



**Developed with  
the NCRI Prostate  
Clinical Studies  
Group**

**Part of the  
National Cancer  
Research Network  
Portfolio**

# STAMPEDE

**Systemic Therapy in Advancing or  
Metastatic Prostate Cancer: Evaluation of  
Drug Efficacy**

A multi-arm multi-stage randomised controlled trial

**MRC PR08**

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**PROTOCOL VERSION 8.0**

**02 sep-2011**

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## **GENERAL INFORMATION**

This document describes a trial coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the known investigators in the trial, but centres entering patients for the first time are advised to contact the Cancer Division, MRC CTU, London to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the Chief Investigator.

### **Sponsor**

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### **Funding**

Clinical Trials Advisory Awards Committee (on behalf of Cancer Research UK, Medical Research Council, and other charities) together with educational grants from Novartis, Aventis and Janssen Pharma NV.

### **Compliance**

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC and applicable national regulations).

### **Authorisation**

The following persons are authorised to sign the final protocol and protocol amendments for the sponsor: Professor N James (Chief Investigator) and Matthew Sydes (Trial Statistician).

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## **SAE REPORTING**

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## ABBREVIATIONS AND GLOSSARY

<b>Abbreviation</b>	<b>Definition</b>
<b>ACE</b>	Angiotensin-Converting Enzyme
<b>ACTH</b>	Adrenocorticotrophic hormone
<b>AS</b>	Androgen suppression
<b>bid</b>	Twice a day ( <i>bis in die</i> )
<b>BP</b>	Blood pressure
<b>BSA</b>	Body surface area
<b>CERES</b>	Consumers for Ethics in Research
<b>CF</b>	Consent Form
<b>CI</b>	Chief Investigator
<b>CI</b>	Confidence interval
<b>COSTART</b>	Coding Symbols for a Thesaurus of Adverse Reaction Terms
<b>Cox-2</b>	Cyclooxygenase-2
<b>CRF</b>	Case Report Form
<b>CRUK</b>	Cancer Research UK
<b>CT</b>	Computerised tomography
<b>CTA</b>	Clinical Trials Authorisation
<b>CTAAC</b>	Clinical Trials Advisory and Awards Committee
<b>CTC</b>	Common Toxicity Criteria
<b>CTU</b>	Clinical Trials Unit
<b>CTV</b>	Clinical Tumour Volume
<b>CXR</b>	Chest X-ray
<b>DDX</b>	Doctors and Dentists Exemption
<b>DNA</b>	Deoxyribonucleic Acid
<b>DPA</b>	Data Protection Act
<b>ERC</b>	Endpoint Review Committee
<b>ICH</b>	International Conference on Harmonization
<b>ECG</b>	Electro cardiogram
<b>FBC</b>	Full Blood Count
<b>FFS</b>	Failure-Free Survival
<b>GCP</b>	Good Clinical Practice
<b>GP</b>	General Practitioner
<b>GRO</b>	General Register Office
<b>HE</b>	Health Economics
<b>hr</b>	Hour
<b>HR</b>	Hazard Ratio
<b>HRPC</b>	Hormone Refractory Prostate Cancer
<b>HT</b>	Hormone Therapy
<b>IDMC</b>	Independent Data Monitoring Committee
<b>IM</b>	Intramuscular
<b>ISRCTN</b>	International Standard Randomised Controlled Trial Number
<b>IU</b>	International Units
<b>IV</b>	Intravenous
<b>LD</b>	Longest diameter
<b>LFTs</b>	Liver Function Tests
<b>LHRH</b>	Luteinising Hormone Releasing Hormone
<b>LREC</b>	Local Research Ethics Committee
<b>MHRA</b>	Medicine and Healthcare Products Regulatory Agency
<b>min</b>	Minutes
<b>MRC</b>	Medical Research Council
<b>MREC</b>	Multi-Centre Research Ethics Committee
<b>MRI</b>	Magnetic resonance imaging
<b>NCI</b>	National Cancer Institute (USA)
<b>NCRN</b>	National Cancer Research Network

