demonstrated since cessation.

	• Documented progression, defined by:
	  • Elevated and rising prostate-specific antigen (PSA).
	  • And/or progression of any unidimensionally or bidimensionally measurable malignant lesion.
	  • And/or at least one new lesion identified on bone scan by radiological assessment of the bone.
	• Life expectancy ≥ 3 months.
	• ECOG performance status 0-2.
	• Adequate haematological function.
	• Adequate renal and hepatic function.
	• Written informed consent.
	
	EXCLUSION CRITERIA
	• Prior cytotoxic chemotherapy for HRPC, other than estramustine monotherapy.
	• Prior radiotherapy to more than 25% of the bone marrow or whole pelvic irradiation.
	• Prior radionuclide therapy for HRPC.
	• Prior treatment with a bisphosphonate for any reason within the previous 2 months.
	• Malignant disease within the previous 5 years, other than adequately treated basal cell carcinoma.
	• Known brain or leptomeningeal metastases.
	• Symptomatic peripheral neuropathy ≥ grade 2 (NCI CTC).
	• Concurrent enrolment in any other investigational clinical trial.
	• Treatment with any other investigational compound within the previous 30 days.
	• Any condition, which, in the opinion of the investigator, might interfere with the safety of the patient or evaluation of the study objectives.

1 BACKGROUND

1.1 Hormone-Refractory Prostate cancer

Prostate cancer is the commonest cancer in men in the UK and other industrialised countries and one of the leading causes of death.

Although adenocarcinoma of the prostate most often presents as local (stage T1 or T2) disease, in which the malignancy is confined to the prostate, a significant proportion of patient's progress despite initial treatment with ablative surgery or radiotherapy, often in combination with hormonal therapy.

Metastatic disease, which is reliably predicted by increasing levels of prostate-specific antigen (PSA), is usually treated by androgen-withdrawal, which can be achieved surgically, by bilateral orchidectomy (castration), or medically, with LHRH-receptor agonists. Initial response rates are very high, but recurrence is almost inevitable and median survival once androgen ablation has failed is typically 12-18 months in the presence of metastatic disease.

Treatment of hormone-refractory prostate cancer (HRPC) is essentially palliative and options include further hormone manipulations, systemic chemotherapy, bisphosphonates, radio-isotopes as well as traditional palliative therapies such as radiotherapy to symptomatic areas and surgery for obstructive symptoms or bone problems such as fracture or spinal cord compression. There are a large number of trials of new agents currently underway in metastatic HRPC (mHRPC) and it is likely that additional effective treatments will become available in the coming years, though it is unlikely that they will supplant the current options (cf herceptin in metastatic breast cancer). James *et al.* published review of the management of metastatic HRPC in 2006[1].

Bone pain is often the most debilitating component of metastatic prostate cancer, occurring in around 80% of cases of HRPC. Current systemic treatment strategies include chemotherapy, bisphosphonates and bone-seeking radioisotopes, including Sr89 and samarium-153. Focal irradiation to bone pain for solitary, painful bone metastases is an effective palliative strategy and may be supplemented by hemibody irradiation for the palliation of widespread metastases.

1.2 Use of Docetaxel (Taxotere) In HRPC

Mitozantrone has previously been compared to steroids alone in the palliative treatment of patients with symptomatic metastatic HRPC and been shown to improve quality of life and progression-free, but not overall, survival[2;3]. More recently, taxane-based chemotherapy has been shown to produce much higher biochemical response rates than mitozantrone and two landmark trials using docetaxel-based therapies published in 2004 demonstrated improved overall survival and quality of life compared to mitozantrone in two trials using docetaxel-based therapies[4;5]. Low numbers of treatment-related deaths occurred in both the docetaxel arms and in the mitozantrone control arms with no clear or consistent differences between arms. Generally the docetaxel regimens were reasonably well-tolerated and the adverse event profiles were similar to those seen with other cytotoxic regimens.

On the basis of these trials, a three-weekly schedule of docetaxel plus prednisolone for up to 10 cycles has emerged as the standard of care for mHRPC and has been approved by the National Institute for Health and Clinical Excellence (NICE) for this purpose in 2006. In this trial we propose to limit initial docetaxel to 6 cycles (the mean number of cycles on the TAX 327 licensing study[6] was 7) to ensure the feasibility of the delivery of Sr89 (see below). Patients still responding to docetaxel (stable disease or better response to therapy, as determined by the treating clinician) after 6 cycles will be eligible to receive a further 4 cycles of chemotherapy.

1.3 Use of Bisphosphonates in HRPC

The use of bisphosphonates in oncology has increased over the last decade, although they remain the subject of controversy in prostate cancer. Bisphosphonates inhibit bone catabolism by reducing the numbers of functioning osteoclasts and have been an established treatment for osteoporosis and similar conditions for many years and more recently have been used to manage bone metastases in breast cancer[7]. In addition, some bisphosphonates, for example zoledronic acid, but, interestingly, *not* clodronate, arrest cell-proliferation, induce apoptosis, and inhibit the growth-factor stimulation of cultured prostate cancer cells[8].

A number of bisphosphonates have been examined in prostate cancer including pamidronate, clodronate and zoledronate. Pamidronate failed to show benefit in a randomised study[9,] A large randomised, placebo controlled study (MRC PR05) reported that clodronate improved the pain-free survival period and overall survival period for patients with metastatic prostate cancer compared with placebo, although the benefits did not achieve statistical significance (i.e. $p>0.05$)[10]. Further, the authors conducting this study reported more gastrointestinal side effects, increased lactose dehydrogenase and required more trial dose modifications, although patients in the clodronate group

were significantly less likely to experience deterioration in their performance status (HR 0.71, 95% confidence interval 0.56 to 0.92, p=0.008). A trial combining clodronate with mitozantrone failed to show any additional palliative benefit from adding this agent to chemotherapy alone[11] and we thus felt that a further study combining this agent with chemotherapy was unwarranted.

Since the publication of the MRC PR05 study, more potent bisphosphonates have been evaluated in mHRPC. The most widely studied has been zoledronate, which has a 40-850 fold higher potency than clodronate in preclinical models of bone resorption[12]. It has also been shown to be more effective than pamidronate (90mg) in controlling malignant hypercalcaemia[13]. In addition, zoledronate has also demonstrated direct anti-cancer activity, including inhibition of proliferation of breast cancer and prostate cancer cells *in vitro*[14].

In randomised studies of mHRPC, zoledronate has been shown to delay, or prevent, skeletal related events (SREs: defined as pathological fracture, spinal cord compression, hypercalcaemia, radiotherapy for bone pain)[15]. However, the drug is administered intravenously every four weeks; this has significant resource implications for oncology or urology departments in terms of both drug costs and clinical time. In the UK, use of this agent is patchy and funding is controversial, for example, the Scottish Medicines Consortium recommended that zoledronate should not be used in mHRPC without further evidence of effectiveness. Previous studies with another bone-targeting agent, Sr89 (see below), have suggested that overall healthcare costs are less with use of Sr89 than with alternative means of palliation. As some of the complications of bone disease are catastrophic for both the patient and the Health Service (e.g. spinal-cord compression leading to paralysis), a strategy of prevention with an expensive agent may well prove to be better than a cheaper alternative in terms of overall quality of life, as well as cheaper overall for the NHS. However, the use of zoledronate requires further evaluation, hence the inclusion of this agent in the trial.

1.4 Strontium-89 (Sr89)

Sr89 is a bone-seeking radionuclide. It is a pure ß-emitter with a half-life of 50 days, has a high uptake in osteoblastic metastases, and remains in tumour sites for up to 100 days. Palliation of bone pain arising from widespread bony metastases may be affected by the intravenous administration of radionuclides that target bone metabolism, for example Sr89, samarium-153 and phosphorous-32. Of these, Sr89 is the most widely used, providing pain-relief in up to 80% of patients, and complete freedom from pain in approximately 10%, for periods that can exceed three months[16;17]. In a randomised controlled phase III trial, the combination of Sr89 injection and external beam radiotherapy improved pain relief, delayed disease-progression and enhanced some quality of life measures compared with external beam radiotherapy alone[18]. However, another phase III randomised controlled trial has suggested that, in some patients, systemic Sr89 may be inferior to local field radiotherapy in terms of survival (11.0 versus 7.2 months, p=0.0457)[19]. The selection of

patients has a significant impact on outcome, response and duration of response to radionuclide therapy, as bone pain palliation is reduced in those with widespread metastatic disease or have a short life expectancy[20;21]. Consequently, the use of radionuclides appears to be optimal at an early stage in disease management. However, their efficacy is reduced or lost with repeated use and over-treatment can also lead to irreversible pancytopenia. Both Sr89 and samarium-153 are only available to a minority of NHS patients. There is some evidence that Sr89 may reduce overall health care costs compared to standard methods of delivering radiotherapy[22].

The benefit of Sr89 in combination with chemotherapy has been evaluated in one small, randomised phase II trail in which 103 HRPC patients received induction therapy with ketoconazole and doxorubicin alternating with estramustine and vinblastine. Seventy two patients who were responders or clinically stable were then randomised to receive doxorubicin either with or without Sr89[23]. Median survival was significantly better in the Sr89 arm (27.7 months vs 16.8 months, p = 0.0014). This intriguing trial has not been repeated and forms the basis for the docetaxel plus Sr89 treatment arms in this study.

1.5 Management of Osteoporosis

Patients eligible for the study will be at risk of osteoporosis in view of their previous therapy (androgen deprivation, possible steroid exposure, age) as well as from some on-study therapies (steroids, docetaxel). Osteoporosis should be considered in the causality of any skeletal related event (SRE) and should be investigated where appropriate. A bone density ancillary/sub-study forms part of this trial. As the results of this sub-study are determined by planned interim analysis, it is possible that further recommendations on the management of osteoporosis in this patient group may be made later in the trial.

1.6 Guidelines for Study Design in HRPC

A consensus group of leading investigators in HRPC formulated recommendations for clinical trial design, in order to improve the evaluation of new agents and combinations (Bubley *et al.,*[24]). The recommendations included eligible patient groups and PSA-based response criteria which have been adopted in this study.

2 RATIONALE

HRPC (Hormone Refractory Prostate Cancer) with metastases is uniformly rapidly fatal and improved therapies are desperately needed. Docetaxel (Taxotere®) has been shown to improve survival in patients when compared against mitoxantrone in a recent phase III randomised clinical trial in patients with HRPC[4] and its favourable toxicity profile allows for combination with other agents.

The beneficial effects of bisphosphonates on bone resorption make zoledronic acid a suitable choice for combination with docetaxel, leading to fewer SREs and improved palliation in HRPC. Furthermore, as bone disease is often the principal cause of morbidity in HRPC, improved bony outcomes may also impact overall survival.

Sr89 also has beneficial effects on bone metastases but acts by a different mechanism from bisphosphonates, raising the possibility of an additive benefit when the two are co-administered. In addition, one small randomised trial[23] showed a statistically and clinically significant advantage to the addition of Sr89 to chemotherapy in HRPC.

This study therefore seeks to assess whether the addition of Sr89 or zoledronic acid offers a significant benefit in combination with docetaxel and prednisolone in HRPC.

3 STUDY OBJECTIVES AND OUTCOMES

The trial incorporates both phase II and phase III components, each with specific objectives and employing several outcome measures (see Table: section 3.2).

3.1 Study Objectives

3.1.1 Phase II

The primary objective of the phase II component is to assess the feasibility, tolerability and safety of the four treatment arms.

3.1.2 Phase III

The phase III component of the trial will assess treatments within a 2x2 factorial design framework i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use). Each of these treatment comparisons will be made in terms of clinical efficacy, with primary outcome clinical progression-free survival time, and health economic outcomes. In addition, the trial will assess if there is any association between biomarkers and clinical outcomes.

3.2 Study Outcomes

Phase	Primary	Subsidiary	Ancillary measures and exploratory outcomes
II	• Feasibility, tolerability and safety in terms of cycles of docetaxel and prednisolone with zoledronic acid and/or Sr89 received, cycle delays, dose reductions and toxicity	• Clinical progression-free survival • Skeletal-related event- free survival • Pain progression-free survival • Overall survival • Costs • Quality of life	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • Patient-reported pain-related outcomes
III	• Clinical progression-free survival • Cost and cost-effectiveness	• Skeletal-related event-free survival • Pain-progression–free survival • Overall survival • Quality of life • Toxicity	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • RECIST criteria-related outcomes • Patient-reported pain-related outcomes.