<b>Abbreviation</b>	<b>Definition</b>
<b>NHS</b>	National Health Service
<b>NSAID</b>	Non-Steroidal Anti-inflammatory Drugs
<b>ONS</b>	Office for National Statistics
<b>OS</b>	Overall Survival
<b>PI</b>	Principal Investigator
<b>PIS</b>	Patient Information Sheet
<b>po</b>	<i>per orum</i> (orally)
<b>PSA</b>	Prostate Specific Antigen
<b>PTV</b>	Planned Tumour Volume
<b>QALY</b>	Quality-adjusted Life Years
<b>qds</b>	<i>quater die sumendus</i> (4 times each day)
<b>QL</b>	Quality of Life
<b>R&amp;D</b>	Research and Development
<b>RECIST</b>	Response Evaluation Criteria In Solid Tumours
<b>SAE</b>	Serious Adverse Event
<b>sc</b>	<i>Sub-cutaneous</i> (under skin)
<b>SNP</b>	Single Nucleotide Polymorphism
<b>SSA</b>	Site Specific Assessment
<b>STAMPEDE</b>	Systemic Therapy in Advancing and Metastatic Prostate Cancer: Evaluation of Drug Efficacy
<b>SUSAR</b>	Suspected Unexpected Serious Adverse Reactions
<b>SWOG</b>	SouthWest Oncology Group
<b>TMG</b>	Trial Management Group
<b>TURP</b>	Trans-Urethral Resection of Prostate
<b>TSC</b>	Trial Steering Committee
<b>ULN</b>	Upper Limit of Normal
<b>U+E</b>	Urea and Electrolytes
<b>WHO</b>	World Health Organisation

# 1 SUMMARY

## 1.1 LAY SUMMARY

Prostate cancers depend upon the male hormone testosterone for their growth. Lowering testosterone levels (either by removing all or part of both testes, or by giving anti-hormone injections) slows the growth of prostate cancers. This type of treatment is called hormone treatment and is often used when prostate cancers have spread outside the prostate gland. Although hormone treatment is usually successful at stopping the cancer growing for a period of time, the cancer will begin to grow again in most men.

A number of newer treatments have recently become available for prostate cancer. These treatments are usually used in prostate cancer when hormone treatment is no longer effective and the cancer has started to grow again. The aim of this trial, which is called STAMPEDE, is to assess four of these newer treatments, given earlier in the course of the disease in combination with hormone treatment.

The treatments assessed from the commencement of the trial are:

**1. Zoledronic acid:** Prostate cancer cells can spread to bones and weaken them. Zoledronic acid is a drug that reduces bone destruction and hardens bones. This may make them more resistant to attack by cancer cells.

**2. Docetaxel:** A drug that stops cells replicating that is currently being used to treat lung, breast and ovarian cancer.

**3. Celecoxib:** An aspirin-like drug that is used to treat arthritis. It slows down the growth of cancer cells in the laboratory. We wished to see if it had the same effect on cancer cells in patients. Recruitment to new patients for the evaluation of this drug is finished as a planned interim analysis failed to demonstrate sufficient activity.

**4. Abiraterone** (included from protocol version 8.0): An inhibitor of steroid hormone synthesis that blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following castration based therapies. The agent prolongs survival when given to men following failure of docetaxel chemotherapy.

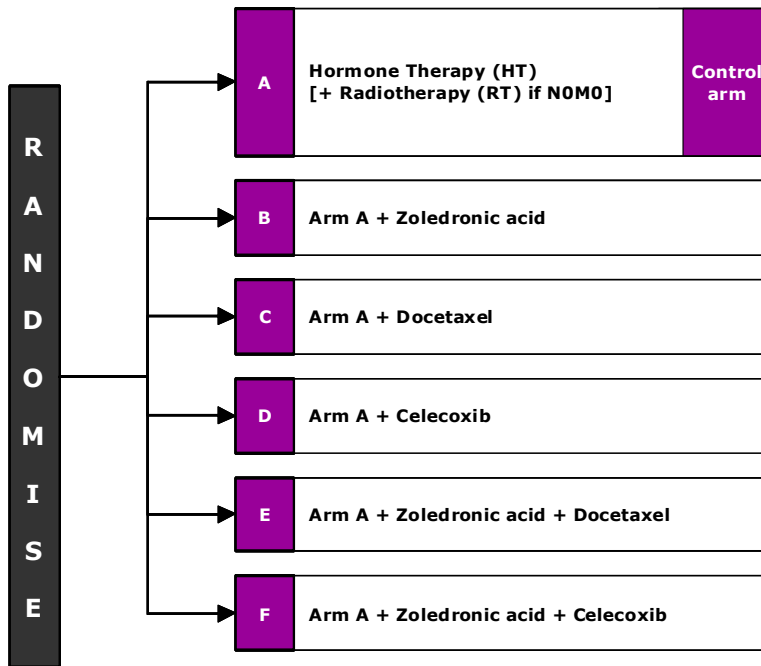
STAMPEDE will look at the effect of combining one or two of the new treatments described above with hormone treatment. A computer program will be used to allocate which