4 STUDY DESIGN

4.1 Study Summary

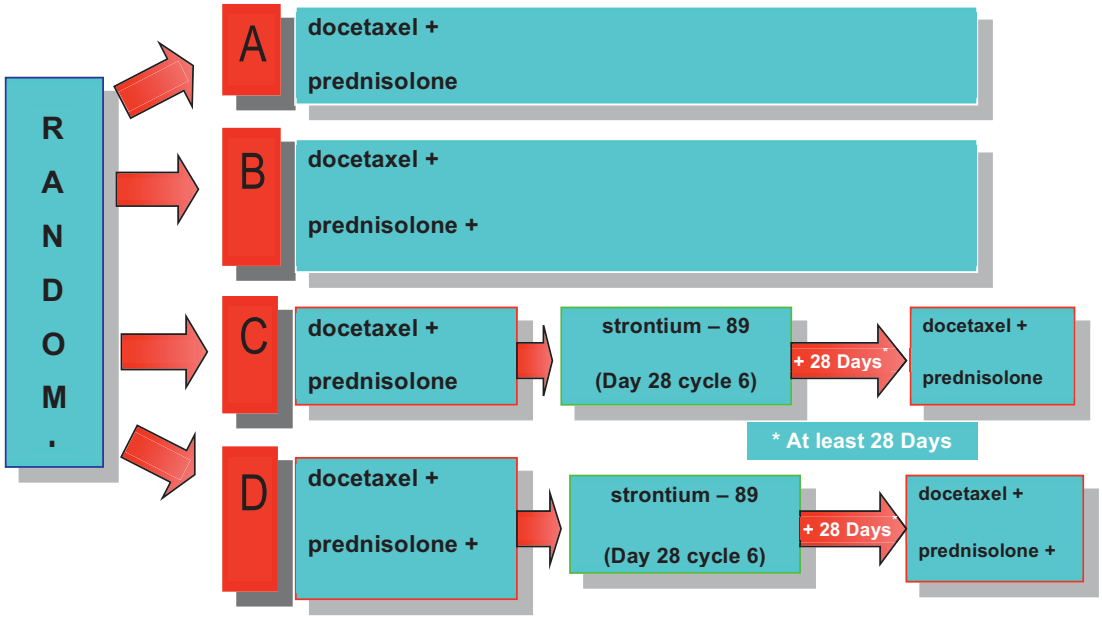

Figure 4.1: Schematic representation of Trapeze study : NB After completion of combined chemotherapy & zoledronic acid cycles on Arms B & D, zoledronic acid is to be administered at four-weekly intervals. At radiological bone progression or at pain progression the local investigator may choose to continue it.

Patients are assessed every three weeks during the study treatment period (during chemotherapy cycles 1-6 and cycles 7-10). After treatment, patients receive monthly follow-up visits for the first three months, with follow-up visits every three months thereafter, until the patient dies or is withdrawn from the study.

All patients will receive a clinical assessment (section 9.3) at the end of cycle 6 (this is the end of the Primary Treatment Period), irrespective of treatment arm.

** In Arms C and D a minimum of 28 days between the date of Sr89 administration and day 1 of cycle 7 of chemotherapy is required. If cycle 7 (day 1) of chemotherapy is delayed and cannot be administered, for any reason, within 8 weeks (56 days) of the date of Sr89 administration then the patient is considered to be 'off–study treatment'. Thereafter, all additional therapy, including any additional docetaxel cycles, will be considered as off-study therapy for the purposes of the trial.

4.2 Study Size

The trial requires 412 events and it is anticipated that a total of 588 patients will need to be recruited to observe this number of events at one year follow-up. We aim to recruit a minimum of 618 evaluable patients which allows for 5% dropout. (see section 12.2 for justification of sample size).

5 STUDY POPULATION

5.1 Inclusion Criteria

- Age ≥ 18 years
- Histologically / cytologically proven prostate adenocarcinoma OR multiple sclerotic bone metastases with PSA≥ 100ng/ml without histological confirmation.
- Radiological evidence of bone metastasis.
- Fit enough to receive trial treatment.
- Prior hormonal therapy for prostate cancer:
    - Bilateral orchidectomy, AND/OR medical castration by LHRH agonist therapy (if LHRH agonist therapy alone, this therapy should be continued).
- For patients who have received prior hormonal drug therapy:
    - Flutamide, nilutamide, bicalutamide, cyproterone acetate or stilboestrol must have stopped at least four weeks prior to enrolment and progression must have been demonstrated since cessation;
    - Estramustine must have stopped at least four weeks prior to enrolment, any adverse events must have been resolved and progression must have been demonstrated since cessation.
- Documented progression, defined by one of the following:
    - Elevated and rising prostate-specific antigen (PSA):
        - PSA > 5ng/ml;
        - Progressive rise in PSA, defined as two consecutive increases in PSA documented over a previous reference value (measure 1). The first increase in PSA (measure 2) should occur a minimum of one week from the reference value (measure 1). This increase in PSA should be confirmed (measure 3) after a minimum of one week. If the confirmatory PSA value (measure 3) is less than the previous value, the patient will still be eligible for the trial provided the next PSA (measure 4) is found to be greater than the second PSA (measure 2). The final sample must have been taken within 28 days of enrolment.
    - And/or progression of any uni-dimensionally or bi-dimensionally measurable malignant lesion
    - And/or at least one new lesion identified on bone scan.
- Life expectancy ≥ 3 months.
- ECOG performance status 0-2.
- Adequate haematological function:
    - Haemoglobin ≥ 10g/dl
    - Neutrophil count ≥ 1.5×10^9/l

- Platelets $\geq 100 \times 10^9$/l

- Adequate renal and hepatic function:
  - Serum creatinine $\leq 1.5 \times$ upper limit of normal
  - Transaminases (ALT, AST or both) $\leq 1.5 \times$ upper limit of normal (unless related to hepatic metastatic disease, where patients may be entered after discussion with one of the Clinical Co-ordinators)
  - Serum bilirubin $\leq 1.5 \times$ upper limit of normal
- Written informed consent.

5.2 Exclusion Criteria

- Prior cytotoxic chemotherapy for HRPC, other than estramustine monotherapy.
- Prior radiotherapy to more than 25% of the bone marrow, or whole pelvic irradiation.
- Prior radionuclide therapy for HRPC.
- Prior treatment with a bisphosphonate for any reason within the previous two months.
- Malignant disease within the previous five years, other than adequately treated basal cell carcinoma.
- Known brain or leptomeningeal metastases.
- Symptomatic peripheral neuropathy $\geq$ grade 2 (NCI CTC).
- Concurrent enrolment in any other investigational clinical trial.
- Treatment with any other investigational compound within the previous 30 days.
- Any condition, which, in the opinion of the investigator, might interfere with the safety of the patient or the evaluation of the study objectives.

6 STUDY TREATMENT

6.1 Study Drug Administration

All four study treatments are IMPs.

6.1.1 Docetaxel

Docetaxel will be administered by intravenous injection in accordance with the instructions in the Summary of Product Characteristics (SmPC) at a dose of 75 mg/m^2 (up to a maximum dose of 165 mg) on day one of the study treatment period and then every three weeks thereafter up to a maximum of 10 cycles.

NOTE: Patients with a body surface area (BSA) greater than 2.2m^2 should be dosed as though they have a BSA of 2.2 m^2. No “ideal” weight should be used for BSA calculations.

6.1.2 Prednisolone

Prednisolone 10mg daily will be given until the completion of chemotherapy, not being interrupted for administration of Sr89. Additional dexamethasone should be given pre- and post-docetaxel infusion to suppress allergic reactions. At the end of chemotherapy treatment, Prednisolone should be tapered off starting 3 weeks from the last administration of docetaxel.

6.1.3 Zoledronic acid

Zoledronic acid will be administered intravenously as a 15 minute infusion in accordance with the instructions in the SmPC at the recommended dose (detailed in the dose table below), every three weeks up to the end of chemotherapy and thereafter monthly. Renal function should be closely monitored throughout the zoledronic acid treatment period.

Serum Creatinine measurements: Serum creatinine should be measured at baseline and within 48 hours prior to every administration of zoledronic acid.
Serum Electrolytes and FBC: Serum electrolytes including calcium, phosphate and magnesium should also be measured prior to each infusion.

Pre-treatment Creatinine Clearance (ml/min)	Zoledronic acid Recommended Dose	Volume of concentrate solution for infusion
>60	4.0 mg	5.0 ml
50-60	3.5 mg	4.4 ml
40-49	3.3 mg	4.1 ml
30-39	3.0 mg	3.8 ml

Patients must also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. These doses are available as a combination tablet. When docetaxel and zoledronic acid are both administered, the recommended sequence of drug administration is the docetaxel infusion prior to zoledronic acid infusion.

Patients must be evaluated prior to and following the administration of the zoledronic acid infusion to ensure that they are adequately hydrated.

If the patient is scheduled to receive a dose of Sr89 (as per study arm, or at any time during the post-study treatment period whilst receiving zoledronic acid), the calcium and vitamin D supplements must be discontinued three weeks before and recommenced four weeks after the Sr89 injection.

Prior to treatment with zoledronic acid, dental examination with appropriate preventive dentistry should be considered for patients with poor dentition. While on treatment these patients should avoid invasive dental procedures if possible. For patients requiring dental surgery, for example tooth extraction, zoledronic acid should be temporarily discontinued prior to dental work and recommenced only when the wound has healed thoroughly.

6.1.4 Strontium-89 (Sr89)

Sr89 will be administered intravenously in accordance with the instructions in the SmPC, as a single dose of 150 MBq given at day 28 after day one of cycle 6, subject to satisfactory recovery of marrow function.

6.2 Planned Interventions

6.2.1 Arm A: Control – Docetaxel plus prednisolone

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily, every three weeks for a maximum of 10 cycles or until disease-progression (as defined by the treating clinician), patient withdrawal, or associated treatment toxicity. It is recommended that all 10 cycles of chemotherapy are administered subject to the above; however, the local clinician can decide to stop therapy at any time for any reason. The reason for discontinuation of therapy must be recorded on the Case Report Form (CRF).

6.2.2 Arm B: Docetaxel plus prednisolone plus zoledronic acid

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily. Zoledronic acid will be administered intravenously at

a dose of 4 mg every three weeks on day one of the chemotherapy cycle up to the end of chemotherapy, and thereafter every four weeks as clinically indicated, or until disease-progression or other discontinuation criteria outlined in Section 8. Patients treated with zoledronic acid will also receive vitamin D and calcium supplements throughout treatment.

6.2.3 Arm C: Docetaxel plus prednisolone plus Sr89

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily, every three weeks thereafter for 6 cycles. At day 28 after the administration of cycle 6 of docetaxel, subject to satisfactory haematological and clinical parameters, Sr89 will be administered as a single dose of 150 MBq. After at least four weeks (28 days) and within 56 days after the Sr89 administration (provided bone marrow function has adequately recovered), the additional chemotherapy cycles (cycles 7-10) will be given until disease-progression (as defined by the treating clinician), patient withdrawal or associated treatment toxicity. It is recommended that all 10 cycles of chemotherapy are administered subject to the above; however the local clinician can decide to stop therapy at any time for any reason.

6.2.4 Arm D: Docetaxel plus prednisolone plus Zoledronic acid plus Sr89

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg), prednisolone 10mg daily and Sr89 150 MBq will be administered as described above for Treatment Arm C. In addition, zoledronic acid will be administered intravenously at a dose of 4 mg every three weeks up to the end of docetaxel chemotherapy, and thereafter every four weeks as clinically indicated or until disease progression (as defined by the local clinician). The zoledronic acid dose on day 28 post-chemotherapy, will be omitted and patients will discontinue the calcium and vitamin D tablets for three weeks before and four weeks after the Sr89 injection.

6.3 Further off-study treatment

All further off-study treatment, i.e. chemotherapy, bisphosphonate and radioisotope therapy, received after study treatment must be captured on the “Concomitant Medication Running Form”. The choice of further treatment is at the discretion of the clinician. However, if clinically indicated the following additional treatments are recommended for all patients:

6.3.1 Zoledronic acid

On development of radiological bone progression or pain progression (as defined in Section 8), patients not randomised to receive zoledronic acid, i.e. treatment arms A and C, should be considered to commence this agent. Patients already on zoledronic acid at radiological bone progression or pain progression can continue with this treatment at the investigator’s discretion.

6.3.2 Strontium-89 (Sr89)

On development of radiological bone progression or pain progression, patients not receiving Sr89, i.e. arms A and B, can receive Sr89 at the investigator's discretion. Patients who have already received Sr89, i.e. arms C and D, can receive further Sr89 at the investigator's discretion, but it is recommended, as per the SmPC, that there is at least a 12 week interval between Sr89 administrations.

6.4 Dose Modification in the Event of Toxicity

6.4.1 General rules

Every effort will be made to administer the full dose regimen to maximise dose-intensity. If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms, including antiemetics for nausea and vomiting, anti-diarrhoeals for diarrhoea, and antipyretics and/or antihistamines for drug fever.

If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment will be adopted.

No more than two docetaxel dose reductions will be adopted per patient. If more than two dose reductions are indicated, the patient must go off study.

6.4.2 Docetaxel dose reductions

Doses must be adjusted according to the following:

- Standard dose: 75 mg/m²
- First level dose reduction: 60 mg/m²
- Second level dose reduction: 45 mg/m²

Doses which have been reduced for toxicity must not be re-escalated.

6.4.3 Docetaxel dose delay

A treatment delay of four days or more must be reported in the CRF, specifying the reason for the delay. Treatment may be delayed no more than 14 days to allow recovery from acute toxicity. In case of a treatment delay greater than 14 days, the patient must be withdrawn from the trial and a Withdrawal CRF completed.

6.5 Myelosuppression

6.5.1 Neutropenia and/or its complications

Adverse event	Action to be taken
- Grade 4 neutropenia* for 7 days or more. - Grade 3-4 neutropenia with oral fever ≥38.5°C - Infection* (ie. documented infection with grade 3-4 neutropenia)	If the patient develops one of these adverse events, the next docetaxel infusion must be given with a one-level dose reduction.

* according to NCI-CTCAE

ANC on day of infusion	Action to be taken
≥ 1.5 x 10^9/L	Treat on time: do not reduce the dose
< 1.5 x 10^9/L	Delay maximum 2 weeks Blood counts have to be performed until ANC ≥ 1.5 x 10^9/L. Then treat with a one-level dose reduction. If no recovery (ANC still <1.5 x 10^9/L) after 2 week delay: the patient will be discontinued from study.

6.5.2 Thrombocytopenia

In case of grade ≥3 platelets (NCI-CTCAE), treatment may be delayed for a maximum of 14 days until platelets recover to ≥100 x 10^9/L, following which treatment will be given with a one-level dose reduction.

6.5.3 Allergy (anaphylactic and hypersensitivity reactions)

Hypersensitivity reactions that occur despite pre-medication are very likely to occur within a few minutes of the start of the first or of the second infusion of docetaxel. Therefore, during the first and the second infusions, careful evaluation of the general sense of well-being and of blood-pressure and heart-rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention can occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation must be immediately available: antihistamine, corticosteroids, aminophylline, and epinephrine.

If a reaction occurs, the specific treatment that can be medically-indicated for a given symptom (e.g. adrenalin (epinephrine) in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild symptoms: Localised cutaneous reaction, such as: pruritus, flushing, rash.	- Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside - then, complete study-drug infusion at the initial planned rate. At subsequent cycles use the pre-medication outlined in section 6.1.1.
Moderate symptoms: Generalised pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. ≤80 mmHg	- stop study drug infusion - give IV antihistamine and IV corticosteroids (*) - resume study-drug infusion after recovery from symptoms. At subsequent cycles, antihistamines* and steroids* will be given IV, one-hour before infusion, in addition to the pre-medication planned in section 6.1.1.
Severe symptoms: e.g. bronchospasm, generalised urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema	- stop study-drug infusion - give IV antihistamine and steroids (*). add adrenaline (epinephrine)** or bronchodilators and/or IV plasma expanders if indicated. - Once all signs and/or symptoms of hypersensitivity reaction disappear, study-drug may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. Pre-medication regimen as described in section 6.1.1 is only recommended when study drug is re-infused more than 3 hours after the interruption. During subsequent cycles, dexamethasone will be given at 20mg orally, 24, 18, 13, 7 and 1 hour before study-drug infusion. Additionally diphenhydramine (or equivalent) will be given at 50mg IV 1 hour before study-drug infusion. If a severe reaction recurs, patient will go off protocol therapy, , and a Withdrawal CRF completed.
antihistamines*: *Chlorpheniramine (*) IV 10-20 mg* *or promethazine (*) IM 25–50 mg, max-100 mg* *corticosteroids: dexamethasone or equivalent (*) IV 5-10 mg of dexamethasone* * Adrenaline (epinephrine): administer standard dose – 500 µg).*	

6.5.4 Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to patients from the first cycle. The use of dexamethasone plus a second anti-emetic such as metoclopramide is recommended. Local protocols that coincide with off study practice are permitted. More aggressive anti-emetic prophylaxis (eg. 5-HT_3 antagonists) should be given to a patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle.

If, despite the appropriate medication, grade ≥3 nausea/vomiting still occurs, reduce the dose of docetaxel by one dose level. Should nausea/vomiting continue or recur at grade ≥3 despite the dose reduction, the patient must go off-study, and a Withdrawal CRF completed.

6.5.5 Diarrhoea

No prophylactic treatment for diarrhoea is recommended from cycle one. However, following the first episode of diarrhoea, the patient should receive symptomatic treatment with loperamide:

- 4 mg following the first episode and then 2 mg following each new episode until recovery of diarrhoea (no more than 16 mg daily).

If diarrhoea grade ≥3 still occurs despite the use of loperamide, reduce the dose of study-drug by one dose level. If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient will go off-study, and a Withdrawal CRF completed.

6.5.6 Stomatitis

Grade ≤2: No change, study chemotherapy should be withheld until resolution to grade ≤1. If grade 3 stomatitis occurs, study drug must be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of study drug must be reduced by one dose level for all subsequent doses.

In case of grade 4 stomatitis, the patient will go off study, and a Withdrawal CRF completed.

6.5.7 Peripheral neuropathy

In case of symptoms or signs experienced by the patient, dose modification should be performed as follows:

- Grade ≤1: no change.
- Grade 2: re-treat with a one-level dose reduction (no further dose reduction is planned).
- Grade ≥3: patient will go off study, and a Withdrawal CRF completed.

6.5.8 Skin toxicity

- Grade 0, 1, 2: No change.
- Grade ≥3: delay until grade ≤1, maximum 2 weeks then reduce dose of study drug by one dose level; if no recovery to grade ≤1 within 2 weeks delay, patient will go off protocol therapy, and a Withdrawal CRF completed.

6.5.9 Liver toxicity

In case of increase of ALT and/or AST to >1.5 x ULN or bilirubin to >ULN, delay study drug treatment for up to 2 weeks until ALT and/or AST returned to ≤1.5 x ULN and bilirubin to ≤ ULN. Then re-treat at one dose level lower.

In the case of a patient entered into the study with elevated bilirubin levels (serum bilirubin ≥1.5 × upper limit of normal) as per the eligibility criteria, the criteria detailed in the above paragraph for dose reduction/treatment delay in relation to bilirubin levels for this patient DO NOT apply. In this

case the individual patient's reading at study entry is considered the normal bilirubin level for that individual. Subsequent dose delays and dose reductions are applied as above, if the individual's bilirubin level increases from baseline after cycle 1 of chemotherapy. This is because any increase in the bilirubin level can be considered toxicity from treatment and not related to the underlying disease at baseline.

6.5.10 Docetaxel-induced fluid retention

In case of fluid retention (peripheral oedema and/or effusions) during the treatment with docetaxel, the signs and symptoms should be graded as mild, moderate, severe or life threatening.

NO DOSE REDUCTION IS PLANNED

The patient's body weight will be recorded and followed as frequently as possible to document any weight gain, which could be related to oedema.

Recommended treatment

Treatment should commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline grade ≥1 not otherwise explained.

Based on the hypothesis of capillary damage due to docetaxel, the following treatment is recommended in case fluid retention occurs: frusemide 20 mg orally once daily.

If the symptoms cannot be controlled adequately i.e. worsening of the fluid retention or spread to another area, the dose of frusemide should be increased to 40 mg. The addition of metolazone orally at the recommended dose together with potassium ± magnesium supplements may be useful.

The clinical tolerance of the patient, the overall tumour response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the study drug. It is recommended, however, that patients with fluid retention of grade ≥3 severity should be withdrawn, and a Withdrawal CRF completed.

In case it is difficult to make a judgment as to whether an effusion is disease-related or study drug-related, the treatment should be continued until progressive disease in other organs is documented, and provided there is no worsening of the effusion during treatment.

6.5.11 Docetaxel-induced hyperlacrimation

The excessive lacrimation (epiphora) seen in some patients receiving docetaxel appears to be related to cumulative dose (median ~300 mg/m^2) and resolves rapidly after treatment discontinuation. Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with oedema) of the lachrymal duct epithelium (producing a reversible lachrymal duct stenosis). If epiphora persists patients should be referred to an Ophthalmologist.

In patients experiencing clinically significant hyperlacrimation, the following approach is recommended:

NO DOSE REDUCTION PLANNED

Frequent instillation of artificial tears.
Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate): 2 drops each eyelid for 3 days starting the day before docetaxel administration in patients without a history of herpetic eye disease.

6.5.12 Zoledronic acid and renal impairment

Please refer to section 6.1.3.

6.5.13 Hypersensitivity to zoledronic acid

If hypersensitivity occurs treatment should be discontinued, or continued with the use of anti-histamines, at the discretion of the treating clinician.

6.5.14 Osteonecrosis of the jaw and zoledronic acid

Long-term use (i.e. >24 months) of zoledronic acid use has been linked to osteonecrosis of the jaw (ONJ). This is of particular concern in patients who have dental disease. If a patient develops ONJ then their zoledronic acid should be immediately and permanently discontinued.

6.5.15 Strontium-89 (Sr89)

This should be omitted if there is inadequate marrow reserve (Hb $\leq$10 g/dL, neutrophils $\leq$1.5 x 10^9/L, platelets $\leq$100 x 10^9/L). There will be no dose reduction : Sr89 must be given at full-dose if it is given as trial treatment.

7 STUDY ORGANISATION

7.1 Duration of Study

It is anticipated that the study will involve up to 50 centres. At a mean recruitment rate of approximately 15 patients per month, accrual should be feasible in the previously estimated 6-year time span. The primary treatment period (i.e. the first 6 cycles of chemotherapy) for each patient will last 18 weeks in arms A and B (the arms that are not randomised to receive Sr89) and 22 weeks in arms C and D (the arms which are randomised to receive Sr89). A further 4 cycles of chemotherapy may be given to all patients; continuous for patients in arms A and B and following a break of at least 28 days (and less than 56 days) for those in arms C and D. Following completion of chemotherapy (docetaxel) patients in treatment arms A and C may receive zoledronic acid monthly (every four weeks) at the clinician's discretion. Follow-up visits will initially occur monthly for three months, and subsequently three-monthly until death or withdrawal for any other reason. Patients withdrawn from the study will be followed-up by ONS flagging, which will provide copies of patients' death certificates. For such patients, a withdrawal CRF must be completed. It is estimated that recruitment of participants into the study will be complete by the end of February 2012.

The Trial Management Group (TMG) is responsible for protocol development and initiation of the study. This group forms the basis for the Trial Steering Committee (TSC) who are responsible for monitoring study-progress, amending the study-protocol as required, overseeing the trial conduct and providing information to the Independent Data Monitoring Committee (IDMC). The Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer Sciences, (formerly within the Institute for Cancer Studies) University of Birmingham, is responsible for the day-to-day running of the study, centre-initiation, reporting to the TSC and IDMC, analysis, and presentation of results. Intellectual property and access to data arising from this trial will be governed by the TSC.

7.2 Site Responsibilities

The Principal Investigator at each participating centre has overall responsibility for the study and all patients entered into the study, but may delegate responsibility to other members of the study team as appropriate. The Principal Investigator must ensure that all staff involved in the trial are adequately trained and that their duties have been logged on the Site Responsibilities Sheet.