treatment the patient receives, using a chance process. The trial will look at the effects of the combined treatments on quality of life and find out whether the new treatment combinations increase the time when the cancer is not growing and ultimately results in patients living longer. The study will also look at which treatment provides the greater value for money for the health service. Around 4000 men will join the trial with answers becoming available over 7-12 years.

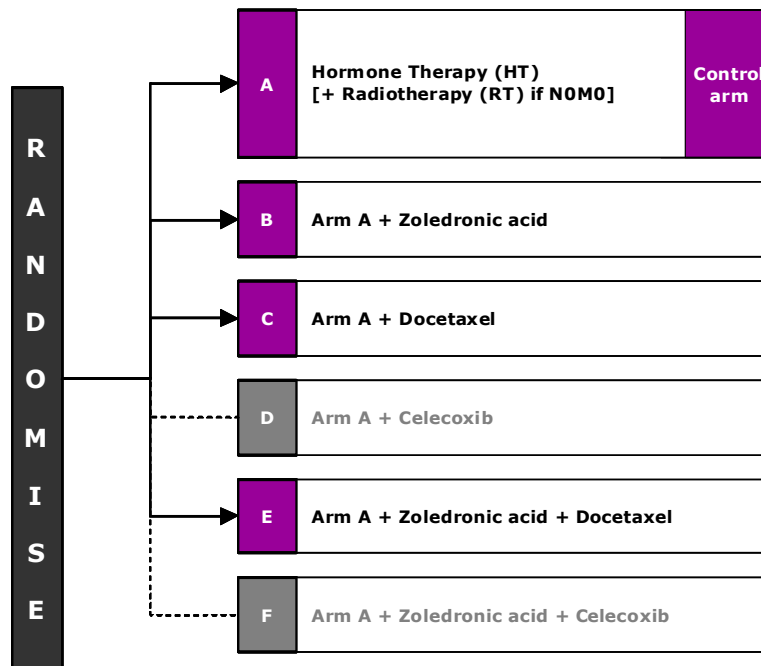
## **1.2 ABSTRACT AND SUMMARY OF TRIAL DESIGN**

STAMPEDE is a multi-centre, randomised controlled trial for patients with locally advanced or metastatic prostate cancer who are about to commence hormone therapy (HT). Patients can have either newly diagnosed disease, or have been previously treated with radical radiotherapy or surgery but now have a rising prostate specific antigen (PSA) (further details on eligibility see **Section 4**). The trial will assess the effects of adding different agents, both as single agents and in combinations, to hormone therapy. The investigational agents are (i) a bisphosphonate, zoledronic acid, (ii) a cytotoxic chemotherapeutic agent, docetaxel and (iii) a cyclooxygenase (Cox-2) inhibitor, celecoxib. (iv) a novel hormone therapy drug called abiraterone, a steroid synthesis inhibitor. Recruitment to the celecoxib arms (D and F) is now closed. An additional arm containing abiraterone has been added in protocol version 8.0. The trial has multiple arms; the control arm of the trial is HT only, achieved through the use of luteinising hormone releasing hormone (LHRH) analogues or LHRH antagonists, or bilateral orchidectomy according to local practice. The other trial arms are summarised in **Figure 1**.