7.3 Study Start-Up and Core Documents

Centres wanting to participate in the study should contact the study office to obtain information. The Principal Investigator should then provide the study office with the following core documents and attend an initiation visit or attend an initiation teleconference before the site is activated:

Core Documents:

- The site contact details.
- The University of Birmingham Clinical Study Site Agreement.
- All Investigators and Co-investigators will provide an up-to-date copy of their CV, personally signed and dated, prior to the start of the study. The CV should detail the Investigators' education, training and experience relevant to their role in the study.
- The study-specific Commitment Statement.
- Site Responsibilities Sheet.
- Trust approval letters.

It is the Principal Investigator's responsibility to apply for site-specific assessment for his/her individual site. Once a site has been approved the Principal Investigator will be informed by the Chief Investigator (or one of his team) that site-specific approval has been granted.

7.4 Forms And Data Collection

Data collected on each subject will be recorded by the investigator, or his/her designee, as accurately and completely as possible as soon as the requested information becomes available. The investigator will be responsible for the timing, completeness, legibility and accuracy of the Case Report Form (CRF) and he/she will retain a copy of each completed CRF. The investigator will supply the study office with any required data from such records.

Entries will be made in black ballpoint pen on the CRF provided and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated by the investigator or his/her designee. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used. Each patient enrolled into the study must have all CRFs completed and signed by the Principal Investigator or his/her designee. This also applies to those patients who failed to complete the study. Data reported on the CRF should be consistent with the source data, or the discrepancies should be explained.

To enable peer review and/or audits from Health Authorities or other regulatory bodies, the Investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed Informed Consent

Forms, copies of all CRFs and detailed records of drug disposition. It is the responsibility of the Principal Investigator to ensure that all essential trial documentation and source records (e.g. signed Consent Forms, Investigator and Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least five years after the end of the trial: participating sites will be sent a letter specifying the permissible disposal date.

7.5 Quality Of Life Data (Sub-study)

Quality of life (QoL) will be assessed using EuroQol EQ-5D and FACT-P, which are patient-completed questionnaires (Appendix 3, 4). Patients will also be asked to complete pain diary sheets during their treatment (Appendix 5). All eligible patients will be asked to consent to both the main trial and also to the QoL part of the trial, as taking part in this part of the trial is optional. QoL questionnaires will be completed at baseline, on treatment (prior to each dose of docetaxel), and at every protocol-defined visit,, including all patient follow-up visits. The patient should be asked to complete the QoL questionnaires prior to consultation with the clinician. It is the intention that in this trial, patients will be asked to complete QoL questionnaires and Pain Diaries from the date of randomisation until death or patient refusal. The completion of these documents is voluntary and should continue throughout patient follow-up (pre- and post-clinical progression) irrespective of any further therapy that an individual patient may receive. All additional therapy post-clinical progression will be recorded in the relevant page of the CRF.

It is essential to explain to the patient that all parts of the QoL questionnaire should be completed as fully as possible. In order to administer these consistently, the QoL questionnaires will be in order and given to the patient in a stapled booklet. Each centre must identify a named individual responsible for administering the QoL questionnaires.

Participation in the QoL sub-study is not compulsory and will not affect the patient's ability to take part in the trial.

7.6 Health Economic Analysis

The economic analysis will be conducted alongside the trial. The main objective of this analysis is to assess the costs and cost-effectiveness across different treatments. The key resource use data will be collected through the CRFs and supplemented by a patient-completed resource-use questionnaire. Health-related QoL will be assessed using the EQ-5D. The EQ-5D is a widely-used, brief, generic utility-based measure of health-related QoL. A utility score will be generated from this questionnaire. Quality-adjusted life-years (QALYs) will be calculated using area under the curve methods. A cost-effectiveness analysis will be conducted in which outcome will be measured as incremental cost per QALY gained within the trial period analysis.

The scope for validating data on resource use by using routine NHS administrative system data will be explored, including obtaining patient consent. Modelling will be required to estimate the cost per life year and per QALY, for sensitivity analysis and also to explore the implications of generalising from the study.

The economic analysis will be undertaken in conjunction with The Health Economics Unit, University of Birmingham, who have extensive experience in such work.

7.7 Biomarkers Data (Sub-study)

The CRCTU will request pathological information at the time of randomisation for all patients entered into the trial. This information will include histology number, location of paraffin-embedded tumour blocks and reporting consultant pathologist. Subject to patient consent, collection of this information will allow for the prospective collection of tissue blocks, which will be analysed at a later date. Immuno-histochemical techniques will be used on tissue sections to test for the presence of biological predictive-markers of treatment benefit (e.g. P53, P27, P20, Ki67, Her2/neu, EZH2).

We will also seek patient consent for the collection and storage of repeat blood samples which can initially be stored at the local centre but ultimately will be sent to CRCTU for future proteomic analysis of known (e.g. PSA, FGS, IGS) and novel protein markers using the expertise within the School of Cancer Sciences in Birmingham and other collaborative centres.

7.8 Computerised Records

Create data – Details of centres and participating staff will be recorded during the study. Patient data records will be created at randomisation and data entered from CRFs during study participation.

Modify and maintain data – Records of centres and participating staff will be modified to maintain accurate details of trial-related personnel and their involvement status. Data from CRFs will be modified to correct any erroneous or missing entries. The reason for these changes will be recorded to facilitate an audit trail.

Archive – At the conclusion of the trial, when all patient data has been collected, and the analysis is complete, all the data stored on the computer system will be archived for 15 years. After trial conclusion, if any audit is required, or new analysis to be performed, the data will be retrieved.

7.9 Monitoring

The study is being conducted under the auspices of the CRCTU according to the current guidelines for Good Clinical Practice. Participating centres will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki.

Participating centres will be monitored by checking incoming forms for compliance against the protocol, consistent data, missing data and timing. Study staff will be in regular contact with centre personnel to check on progress and to deal with any queries they may have.

On-site monitoring will be carried out as required following a study-specific risk assessment and as documented in the study-specific monitoring plan.

8 STUDY PROCEDURES

8.1 Patient Screening

The investigator will provide patients who appear to meet the criteria for participation in the study with information to allow them to make an informed decision regarding their participation. If informed consent is given, the investigator will conduct a full screening evaluation to ensure that the subject satisfies all inclusion and exclusion criteria. If the screening is successful, it is recommended that the patient commences trial treatment within two weeks of randomisation.

8.2 Randomisation of Patients

Randomisation will be undertaken by the CRCTU, School of Cancer Sciences, University of Birmingham.

8.2.1 Stratification

Patients will be randomised to treatment arms in a 1:1:1:1 allocation ratio using a computerised minimisation algorithm. Randomisation will be stratified by centre and ECOG performance status (0,1,2) to avoid imbalance in the four treatment arms.

8.2.2 Randomising a patient

To randomise a patient:

- Obtain the patient's written informed consent to participate in the study.
- Complete the Randomisation Form
- Telephone:

Mon-Fri, 9.00 –5.00

Tel: [redacted] or [redacted]

Fax: [redacted] (24hrs)

The patient will be allocated their treatment and a trial number, which must be noted on the Randomisation CRF. The investigator should send the patients' GP a letter and information sheet indicating their participation in the study.

8.3 Study Treatment Period

Day 1 of the study treatment period is the day on which the first dose of docetaxel is administered and prednisolone commenced. The first 22 weeks is the primary treatment period: 6 cycles of docetaxel +/- Sr89 +/- zoledronic acid, according to the randomisation treatment allocation. A further

4 cycles of docetaxel can then be given according to the details in section 6 of the protocol. This period will be classed as the secondary treatment period. Prednisolone should be tapered off starting 3 weeks from the last administration of docetaxel.

If a patient has been randomised to receive zoledronic acid, this will be continued 4 weekly thereafter until protocol-defined disease progression, patient or clinician withdrawal (for toxicity), or patient choice. Further treatment (including the use of zoledronic acid) after clinical disease progression will be given according to local clinical practice.

8.4 Follow-up Period

The follow-up period begins after the completion of the primary and secondary (if given) treatment periods. Patients are followed-up every month for the first three months and then every three months until death or patient withdrawal for any other reason.

8.5 Discontinuation of Study Treatment

Discontinuation of any study medication(s) must be reported by completing the Withdrawal CRF.

8.5.1 Discontinuation of study docetaxel

A patient should be withdrawn from docetaxel treatment in the event of any of the following:

- Progression due to either:
    - Pain progression (as defined by the local clinician), or
    - Clinical Disease progression, as defined by the local clinician.
      NOTE: biochemical (PSA) progression alone is NOT a reason to discontinue treatment unless the investigator deems it to be in the best interests of the patient.
- Development of a life-threatening and/or irreversible toxicity not manageable by symptomatic care, dose reduction, or dose delay. A maximum of two docetaxel dose reductions are permitted per patient (see Section 6.4.1). A maximum dose delay of 14 days is permitted on each cycle of docetaxel (see Section 6.4.3).
- Administration of any other anti-tumour chemotherapy, radiotherapy or investigational agent during the trial.
- Development of any condition, or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue trial treatment or to withdraw (consent) from other aspects of the trial, e.g. completion of QoL booklets, participation in tumour-block collection or proteomic (blood sample) collection.

8.5.2 Discontinuation of study zoledronic acid

A patient should discontinue on-going zoledronic acid in the event of any of the following:

- Development of any of the toxicities requiring discontinuation as described in section 6.5.12.
- Pain progression or clinical disease progression (as defined by the local clinician). NOTE zoledronic acid may continue to be given (off-study) at the investigator's discretion.
- Development of any condition or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue trial treatment or to withdraw from the trial.

8.5.3 Omission of study Sr89

The planned treatment of Sr89 should be omitted in the event of any of the following:

- Unsatisfactory haematological and clinical parameters as described in section 6.5.14.
- Failure to complete 6 cycles of study docetaxel.
- Development of any condition or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue treatment or to withdraw from the trial.

8.6 Study Completion

A patient will be considered to have completed the study in the event of death or of loss to follow-up.

9 STUDY ASSESSMENTS

9.1 Baseline Assessments

The following must have been done not more than 28 days **prior** to enrolment, with one exception as detailed below:

- Medical history.
- Physical examination.
- ECOG performance status
- Tumour assessment by any or all of: CT scan, MRI scan, bone scan and ultrasound:
    - The trial management team *recommend* that the tumour assessment is performed within 56 days of patient randomisation.
    - The same technique must continue to be used for a given lesion throughout a patient's study course.
    - As per eligibility criteria, radiological evidence of bone metastasis is required for study entry. If a patient has received additional cancer therapy after the radiological imaging, but prior to randomisation into the trial, new imaging is required to confirm that the patient has continued disease involvement of the bone
- Chest X-ray (required if no CT scan of chest) or CT scan.
- Dual energy X-ray absorption scan (DXA) – Bone Density Scan.

(The requirement for a DXA scan may not be required if the participating centre is not taking part in the relevant sub-study, or if a patient has declined to participate in this part of the study).

- Proteomic blood sample (subject to individual investigator site participation)
- Serum PSA.
- Haematology tests: haemoglobin, WBC count, neutrophil count and platelet count.
- Clinical chemistry tests: urea, serum creatinine, potassium, sodium, calcium, magnesium, aminotransferases (AST, ALT or both), alkaline phosphatase, total bilirubin and blood glucose.
- Pain score and analgesic use (see Section 9.5). Both pain and analgesic-use scores will be derived from the record of the week immediately prior to assessment.
- Questionnaires: QoL using EuroQol EQ-5D and Fact-P questionnaires, the resource-use questionnaire.

9.2 Assessments During Study Treatment Period (Cycles 1-10 of Chemotherapy)

The following assessments will be carried out at the indicated intervals during the course of the study:

- Tumour assessment as clinically indicated - each lesion to be assessed using the same technique as used for that lesion at baseline.
- Chest X-ray or CT scan – as clinically indicated.
- Physical examination.
- Serum PSA: immediately prior to each dose of docetaxel, then every 12 weeks during secondary treatment period.
- Proteomic blood sample at end of cycles 2, 4 and 6 of chemotherapy. If further chemotherapy is given (i.e. cycles 7 to 10) then samples will be taken at the end of cycles 8 and 10 (subject to individual investigator site participation).
- Haematology tests (as at baseline): immediately prior to each dose of docetaxel or assessment.
- Clinical chemistry tests (as at baseline): immediately prior to each dose of docetaxel or assessment.
- Pain score and analgesic use: recorded by patient during the week immediately prior to each dose of docetaxel or assessment (see section 9.5).
- QoL using the EuroQol EQ-5D and Fact-P questionnaires, and the resource-use questionnaire: immediately prior to each dose of Docetaxel or assessment.
- ECOG performance status.

9.3 End of Primary Treatment Period Chemotherapy Assessments (ALL Patients)

Following completion of the 6th cycle of protocol-defined therapy, all patients should have the following assessment completed 21 days after receiving cycle 6 docetaxel. The CRF form to complete is titled 'Post Cycle 6 Docetaxel Assessment Form'. This assessment is not required for patients who do not complete 6 cycles of chemotherapy, nor is it required after the last cycle if more than 6.

For patients not randomised to receive Sr89, the following assessments are the same as those normally performed for pre-chemotherapy assessment required for cycle 7 treatment. It is not necessary to repeat any tests for this assessment, only to record it on the above CRF.

- Physical examination.
- ECOG performance status.
- Imaging required if disease progression is suspected either clinically or biochemically.
- Proteomic blood sample (subject to individual investigator participation).
- Haematology tests: (as at baseline).
- Clinical chemistry tests: (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5). Both pain and analgesic-use scores will be derived from the record of the week immediately prior to assessment.
- Questionnaires: QoL using the EuroQol EQ-5D and Fact-P questionnaires, resource-use questionnaire.

9.4 Follow-up Assessments

Patients who have clinically progressed, i.e. having pain progressed, date of first skeletal-related event, as described in section 10.1.2, should progress to 3 monthly follow-up.

Table : Patient's pathway post-progression

Type of progression	**Discontinue docetaxel**
Increasing PSA	No
Tumour (radiology)	Yes
Pain progression	Yes
1st SRE	Only if disease related
Death	-

Please note that withdrawal from trial treatment due to disease progression must be reported on a Disease Progression CRF and not a Withdrawal CRF.

9.4.1 Monthly follow-up, for first three months only

During follow-up the following assessments will be performed every month for the first 3 months only, or until the patient completes or is withdrawn from the trial:

- Haematology tests (as at baseline).
- Clinical chemistry tests (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5).
- QoL using EQ-5D and Fact-P questionnaires, resource-use questionnaire.
- Imaging as required. The exact timing of any imaging will be determined by the local clinician, and therefore may not occur at one or more follow-up visits.
- ECOG performance status

9.4.2 Three-monthly follow-up, after first three months:

During follow-up the following assessments will be performed every three months (after the first three-monthly follow-up assessments), until the patient completes, or is withdrawn from, the study:

- Haematology tests (as at baseline).
- Clinical chemistry tests (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5).
- QoL using EQ-5D and Fact-P questionnaires, resource-use questionnaire.
- Imaging as required. The exact timing of any imaging will be determined by the local clinician, and therefore may not occur at one or more follow-up visits.
- ECOG performance status.

9.5 Patient Pain Diaries

To enable an exploratory analysis of patient-reported pain outcomes, patients will be asked to complete pain diaries. These diaries will provide a daily record of the pain experienced by a patient and their analgesic intake for the seven day period prior to every protocol-defined visit.

The first diary must be collected after patient consent and prior to the first docetaxel treatment. Thereafter, a diary will be completed for the seven day period prior to the:-

- Start of each subsequent chemotherapy cycle (day 1).
- End of the primary treatment period.
- Follow-up assessment visits, and at every protocol-defined visit thereafter.

The diaries will then be promptly reviewed (ideally with the patient present) for compliance by the investigator or nurse. Any potential problems, i.e. dose of drug missing, will be reviewed and amended by the individual patient (if possible) at this time.

It is intended that the pain diaries will be completed by patients throughout the treatment and follow-up periods of the study, until the occurrence of one of the following: death, loss to follow-up or patient refusal. A patient can decide to stop completing pain diaries at any time without giving a reason. Patient participation in the pain diary sub-study is not compulsory and will not affect the patient's ability to take part in the trial.

Pain-scoring will use both the Present Pain Intensity (PPI) six-point scale (0=no pain to 5 = excruciating pain) from the McGill-Melzack questionnaire and the analgesic score, calculated by a member of the participating centre trial team using the following table :

SCORES associated with ANALGESICS TYPE AND DOSES					
Non Narcotic Medications		**Narcotic Medications**			
1 POINT		**4 POINTS**			
Any route		**Oral/Rectal**		**IV/IM/SC**	
Generic Name	**Dose (mg)**	**Generic Name**	**Dose (mg)**	**Generic Name**	**Dose (mg)**
Aceclofenac	100	Anileridine	25		
Acemetacin	90	Buprenorphine	0.8	Buprenorphine	0.8
Acetaminophen / Paracetamol	325			Butorphanol	1
Aminophenazone	500	Codeine	60		
Aspirin	325	Dextropropoxyphene	50		
Celecoxib	100	Dihydrocodeine	30		
Diclofenac	25	Fentanyl*	100 µg	Fentanyl*	50 µg
Diflunisal	250	Hydrocodone	10	Hydrocodone	5
Dipyrone/ Metamizole	500	Hydromorphone	2	Hydromorphone	1
Etodolac	200	Levorphanol	2	Levorphanol	2
Fenoprofen	200	Meperidine/ Pethidine	100	Meperidine/ Pethidine	50
Flurbiprofen	50	Methadone	10		
Ibuprofen	200	Morphine	10	Morphine	5
Indomethacin	25	Oxycodone	5	Oxycodone	2.5
Ketoprofen	25	Oxymorphone rectal	2.5		
Ketorolac	10			Papaveretum	15.4
Mefenamic Acid	250	Pentazocine	50	Pentazocine	30
Nabumetone	500	Piritramide	15		
Naproxen	250	Propoxyphene	50		
Nefopam	20	Tilidine	50		
Nimesulide	100	Tramadol	50	Tramadol	50
Piroxicam	10				
Propyphenazone	250				
Rofecoxib	12.5				
Tenoxicam	20	* Fentanyl patch (TTS): 36 points / day for 25µg/hour patch			

9.6 Other Assessments (One Year Post-Randomisation Date)

Dual energy X-ray absorption (DXA) scan, bone density scan (1 year post-randomisation date only, +/- 3 months)

The DXA scan is only required if the participating centre is participating in the Bone Density sub-study.

9.7 Flow Chart of Trapeze Study Procedures and Assessments

Investigations	Pre-randomisation	On Treatment Primary Treatment Period (cycles 1 – 6)	Post-primary treatment period (cycles 1 - 6) assessment	Follow-up
1. Informed consent	✓			
2. History / physical exam (including clinical tumour assessment and new skeletal events)	Within 28 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	Clinical tumour assessment: Every 3 months
3. Haematology [1] & clinical chemistry tests [2]	Within 28 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	Every month for the first 3 months, then every 3 months until study completion or patient withdrawal
4. Serum Creatinine	Within 28 days	Every 3 weeks throughout treatment, prior to each infusion	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	-
5. PSA [3]	Within 28 days	Every 3 weeks (day 1 before infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	At each follow-up assessment until disease progression
6. Adverse events reporting / collection [4]	Within 28 days	AEs logged for all treatment period	-	Until 60 days after the last study drug administration
7. *Radiology tumour assessment (CT scan/ chest x-ray/ bone scan)	Recommend within 56 days	As clinically indicated	If disease progression suspected, clinically or biochemically	If disease progression suspected, clinically or biochemically
8. CT scan or chest x-ray **	Within 28 days	As clinically indicated	As clinically indicated	As clinically indicated
9. DXA bone density scan	Within 28 days	-	-	1 year from randomisation date
10. Quality of life & Health economics[5]	Within 3 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before SR89 infusion or subsequent treatments	Every visit (until study completion or patient withdrawal)
Pain assessments: PPI + Analgesic Score	Within 3 days, averaged over 7 days	Every 3 weeks (prior to docetaxel infusion) averaged over 7 days	Cycle 6 (Day 21) Before SR89 infusion or subsequent treatments	Every visit (until study completion or patient withdrawal)
Proteomic blood sample	Within 28 Days	Every 2 Cycles Cycle 2,4,6	Every 2 cycles Cycle 8, 10 and end of treatment	-

[1] WBC, neutrophils, platelet, haemoglobin
[2] Urea, serum creatinine, potassium, sodium, calcium, magnesium, AST ALT, alkaline phosphatase, total bilirubin, blood glucose
[3] Refer to inclusion criteria section 5 for rising and elevated PSA assessments
[4] Refer to section 11 for specific adverse event reporting.
[5] Self administered EuroQol & Fact-P questionnaire, plus health problems questionnaire for health economics. QoL questionnaire should be administered before randomization or at randomization, but in any case before the patient is informed of the treatment to which he is assigned
* To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ultrasounds/scans to assess response must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Each lesion must be followed with the same method throughout the study (from baseline until follow-up).
** To be performed at baseline:

10 MEASUREMENT OF OUTCOME

Table 10.1: Measurement of Outcome

Phase	Primary	Subsidiary	Ancillary measures and exploratory outcomes
II	• Feasibility, tolerability and safety in terms of cycles of docetaxel, prednisolone, zoledronic acid and Sr89 received, cycle delays, dose reductions and toxicity	• Clinical progression-free survival • Skeletal-related-event-free survival • Pain progression-free survival • Overall survival • Costs • Quality of life	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • Patient-reported pain-related outcomes
III	• Clinical progression-free survival • Costs and cost-effectiveness	• Skeletal-related-event-free survival • Pain progression-free survival • Overall survival • Quality of life • Toxicity	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • RECIST criteria-related outcomes • Patient-reported pain-related outcomes

10.1 Primary Outcome Measures

10.1.1 Phase II primary outcomes: feasibility, tolerability and safety

The primary outcomes for the phase II analysis are feasibility, tolerability and safety, and will be measured in terms of:

Treatment Received

- Mean number of cycles of docetaxel received per patient and the proportion of patients receiving 6 cycles.
- Mean number of cycles of zoledronic acid received per patient and the proportion of patients receiving 6 cycles.
- The proportion of patients who receive Sr89 after receiving 6 cycles of chemotherapy.

Dose Delays and Reductions

- Mean number of cycles of docetaxel per patient with dose delay, and proportion of patients who experience at least one dose delay.
- Mean number of cycles of docetaxel per patient with dose reduction and proportion of patients who experience at least one dose reduction.

Adverse Events

- Proportion of patients with at least one grade 3 or 4 adverse event.
- Proportion of patients experiencing at least one grade 3 or 4 adverse event for specific categories of toxicity, i.e. infection, musculoskeletal or haematological.

Serious Adverse Events (SAEs)

- Mean number of SAEs per patient, and proportion of patients with at least one SAE.
- Proportion of patients with at least one Serious Adverse Reaction (SAR).
- Proportion of patients with at least one Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.1.2 Phase III primary outcome: clinical progression-free survival

The primary outcome for the phase III analysis is clinical progression-free survival (CPFS). CPFS time is defined as the time, in whole number of days, between the date of randomisation and the date of clinical progression. Clinical progression is defined as the earliest of the:

- date of occurrence of pain progression;
- date of occurrence of a skeletal-related event, if disease related;
- date of death from any cause.

CPFS is a composite endpoint with three component events in the definition, the occurrence of any one of which means that the patient has reached clinical progression and must therefore be withdrawn from *all* trial treatments. For patients who are withdrawn from the study or lost to follow-up, CPFS time will be censored at the date they were last known to be alive. For those patients who do not experience at least one of these component events during the course of the trial, CPFS time will be censored at their last follow-up date.

Pain Progression

Pain progression is defined as clinical evidence of an increase in pain which, in the opinion of the treating clinician, is sufficient to warrant discontinuation of trial treatments and to trigger a change in therapy (e.g. to radiotherapy). The date of pain progression is defined as the date on which the decision to discontinue trial treatment is made.

NOTE: Prior to baseline, on the development of pain in an area, which involves a new area of the skeleton not present at baseline (randomisation into the clinical trial), we recommend that a radiological assessment of the bone should be performed (via CT scan, MRI, plain X-ray or bone scan) to assess if there is bone disease progression.