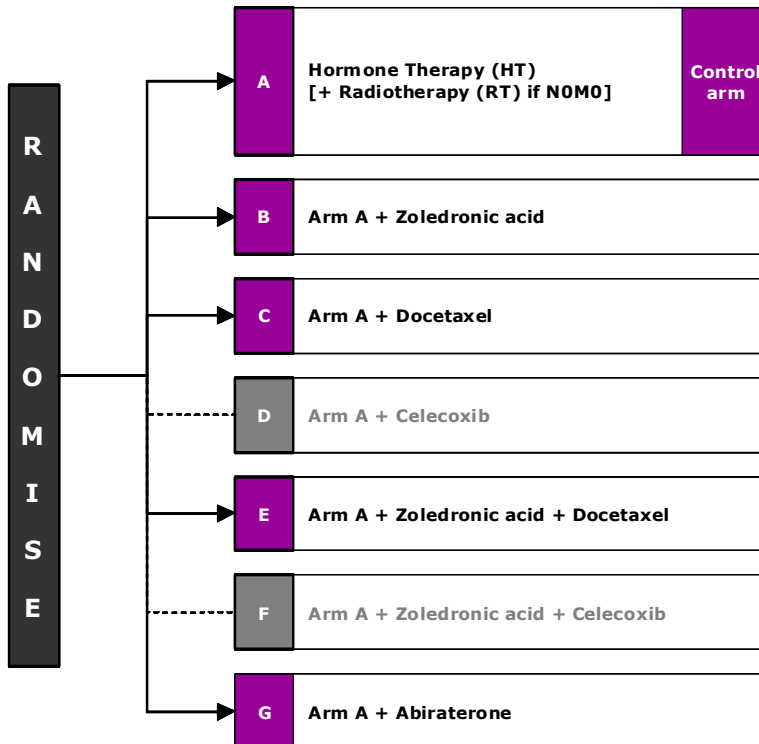
**Figure 1a: Recruiting arms of the STAMPEDE Trial to April 2011**



**Figure 1b: Recruiting arms of the STAMPEDE Trial from April 2011**



**Figure 1c – Arms of the STAMPEDE Trial from protocol version 8.0**



For each comparison of research arm against control, the trial will be conducted in five stages: a Pilot Phase, Activity Stages I to III and Efficacy Stage IV. The primary outcome measure of the Pilot Phase is the safety, with 30 patients recruited to each research arm. Research arms will only continue to recruitment in the next stage if they have been shown to be both safe and feasible, although patient data from all patients and all stages will be included in the final analyses. In Activity Stages I-III the primary outcome measure is failure-free survival (FFS). Further patients will be recruited until a certain number of FFS events have been observed in the control arm (see **Section 9** for further detail). Some evidence of activity will be required for a research arm to proceed to further recruitment in each stage and guidelines are in place. In Efficacy Stage IV, patients will be recruited until around 403 deaths have been reported in the control arm for the original research comparisons and 267 for the abiraterone comparison. The exact number of patients and duration of the trial will depend on the observed accrual rate, observed event rate and the number of patients accruing at each stage.

Recruitment to arms D (HT + celecoxib) and F (HT + zoledronic acid + celecoxib) was stopped in April 2011 after the second planned activity analysis revealed a lack of sufficient

activity. Refer to **Section 9.3.3** for further information regarding the guidelines for stopping accrual to research arms during the activity stages of the trial.

In version 8.0 of the protocol a new arm G (HT + abiraterone) has been added. The trial stages remain as at trial inception but will be staggered with respect to the stages for the original arms A-F.

Patients will be assessed 6 weekly for the first 24 weeks after randomisation and then every 12 weeks up to 2 years, then 6-monthly until 5 years and annually, thereafter. The first 700 patients on trial completed questionnaires aimed at assessing the effects of the investigational treatments on their quality of life (QL) and on their use of health care resources (Health Economics (HE) study). With the introduction of abiraterone in version 8.0, the QL and HE study has been re-opened to all new patients to obtain data on this new agent and further data on the original agents.

In addition, there are translational sub-studies. Patients willing to participate will be asked to donate a droplet of blood at randomisation which will be stored for either DNA and protein analysis in order to try to identify markers that are associated with response to therapy, side-effects or susceptibility to prostate cancer.