Skeletal-Related Event (SREs)

Any given patient may experience more than one occurrence of an SRE. **All** SREs must be recorded, but the date of occurrence of the earliest SRE must be used for the purposes of determining the date of clinical progression. Each of the following events constitute an SRE:

- Symptomatic pathologic bone fractures
- spinal cord or nerve root compression likely to be related to cancer or to treatment
- cancer-related surgery to bone (includes procedures to set, or stabilise, pathologic fractures or areas of spinal cord compression and procedures to prevent imminent fracture or spinal cord compression)
- radiation therapy to bone (including the use of radioisotopes)
- change of anti-neoplastic therapy to treat bone pain due to prostate cancer
- Hypercalcaemia
- Initiation of bisphosphonate therapy in response to new bone pain symptoms

Death

Death from any cause will be included as an event.

10.1.3 Phase III Primary Outcome: Health Economics Outcomes

One of the primary objectives of the trial is to compare treatment arms in terms of costs and cost-effectiveness. The economic analysis will be carried out from UK NHS and social service perspectives. Key resource-use data will be collected; by the CRF and supplemented by patient-completed resource use questionnaires. This will include primary care consultations, medication and use of secondary care services (outpatient visits, A&E visits and, inpatient hospital stays). The itemized use of each resource will be weighted by its unit cost to give the aggregate cost per patient. Unit costs will be obtained from NHS reference costs and relevant routine sources – PSSRU (Curtis and Netten, 2006). QoL will be assessed using the EQ-5D questionnaire. A utility score will be generated from this questionnaire. QALYs will be calculated. A cost-effectiveness analysis will be conducted in which outcome will be measured as incremental cost per-QALY gained within the trial.

10.2 Subsidiary Outcomes

10.2.1 Skeletal Related Event-Free Interval (SREFI)

SREs are defined in the section describing clinical progression-free survival. The skeletal related event-free interval (SREFI) is defined as the time in whole number of days between the date of randomisation and the date of the first skeletal related event. For patients who do not experience a skeletal related event, SREFI will be censored at either the date of death, date of last follow up or date withdrawn consent, whichever is earliest..

10.2.2 Pain Progression-Free Interval (PPFI)

Pain progression is defined in the section describing clinical progression-free survival. Pain progression-free interval (PPFI) is defined as the time in whole number of days between the date of randomisation and the date of pain progression. For those patients who do not experience pain progression, PPFI will be censored at either the date of death, date of last follow up or date withdrawn consent, whichever is earliest.

10.2.3 Overall survival

Overall survival time is the time in whole number of days between the date of randomisation and the date of death, from any cause. For patients who are withdrawn from the study or who are lost to follow-up, survival time will be censored at the date they were last known to be alive. For patients who do not die during the course of the study, survival time will be censored on the date they were last known to be alive.

10.2.4 Quality of life

QoL will be assessed using the EQ-5D and FACT-P and Health Problems questionnaires, which are patient completed questionnaires (see appendix 3). The EQ-5D is a generic utility-based measure of health-related QoL that has been widely used in economic analyses of healthcare interventions. It is being used in this trial in order that improvements in overall QoL can be estimated and measured in terms of the strength of preference for such improvements. The instrument is designed to be self-completed and so, where possible, the patient will provide the data. Patients will also be asked to complete pain diary sheets and QoL questionnaire booklets, which include the EQ-5D, FACT-P, and study-specific heath-related questionnaires, during their treatment (see appendices 3-5).

10.2.5 Toxicity of treatment

Toxicity of treatment will be measured in terms of the occurrence, severity, type and causality of adverse events during the treatment period.

10.3 Outcomes from Ancillary Biomarker Studies

10.3.1 Bone mineral density changes

Changes in bone density will be monitored by a DXA scan. These scans will be done at baseline (within 28 days of randomisation) and at 1 year following the date of randomisation. The results of these scans will be analysed along with the recording of any disease in the region of bone density measurements. The regions of the skeleton used for the bone density measurement will be the right or left-forearm (non-dominant arm) as well measurements at spine, hip and neck of femur if unaffected by metastases. Patient participation in this part of the study will be voluntary; declining to participate will not prevent entry into the main study.

10.3.2 Biological profiling for prognostic and predictive indicators

Blood (serum) samples will be taken at regular intervals during the treatment phase of the study, i.e. baseline and end of treatment cycles 2, 4, 6, 8 and 10. Patient consent for the collection of these samples will be recorded on the patient consent form. Patient participation in this part of the study will be voluntary; declining to participate will not prevent entry into the main study.

In addition to blood samples, archived diagnostic or other subsequent tissue biopsies from the prostate or metastatic sites (paraffin fixed and embedded tissue blocks) from a proportion of patients will be collected, subject to patient consent. These samples will subsequently be sent to the Trapeze co-ordinating centre by individual participating centres. This collection of tissue blocks will only occur subject to adequate funding arrangements. It is proposed that the collection of these samples will take place towards the end of the recruitment phase of the trial. These samples will then be subject to biological profiling of prognostic and predictive indicators. This information will then be collated with the clinical data derived from the trial.

10.4 Exploratory Outcomes

Exploratory outcomes will not be used to directly evaluate the treatments being compared in this trial, but rather to investigate the extent to which they are associated with other outcomes.

10.4.1 Patient-reported pain events

The primary analysis of differences in pain-related outcomes between treatment arms will be based on clinician-reported pain (see section 10.1.2). However, further exploratory analyses will also be undertaken using the patient-reported pain data recorded in pain diaries (see section 9.1.4), including measures of pain response and patient-reported pain progression.

10.4.2 PSA-related events

PSA will be measured at every study assessment and protocol-defined patient visit. Exploratory analyses of several conventional PSA-related events will be undertaken.

10.4.3 Number of SREs

The number of SREs is defined as the number of SREs occurring between the date of randomisation and the earliest of: the date of death; and the date of the end of follow-up.

10.4.4 RECIST criteria-related events

Patients will be evaluated with respect to RECIST (version 1.0) criteria, as appropriate (see Appendix 2). Exploratory analyses of several conventional RECIST criteria related events will be undertaken.

11 SAFETY ASSESSMENT

11.1 Definitions

11.1.1 Adverse event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered either docetaxel, prednisolone, zoledronic acid or Sr89, either administered alone or in combination, and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

11.1.2 Adverse reaction

An Adverse Reaction (AR) is defined as all untoward and unintended responses to a study drug related to any dose administered.

Comment*:* An AE judged by either the reporting Investigator or Sponsor as having a causal relationship to the IMP qualifies as an AR. The expression causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An Unexpected Adverse Reaction (UAR) is defined as an AR, the nature or severity of which is not consistent with the applicable with the current product information. The Summary of manufacturer's Product Characteristics (SmPC) for each of the study drugs (docetaxel, zoledronic acid, prednisolone and Sr89) will be used to assess each AE reported as part of a SAE.

Comment: When the outcome of an AR is not consistent with the applicable product information, the AR should be considered unexpected.

Severity: The term "severe" is often used to describe the intensity of a specific event. This is not the same as "serious", which is based on patients/event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is defined as any untoward medical occurrence or affect that at any dose:

- Results in death
- Is life-threatening[1]

- Requires inpatient hospitalisation[2] or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect[3]

Comment: Medical judgment should be exercised in deciding whether an AE or AR is serious in other situations. An AE or AR that is not immediately life-threatening or does not result in death or hospitalisation but may jeopardise the subject in some way or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

[1] Life-threatening in the definition of an SAE or SAR refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

[2] Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

[3] This will include children of fathers receiving study therapy

11.1.5 Suspected unexpected serious adverse reactions

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAR that is unexpected, i.e. the nature, or severity, of the event is not consistent with the applicable summary of product information (SmPC).

A SUSAR should meet the definition of an AR, UAR and SAR as detailed above.

11.1.6 List of expected adverse reactions (SARs)

For a list of all expected adverse reactions please refer to the relevant SmPC.

11.1.7 SAEs that do not require reporting for Trapeze

The following reasons for hospitalisation do not require reporting as SAEs for Trapeze unless associated with other serious advents:

- Admissions for study therapy;
- Admissions for procedures related to the patient's disease (e.g. placement of an indwelling catheter or a planned admission for a blood transfusion for low haemoglobin levels only).

11.1.8 Reporting period

Details of all SAEs must be documented from the date of consent until 60 days after the last administration of study drug. Patients must be followed-up until resolution of the SAE.

NB: Zoledronic acid will be considered a study drug only if the drug was assigned during the randomisation process (Arms B and D). If zoledronic acid is prescribed AFTER the patient has progressed, as defined by section 8.5.2, the drug will no longer be considered a study drug and will not be subject to the SAE reporting procedures. In such a case zoledronic acid administrations should be recorded on the Concomitant Medications Running Log.

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There is no time limit for reporting SAEs thought by the Investigator to meet the definition of a post-study SUSAR.

11.2 Assessment of Adverse Events

All adverse events (AEs) will be collected for patients with TNOs below 300. For those with TNOs above 300 grades 3 and 4 will be will be collected. All AEs must be graded according to the NCI CTCAE Toxicity Criteria (Version 3).

For adverse events not listed in the toxicity table, severity should be recorded as:

Mild	does not interfere with subject's usual functioning
Moderate	interferes to some extent with subject's usual functioning
Severe	interferes significantly with subject's usual functioning

Life-threatening risk of death, organ damage or disability

Relationship to study therapy will be assessed using the following definitions:

Unrelated	There is no evidence of any causal relationship.
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant event).
Possibly related	There is some evidence to suggest a causal relationship, e.g. the event occurred within what the treating clinician felt was a reasonable period following administration of the trial medication. However, the influence of other factors may have contributed to the event, e.g. the patient's clinical condition, other concomitant events.
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

NOTE: All adverse events considered to be “possibly related”, “probably related”, or “definitely related” will be reported as a SAR or SUSAR in all Trapeze-related safety reports. In line with MHRA guidance and CRCTU practice, “unlikely to be related” events will not be reported as SARs or SUSARs.

11.3 Reporting of Adverse and Serious Adverse Events

11.3.1 Adverse events

Adverse Events must be recorded on the Adverse Event Running Log of the CRF, including date of onset, severity, duration and relationship to study therapy, whether on-going and stop date. AEs which are also SREs must also be recorded on an SRE CRF.

If more than one AE occurs, each one must be recorded separately. The Investigator should take all therapeutic measures necessary for resolution of any AE. Any medication necessary for the treatment of an AE must be recorded on the patient’s Concomitant Medication Running Log.

11.3.2 Serious adverse events

In the case of an SAE the Investigator must immediately:

Complete a SAE Form – the form can be completed and signed by a member of the site trial-team who has been delegated this responsibility by the Investigator, but should be checked and counter signed by the local Investigator at a later date.

Send the original SAE form with fax coversheet to the Trials Office once signed by the Investigator;
Report SAE in accordance with local institutional policy:

Fax form to [redacted] (or [redacted], if primary number is unobtainable)

Continue follow-up of the subject until clinical recovery is complete or any sequelae have stabilised;
Provide follow-up information on a SAE Form on resolution of the event;

On receipt of a SAE CRF, seriousness and causality of the event will be determined independently by a Clinical Co-ordinator. An SAE judged by either the local investigator or Clinical Co-ordinator, or both, to have a reasonable causal relationship with the trial medication will be regarded as a SAR. The Clinical Co-ordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected in nature it will be classified as a SUSAR.

11.4 Reporting of Events to Other Organisations

11.4.1 Regulatory authorities and main research ethics committee

SUSARs

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life-threatening SUSAR, to the Medicines and Healthcare products Agency (MHRA) and main Research Ethics Committee (MREC) within seven days. Detailed follow-up information will be provided within an additional eight days. All other events categorised as SUSARs will be reported within 15 days.

SARs

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and MREC annually, from the date of the Clinical Trial Authorisation, in the form of an Annual Safety Report.

AEs

Details of all reported AEs experienced during chemotherapy (i.e. grades 1-4 for patients 1-300; grades 3-4 for patients 301+) will be reported to the MHRA on request.

Other Safety Issues Identified During the Course of the Trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

11.4.2 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to all Trapeze Investigators.

11.4.3 Independent data monitoring committee

An Independent Data Monitoring Committee will review all SAEs annually.

11.4.4 Novartis Oncology, Sanofi-Aventis and GE Healthcare

All SAEs classified as “unlikely to be related”, “possibly related”, “probably related” or “definitely related” to docetaxel, zoledronic acid and Sr89, must be reported to Sanofi-Aventis, Novartis Pharmaceuticals (UK) Ltd, or GE Healthcare, respectively, within 24 hours by fax.