Patients will also be asked to give permission to use some of their stored material for further studies on the causes and nature of prostate cancer. In selected centres patients will also be asked to participate in a bone mineral density sub-study. There are separate patient information sheets for the QL and HE study and the translational sub-studies (For further details of ancillary studies, see **Section 17**).

### **1.3 TRIAL DOCUMENTATION**

**Figure 2** presents a summary of the required trial documentation for participating centres and **Figure 3** presents a summary of the timings of the case report forms (CRFs) for your randomised patients.

**Figure 2: Summary of trial documentation required ahead of accreditation**

<b>Trial documentation</b>	<b>Timing</b>
R&D approval	Before centre participation
Investigator Statement	Before centre participation
Signature list & delegation of responsibilities	Before centre participation
Trial personnel contact details	Before centre participation
PIS, GP & CF on local paper	Before centre participation
Signed Clinical Trial Agreement between Trust and Sponsor	Before centre participation

## **2 BACKGROUND**

### **2.1 INTRODUCTION AND RATIONALE**

Prostate cancer is a major health problem world-wide and accounts for nearly one fifth of all newly diagnosed male cancers. In the UK, approximately 35,000 men are diagnosed with prostate cancer each year and in 2008 almost 10,000 men died from the disease. (1)

The initial (first line) treatment for locally advanced or metastatic prostate cancer is hormone therapy (HT) achieved either surgically with bilateral orchidectomy, or medically with LHRH agonists or antagonist or oral anti-androgens alone. (2) This latter therapy is no longer permitted within the trial, however (from version 8.0). HT produces responses in up to 95% of patients but it is not curative and disease recurs in virtually all patients, with a median time to progression of 18-24 months. (2) Such disease is referred to as hormone or increasingly as castrate refractory prostate cancer (HRPC or CRPC).

There are increasing numbers of treatments, which are used post relapse of first-line hormone therapy in patients with CRPC, but little evidence as to which is associated with the best response, how they may be combined or sequenced or whether any of them might have a role in first-line treatment; these include further hormonal manipulations (3), bisphosphonates, (4) cytotoxic chemotherapy (5) and new hormone therapies (6). The traditional approach to the testing and introduction of new treatments for prostate cancer is in castrate refractory disease. An alternative approach is to investigate new drugs and new approaches to treatment as first-line therapy in patients starting hormone therapy. At this point patients would be fitter and better able to tolerate treatment than when they have CRPC, and there is also the possibility of having a larger and more durable effect.

STAMPEDE (also known as MRC PR08) is an innovative, multi-arm multi-stage, multi-centre, randomised controlled trial. It initially assessed the effects of a bisphosphonate (zoledronic acid), a cytotoxic chemotherapeutic agent (docetaxel) and a cyclooxygenase (Cox-2) inhibitor (celecoxib), as single agents or combinations, in patients commencing hormone therapy for advancing or metastatic prostate cancer. The trial is divided into five stages such that, for each investigational arm, safety and activity data are generated in the first four stages; an investigational arm will only proceed to the fifth and final stage of recruitment, where it will be assessed for its effect on overall survival, if it has been shown to be safe and active. It is important to note, however, that patient data from all arms and all stages will be included in the final analyses of the primary outcome measure, even if the investigational arm did not proceed to the final stage. Planned interim analysis failed to demonstrate sufficient efficacy for celecoxib and this agent has now been removed from the trial and

remaining patients on treatment reverted to standard care. Amendment to version 8.0 adds a new drug abiraterone to the study as an additional arm.

## **2.2 BISPHOSPHONATES**

The bisphosphonates are a class of drug that act by reducing osteoclast formation, inhibiting osteoclast activity and inducing osteoclast apoptosis. They are effective at controlling hypercalcaemia and preventing skeletal complications associated with malignant disease. (7, 8) Zoledronic acid is a new, highly potent, third generation bisphosphonate; studies comparing the efficacy of zoledronic acid to other bisphosphonates suggest that zoledronic acid has a 40-850 fold higher potency than clodronate in preclinical models of bone resorption. (9). It has also been shown to be more effective than pamidronate (90mg) in controlling malignant hypercalcaemia. (10) In addition, zoledronic acid has also demonstrated direct anti-cancer activity, including inhibition of proliferation of breast cancer and prostate cancer cells *in vitro*. (11)

In randomised controlled trials of 1,648 patients, 4mg zoledronic acid was more effective than pamidronate in reducing the risk of skeletal complications in patients with bone metastases from breast cancer. (12, 13) Also, in metastatic prostate cancer, zoledronic acid has been shown to reduce the rate of skeletal related events compared to placebo in a trial involving 429 men. (14) In April 2002, zoledronic acid received approval from the Committee for Propriety Medicinal Products for the prevention of skeletal related events (for example, fractures) in patients with any advanced malignancies involving bone.

The MRC PR05 prostate cancer trial showed that a first generation bisphosphonate (clodronate) commenced at the time of hormone therapy initiation, delayed time to progression in patients with bony metastatic disease and there was some evidence that it may also improve survival. (15) There is, therefore, a good rationale for investigating a more potent bisphosphonate in patients with prostate cancer who are about to commence HT therapy.

## **2.3 CHEMOTHERAPY**

Over recent years there has been increasing evidence of the clinical efficacy of chemotherapy in prostate cancer. (5) Two randomised phase III trials in patients with metastatic hormone refractory prostate cancer (HRPC) using a docetaxel-containing regimen have been completed: the SWOG 9916 study (16) and the TAX-327 study. (17) Both studies show that the use of a docetaxel-based regimen improved survival for patients with

metastatic HRPC and had significantly greater PSA response rates compared to the mitoxantrone plus prednisolone arm.

In the TAX-327 trial, (17) 1,006 patients with metastatic HRPC were randomized to receive either mitoxantrone 12 mg/m<sup>2</sup> with prednisone 10mg daily (Arm C) or docetaxel 75mg/m<sup>2</sup> 3-weekly for 10 cycles with prednisone (Arm A) or docetaxel 30 mg/m<sup>2</sup>/wk x 5 of 6 weeks x 5 cycles with prednisone (Arm B). Median overall survival was 16.5 months for patients treated with mitoxantrone versus 18.9 months for the 3-weekly docetaxel regimen (hazard ratio 0.76 (0.62-0.94)). There was also improvements for 3-weekly docetaxel in pain (22% vs 35%, p = 0.01) and PSA response (32% vs 45%, p = 0.0005).

In June 2006 in the UK docetaxel was given NICE (National Institute for Health and Clinical Excellence) approval for use in hormone refractory prostate cancer patients.

## **2.4 CYCLOOXYGENASE-2 INHIBITORS**

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

Cyclooxygenase-2 (Cox-2) is an isoenzyme induced by a variety of mitogens, cytokines and growth factors that are associated with a range of process including inflammation, (18) and carcinogenesis. (19, 20) There is a growing body of evidence that inhibition of Cox-2 may play an important role in the prevention of cancer and the delay of progression in established cancer. A number of case-control studies have shown a reduction in risk of prostate cancer associated with the use of non-steroidal anti-inflammatory drugs (NSAID), which include inhibition of Cox-2 amongst their mode of action. (21) Pathological studies show Cox-2 is upregulated in carcinomas (22) and one study suggested that NSAID use may delay progression from subclinical to clinical prostate cancer. (23)

Celecoxib, a Cox-2 inhibitor, is better tolerated than other NSAIDs and there is evidence that it is active as a chemoprevention agent. (24) It also has important antineoplastic properties such as the ability to inhibit angiogenic factors and induce apoptosis in human cancer cells including prostate cancer. (25)

Evidence has suggested that an anti-cancer effect is only seen at higher doses of celecoxib than required for an anti-inflammatory effect. (26) Therefore, the dose of 800mg/day for STAMPEDE patients has been chosen. Although there is some high profile evidence of a small absolute increase in CVS toxicity risk associated with higher doses of celecoxib, (27) most current cancer trials are using a dose of 800mg/day as it is believed that a higher dose will result in a greater increase in cancer effect.