12 STATISTICAL CONSIDERATIONS

12.1 Study Analysis

The definitive study analysis will be conducted on an intention-to-treat basis. All tests of statistical significance will be conducted at the 5% two-sided significance level. The phase II analysis will compare all four treatment arms with respect to feasibility, tolerability and safety whereas the phase III analysis will assess treatments with respect to efficacy within a 2x2 factorial design framework, i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use).

12.1.1 Analysis of outcome measures

Feasibility, tolerability and safety. In the primary phase II analysis, the feasibility, tolerability and safety of each treatment arm will be reported in terms of the measures specified in section 10.1.1. The analysis will be purely descriptive and the data on the control arm will act as a benchmark against which to assess the experimental treatment arms. Proportions and means will be calculated, and 95% confidence intervals constructed as appropriate.

Clinical progression free survival (CPFS). The primary phase III analysis will compare ZA versus no ZA (stratified for Sr89 use) and Sr89 versus no Sr89 (stratified for ZA use) in terms of CPFS. Treatments will be compared using the Kaplan-Meier method and a log-rank test. Statistical models for time-to event data that account for other factors which are potentially related to outcome, in addition to treatment, will also be used. In particular, Cox regression models will be considered, and the possibility of fitting parametric survival models investigated. Time-to-event will be measured between date of randomisation and date of first detection of the event, with censoring dealt with appropriately (see section 10).

Overall survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse overall survival time.

Pain-progression-free survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse pain-progression-free survival time.

Skeletal-related event-free survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse skeletal-related event-free survival time.

Quality of life. Quality of life data will be analysed using longitudinal statistical methods and consideration will be given to missing data that occurs due to dropout and death. The balance between quality of life and survival will be analysed by comparing treatments in a quality-adjusted survival analysis[28].[25]

Health economic analysis. The cost-effectiveness of treatments will be evaluated primarily by balancing the healthcare costs on each of the treatment arms during clinical progression-free survival time against the measure of clinical effectiveness. In addition cost-effectiveness (cost-per-life-year gained) and cost-utility (cost-per-quality-adjusted life-year) analyses will be undertaken. Both probabilistic and univariate sensitivity analyses will be performed, with results reported using both cost-effectiveness planes and cost-effectiveness acceptability curves (plot of CE thresholds against the probability that the intervention is cost-effective). Given the planned long-term follow-up of patients in the trial, lifetime costs and effects will largely be observed and so it is not envisaged that extrapolation beyond the trial will be required.

The mean difference in costs across treatment arms and the associated 95% confidence interval will be estimated using non-parametric bootstrapping to account for the expected skewed distribution of the cost data. An incremental cost-effectiveness analysis will be conducted. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences (including data on quality of life, etc.). If this identifies a situation of dominance then further analysis will not be required. If no dominance is found then cost-effectiveness analyses (i.e. cost-per-clinical progression-free life-year and cost-per-life-year) and cost-utility analysis (i.e. cost-per-quality-adjusted life-year) will be employed. Quality-adjusted life-years (QALYs) will be calculated using EQ-5D data collected as part of the trial. The results of the economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We will also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the ability to generalise the results.

Toxicity. The analysis of toxicity will be purely descriptive. Proportions and means will be calculated, and 95% confidence intervals constructed as appropriate.

Measures from ancillary biomarker studies. The analysis of changes in bone mineral density will be exploratory and entirely descriptive, with summary statistics and their associated 95% confidence intervals constructed as appropriate. It is anticipated that the same approach will be adopted for the analysis of prognostic and predictive indicators, but this will be re-examined prior to seeking separate funding for these sub-studies.

Exploratory outcomes. The analysis of patient-reported pain outcomes, PSA-related outcomes, and RECIST criteria-related outcomes which can be considered time-to-event data will be analysed using the approach adopted for the analysis of clinical progression-free survival; outcomes which can be treated as repeated measurements will be analysed using methods suitable for longitudinal data. Number of skeletal-related events will be analysed using methods appropriate to count data.

12.2 SAMPLE SIZE

12.2.1 Phase II

The analysis of the phase II component of the trial will be entirely descriptive and will not involve any statistical hypothesis testing. The primary outcomes are feasibility, tolerability and safety and these will be measured as proportions or means, as appropriate: recruitment of 50 patients into each arm will ensure that proportions are estimated with a precision of at least 15%, and provide sufficient data to be able to assess the arms in terms of their suitability for progression into the phase III component of the trial.

12.2.2 Phase III

Sample size calculations are based on the primary outcome measure of clinical progression-free survival time (CPFS). The calculations are the same for both the comparison of ZA versus no ZA and Sr89 compared to no Sr89. The trial aims to detect a hazard ratio of 0.76 (equivalent to 1 year CPFS rates of 30% vs 40%, assuming CPFS follows an exponential distribution). The number of *events* required to detect this difference in each group for either treatment comparison, using a two-sided 5% significance level and 80% power, is 206; it is estimated that approximately 294 patients per arm i.e. 588 patients in total will need to be recruited to observe this number of events. We will aim to recruit a minimum of 618 evaluable patients, which allows for 5% dropout.

12.2.3 Timing of analyses

Interim analysis will be carried out at least once a year for consideration by the independent Data Monitoring Committee (DMC), and more often if required. Final analysis of the phase II data wasl presented to the DMC after 200 patients were recruited and followed-up for at least seven months, and all relevant data returned to the trial office. At this point the IDMC determined that the trial should continue into phase III. Final analysis of the phase III trial will take place once all patients have been followed up for one year, and all patients have complete data.

12.4 Milestones

The target recruitment rate is 15 to 25 patients per month, from a total of up to 50 centres. It is anticipated that 618 evaluable patients will have been recruited by the end of the first quarter of 2012.

The milestones below are guidelines based on predicted future recruitment rates, as well as dates of real events which occurred prior to the preparation of this version of the protocol.

Dec 2004	Start randomisation
Sept 2006	First Report to DMC
Dec 2007	Second Annual DMC meeting to review safety data and recruitment
July 2008	DMC Meeting to review safety data and recruitment
Oct 2008	TSC Meeting to review clinical trial, DMC recommendations and recruitment
Nov 2008	Accrual of 300 patients reached
Feb 2009	DMC Meeting to review safety data
May 2009	Determination of Phase III protocol treatment arms and study numbers (if required: a protocol amendment to be submitted to Ethics and MHRA for approval). The Milestones after this date to be determined by the exact finalised protocol details.
Sept 2010	DMC Meeting to review safety data and recruitment
Oct 2010	TSC Meeting to review clinical trial, DMC recommendations and recruitment
June 2011	DMC Meeting to review requested further data
Jan 2012	DMC Meeting to review requested further safety and SRE data
Mar 2012	TSC Meeting to review clinical trial, DMC recommendations and recruitment
End Feb 2012	Trial closing to recruitment

13 TRIAL COMMITTEES

13.1 Trial Management Group

The Trial Management Group (TMG) is comprised of the Chief Investigator, other co-investigators and members of the CRCTU as detailed in the front sleeve of the protocol. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference, or in person, as required. See Figure 1 for the relationship between all committees.

13.2 Trial Steering Committee

An independent Trial Steering Committee (TSC) will provide overall supervision for the trial and provide advice to the TMG. Membership includes the Chief Investigator or his deputy, and an independent oncologist, urologist and statistician. The ultimate decision regarding continuation of the trial lies with the TSC. The TSC will meet at least once a year or more often if required.

13.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (DMC) has been established for this study. The DMC will be the only group who see the confidential reports on the data accumulating to the trial. Their main objective will be to advise the TSC as to whether there is any evidence or reason as to why the study should be amended or terminated based on the recruitment rate or safety. Reports to the DMC will be produced by the CRCTU. The first meeting of the DMC occurred when 121 patients had been randomised into the trial. Thereafter, the DMC will meet at intervals determined by the DMC (at least every year), to monitor recruitment to the trial, protocol compliance, toxicity, and serious adverse events. The DMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable, or if there are cases of excessive toxicity. The DMC would also stop the trial early if the interim analyses showed differences between treatments, which, in their opinion, were deemed to be convincing to the clinical community. Further details of DMC functions and the procedures for interim analysis and monitoring are provided in the DMC charter (available on request).

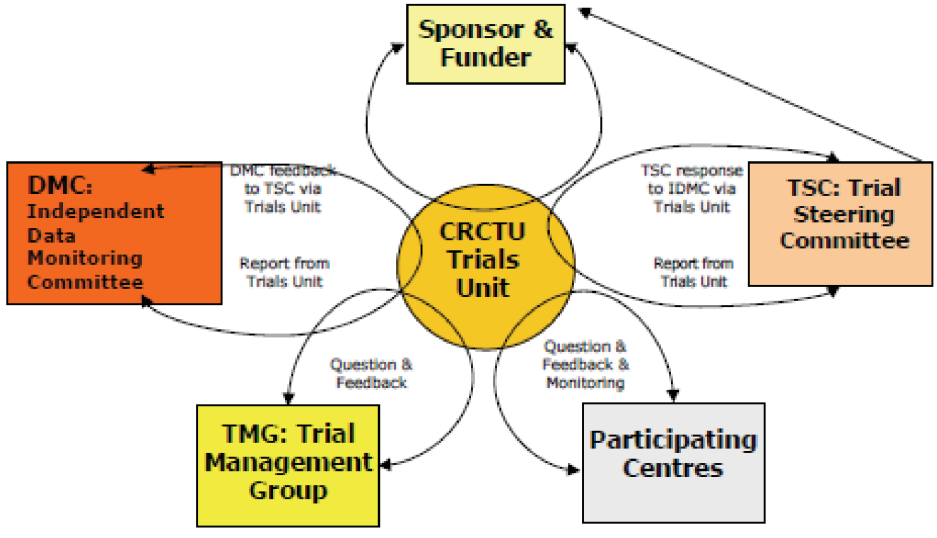


Figure 2: Diagram of the Relationship between Committees and the CRCTU Trials Unit

14 REGULATORY & ETHICS COMMITTEE (EC) APPROVAL

14.1 Ethical Considerations

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments. Copies of the declaration may be obtained by contacting the Trapeze Study Office, or directly from the WMA website at http//www.wma.net/e/policy/17-c_e.html.

The protocol has gained ethical approval from the South West MREC. Before entering patients into the study, the Principal Investigator must ensure that the protocol has approval from their local Research Ethics Committee and local Research and Development (R&D) Office.

14.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient prior to entering the trial, in compliance with national requirements.

14.3 Patient Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their initials, date of birth, and hospital number will be recorded on the case report forms. With the patient's permission, their name will be collected at randomisation to allow flagging with the Office of National Statistics. The Principle Investigator must ensure the patient's anonymity is maintained. The Investigator must maintain documents which are not intended for submission to the trials office in strict confidence.

The trials office will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients must be reassured that their confidentiality will be respected at all times.

In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

15 INDEMNITY & INSURANCE

This study is a clinician-initiated and clinician-led study with education grants provided by Sanofi-Aventis and Novartis Pharmaceuticals (UK) Ltd. In addition a Health Technology Assessment (HTA) programme grant was approved in December 2006. This grant was activated in April 2007 and will provide funding for the study until 2013. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer Sciences (Formerly Institute for Cancer Studies), The University of Birmingham. The University of Birmingham will act as the sponsor for the study. As sponsor, the University is responsible for the general conduct of the study and shall indemnify the Investigation Centre against any claims arising from any negligent act or omission by the University in fulfilling the Sponsor role in respect of the Study. The University is under no obligation to indemnify the Investigation Centre against any claims arising from the conduct of the Study at the Centre.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated by them, whether or not the patient is taking part in a clinical trial. Compensation is therefore only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring though participation in the study, whether from the side-effects listed, or others as yet unforeseen.

Novartis Pharmaceuticals (UK), Sanofi-Aventis, and GE Healthcare Ltd are liable, on a no fault basis, for the quality and fitness-for-use of their products.

16 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trapeze Trial Steering Committee, Trial Management Group and high-accruing Investigators. The CRCTU and all participating centres and Investigators will be acknowledged in this publication. All presentations and publications relating to the trial must be authorised by the Trapeze Trial Steering Committee.

17 STUDY COSTS AND RELATIONSHIP WITH PHARMACEUTICAL INDUSTRY

Sanofi-Aventis and Novartis provided an educational grant to CRCTU, CRUK, School of Cancer Sciences (formerly the Institute for Cancer Studies), University of Birmingham, to conduct the study (first 300 patients only). Subsequently, a grant from the Health Technology Assessment (HTA) programme was secured in December 2006 to provide funding and support for the expansion of the initial programme into a Phase III clinical trial. This funding is secured until April 2013 (subject to conditions).

Sanofi-Aventis and Novartis Pharmaceuticals (UK) Ltd also provided study drugs (Taxotere® (docetaxel) and Zometa® (zoledronic acid), respectively) free-of-charge for the first 300 patients recruited into the trial. Docetaxel is now NICE approved and therefore funding is nationally endorsed for this medicine for mHRPC patients. From patient 301 onwards docetaxel will be purchased by individual hospitals at local hospital prices. Sanofi-Aventis continued to support the clinical trial with a £300 grant (paid to the national co-ordinating centre) for patients recruited into the trial with trial numbers 301 to 700.

For patients 301 and above, the following other arrangements will apply:

Zoledronic acid (Zometa®) will be supplied to participating centres with a 28.2% discount on the standard NHS list price. This means that each 4mg vial will cost £140.

GE Healthcare Limited have extended their trial discount (5%) Metastron® (Sr89), for patients entered into Trapeze to receive a single administration of Metastron®, for the period 1 September 2011 until 31 October 2012.

The trial data, including quality of life information, the health economic study and pathological material collected as part of the biological studies, will remain the property of the Trial Management Group.

Reference List

1. James, N. D., Bloomfield, D., and Luscombe, C. The changing pattern of management for hormone refractory, metastatic prostate cancer. Prostate Cancer Prostatic.Dis. 2006.
2. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ *et al*. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points [see comments]. *Journal of Clinical Oncology* 1996;14:1756-64.
3. Kantoff PW, Halabi S, Conaway M, Picus J, Kirshner J, Hars V *et al*. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study.[comment]. *Journal of Clinical Oncology* 1999;17:2506-13.
4. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N.Engl.J Med.* 2004;351:1502-12.
5. Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N.Engl.J Med.* 2004;351:1513-20.
6. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N.Engl.J Med.* 2004;351:1502-12.
7. Coleman RE. Bisphosphonates in breast cancer. *Ann Oncol* 2005;16:687-95.
8. Green JR. Preclinical pharmacology of zoledronic acid. [Review] [51 refs]. *Seminars in Oncology* 2002;29:3-11.
9. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin.Oncol* 2003;21:4277-84.
10. Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC *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;95:1300-11.
11. Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ *et al*. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *Journal of Clinical Oncology* 2003;21:3335-42.
12. Green JR, Muller K, Jaeggi KA. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. *Journal of Bone & Mineral Research* 1994;9:745-51.
13. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD *et al*. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *Journal of Clinical Oncology* 2001;19:558-67.
14. Santini D, Vespasiani GU, Vincenzi B, Picardi A, Vasaturo F, La Cesa A *et al*. The antineoplastic role of bisphosphonates: from basic research to clinical evidence. *Ann Oncol* 2003;14:1468-76.

15. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L *et al*. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl.Cancer Inst.* 2004;96:879-82.
16. Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD *et al*. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;31:33-40.
17. Bolger JJ, Dearnaley DP, Kirk D, Lewington VJ, Mason MD, Quilty PM *et al*. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial. UK Metastron Investigators Group. *Seminars in Oncology* 1993;20:32-3.
18. Porter AT,.McEwan AJ. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. *Seminars in Oncology* 1993;20:38-43.
19. Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der MH *et al*. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. *Eur.Urol* 2003;44:519-26.
20. Dafermou A, Colamussi P, Giganti M, Cittanti C, Bestagno M, Piffanelli A. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. *European Journal of Nuclear Medicine* 2001;28:788-98.
21. Kraeber-Bodere F, Campion L, Rousseau C, Bourdin S, Chatal JF, Resche I. Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. *Eur.J Nucl.Med.* 2000;27:1487-93.
22. McEwan AJ, Amyotte GA, McGowan DG, MacGillivray JA, Porter AT. A retrospective analysis of the cost effectiveness of treatment with Metastron in patients with prostate cancer metastatic to bone. *European Urology* 1994;26 Suppl 1:26-31.
23. Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC *et al*. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial.[comment][erratum appears in Lancet 2001 Apr 14;357(9263):1210]. *Lancet* 2001;357:336-41.
24. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M *et al*. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group.[erratum appears in J Clin Oncol 2000 Jul;18(13):2644]. *Journal of Clinical Oncology* 1999;17:3461-7.
25. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N.Engl.J Med.* 2004;351:1502-12.
26. Billingham LJ,.Abrams KR. Simultaneous analysis of quality of life and survival data. *Stat.Methods Med.Res.* 2002;11:25-48.
27. Makuch RW,.Simon RM. Sample size requirements for comparing time-to-failure among k treatment groups. *J.Chronic.Dis.* 1982;35:861-7.

PROTOCOL APPENDIX 1: ECOG PERFORMANCE STATUS SCALES

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

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

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

PROTOCOL APPENDIX 2 ; RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

1.0 Definition of Measurable and Non-Measurable Lesions.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one-dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e. leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than four weeks before the beginning of the treatment.

2.0 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT and MRI scans: CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this specification applies to tumours of the chest, abdomen and pelvis, while head and neck tumours and those of extremities usually require specific protocols.

Chest X-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Cytology and histology can be used to differentiate between Partial Response and Complete Response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

Clinical examination: Clinically selected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography- including a ruler to estimate the size of the lesion -is recommended.

3.0 Selection of “Target” and “Non-Target” lesions

Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements, either by imaging techniques or clinically. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterise the objective tumour-response.

Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

4.0 Response

Response criteria for this study are defined below

Evaluation of Target Lesions

Progressive Disease (PD): at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Evaluation of Non-Target Lesions

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

5.0 Overall Responses

The table below provides overall responses for all possible combinations of tumour responses in target and non-target lesions, with or without the appearance of new lesions.

In assessing tumour progression in this study, only the last three shaded rows in the table on the next page are relevant.

Table of Overall response (taken from RECIST)

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

PROTOCOL APPENDIX 3: EUROQOL EQ-5D & FACT-P QUALITY OF LIFE QUESTIONNAIRES

Health Questionnaire **EQ-5D**

The next few questions are about your general health at present.

For each of the five sets of statements below, please tick the **one** box that best describes your own health state today.

1. Mobility

I have no problems in walking about…….….. ☐
I have some problems in walking about …….. ☐
I am confined to bed ……..… ☐

2. Self-care

I have no problems with self-care.…… ☐
I have some problems washing and dressing myself.…….….. ☐
I am unable to wash or dress myself.…….… ☐

3. Usual activities

(e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities.…… ☐
I have some problems with performing my usual activities.…… ☐
I am unable to perform my usual activities.…….. ☐

4. Pain/discomfort

I have no pain or discomfort..…….… ☐
I have moderate pain or discomfort..……..… ☐
I have extreme pain or discomfort..…… ☐

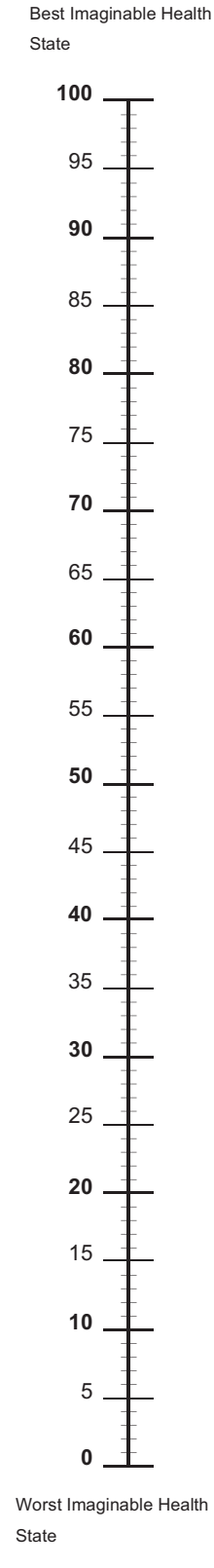
5. Anxiety/depression

I am not anxious or depressed……. ☐
I am moderately anxious or depressed..……..… ☐
I am extremely anxious or depressed..……..... ☐

6. Health State Scale

To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Your own health state today



QUALITY OF LIFE QUESTIONNAIRE
Fact P (Version 4)
Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea (I feel sick)	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain areas of my body where I experience significant pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my current level of physical comfort	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating (passing water)	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

PROTOCOL APPENDIX 4 – HEALTH ECONOMICS QUESTIONNAIRE

Trapeze health problems questionnaire for patients on study treatment

During the last 3 weeks (i.e. since your last visit to hospital for study treatment) we would like you to tell us about any health problems you may have had. Please answer all of the questions yourself by ticking the box that **best** applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) During the three weeks ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ (if no, go straight to question 2)

If Yes:

b) How many times did you talk to a doctor in these two weeks? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor

1 a GP (i.e. a family doctor), ☐

2 a specialist, ☐

3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐

2 at your home, ☐

3 in the doctor's surgery, ☐

4 at a health centre, ☐

5 elsewhere ☐

f) Did the doctor prescribe you any medication (in addition to your study drugs)?

Yes ☐ No ☐ (If no, please go to question 2)

If yes, was this prescribed over a short period or permanently?

Short ☐ Permanently ☐

Please list prescription medication below:

_____

2. Hospital visits

During the last 3 weeks have you been to hospital for any reason?

Yes ☐ No ☐ (if no, please go to question 3)

If yes, please give details of your attendance or admittance?

1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 3 weeks has a nurse visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 4)

If yes, how many times? _____

4. During the last 3 weeks has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 5)

If yes, how many times? _____

5. During the last 3 weeks has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 6, what was the problem?

_____

_____

_____

TRAPEZE health problems questionnaire for patients on follow-up

During the last 3 months (i.e. since your last visit to hospital) we would like you to tell us about any health problems you may have had. Please answer all the questions yourself by ticking the box that best applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) During the three months ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ (if no, go straight to question 2)

If Yes:

b) How many times did you talk to a doctor in these three months? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor

1 a GP (i.e. a family doctor), ☐

2 a specialist, ☐

3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐

2 at your home, ☐

3 in the doctor's surgery, ☐

4 at a health centre, ☐

5 or elsewhere? ☐

f) Did the doctor prescribe you any medication?

Yes ☐ No ☐

If yes, was this prescribed for use over a short period or permanently?

Short ☐ Permanently ☐

Please list the prescribed medication below:

2. Hospital visits

During the last 3 months have you been to hospital for any reason?

Yes ☐ No ☐ (if no, please go to question 3)

If yes, please give details of your attendance or admittance?

1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 3 months has a nurse visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 4)

If yes, how many times? _____

4. During the last 3 months has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 5)

If yes, how many times? _____

5. During the last 3 months has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 6, what was the problem?

APPENDIX 5: PAIN DIARY SHEETS

TRAPEZE

CONFIDENTIAL

Patient Pain Diary

Patient Initials: ___ ___ ___

(First - middle - last)

Patient Number: _____

Centre Name: _____

Investigator: _____

This diary should be carried with you at all times.

For the seven-day period prior to your next appointment, please complete one page for each day as carefully as possible.

Next appointment: Date: _____

Time: _____

Please take this diary with you when you return to the clinic/hospital:

This patient is in a clinical study. In the event of a medical emergency, please telephone one of the following numbers listed below:

1. _____

2. _____

Patient: please complete the following:

These questions were answered on: 20

Day of week _____ Day ____ Month _____ Year _____

Please list the type of pain relief (analgesic) medication that you have taken over the last 24 hours and the amount. Only information about pain medication is needed. Please do not include medication for other conditions ,(e.g. heart problems)

To be completed by the patient			These shaded boxes to be completed by the clinical Research Nurse/ Associate (*refer to analgesic score table in protocol)			
Product name (trade name and dose)	Type of dose (tablet, injection, patch…)	Number of doses in 24 hours	Type of analgesic and total dose (in 24 hours)	Total dose / analgesic dose (A)	Score value (B)	Total units per 24 hours (A x B)
				Total daily score	(C)	

Do you think you have remembered everything you have taken? Yes ☐ No ☐

Present Pain Intensity (PPI)

Please circle the appropriate number according to how much pain you felt on average during the past 24 hours.

0	1	2	3	4	5
No pain	Mild	Discomforting	Distressing	Horrible	Excruciating