There is also some evidence of a schedule effect on CVS toxicity. It has been observed that CVS toxicity becomes evident after one year of taking celecoxib. (27) Therefore, a maximum duration of

one year has been set for celecoxib use in this trial. Any potential risks of course have to be weighed against any potential benefits of celecoxib in the delay of progression in established prostate cancer.

Given case-control data suggesting effects on prostate cancer, pathological expression of Cox-2 in prostate cancer and *in vitro* data suggesting that inhibition of Cox-2 inhibits growth and invasiveness, further investigation in prostate cancer is warranted.

## **2.5 STEROID SYNTHESIS INHIBITORS**

Recent evidence suggests that an important mechanism for escape from tumour control by androgen ablation is the intracellular conversion of steroids precursors to androgenic steroids by prostate cancer cells. A key enzyme in this process is CYP17, which therefore represents a logical target for therapy in CRPC. (6) Abiraterone is a selective inhibitor of CYP17 and is highly active in patients developing resistance to standard androgen ablation therapies. (28-30) Recruitment to a phase III study comparing abiraterone to placebo in CRPC patients post-docetaxel completed accrual in 2009 and reported initial results in 2010 with an improvement in overall survival of around 4 months and a hazard ratio of 0.65. (31) The drug has now received a marketing authorisation in the USA and in the EU from September 2011. A second trial in pre-chemotherapy CRPC patients completed recruitment April 2010 and results are currently awaited. Side effects with abiraterone are modest with the main adverse effects being elevated transaminases (usually mild), hypokalaemia and hypertension due to secondary hyperaldosteronism (preventable by low doses of glucocorticoids) and fluid retention. Due to the secondary hyperaldosteronism, it is recommended that prednisolone (or prednisone) 10mg daily be administered in the CRPC setting. Within more recent studies in earlier stage patients, lower doses (typically 5mg of prednisone/prednisolone) are being used due to concerns about long-term exposure to glucocorticoid side effects. More recent evidence even suggests that for most patients, no glucocorticoids may be needed. (32) Within the STAMPEDE trial, we propose to use a prednisone/prednisolone dose of 5mg daily.

We hypothesise that the agent may be more active still when given up-front in combination with first-line hormone therapy by preventing or delaying the development of castrate refractory disease.

## **2.6 TREATMENT COMBINATIONS**

### **2.6.1 BISPHOSPHONATE AND CHEMOTHERAPY**

Zoledronic acid and docetaxel have different mechanisms of action. In addition to its skeletal protection activity, zoledronic acid has shown direct activity against prostate cancer cells, both *in vitro* and *in vivo*. (11) There is also *in vitro* and *in vivo* evidence to suggest synergy between zoledronic acid and chemotherapy in breast cancer cells and anti-angiogenic effects in patients. (33, 34)

Toxicities of the two agents are complementary and administration in combination is expected to be feasible and safe. These aspects will be evaluated in the initial Pilot Phase of the trial. Since both agents show considerable promise as single agents and there is *in vitro* evidence of synergy, we believe there is a strong rationale for evaluating these two agents in combination.

### **2.6.2 BISPHOSPHONATE AND CYCLOOXYGENASE-2 INHIBITORS**

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

An alternative approach to combination therapy is to target the principal site of relapse and a key mode of progression and this is the rationale for combining zoledronic acid with a Cox-2 inhibitor. Bisphosphonates have already been shown to delay bone disease progression in hormone refractory disease. (15) Cox-2 appears to play a crucial role in the molecular phenotype of advanced prostate cancer as outlined above, and this effect is likely to be apparent in both soft tissue and in bone. Toxicities of the two agents are likely to be complementary and there is no strong *a priori* reason to anticipate unacceptable toxicity. The Pilot Phase of the trial will evaluate tolerability and safety of the combination. Targeting both bone progression and the underlying molecular changes leading to progression can be expected to have synergistic benefits in terms of delaying development of hormone refractory disease.

## **2.7 ROLE OF RADIOTHERAPY**

Two randomised trials, SPCG7 (35) and NCIC PR.3 / MRC PR07 (36, 37) have tested the question of whether hormone therapy alone or combined with radiotherapy is the best treatment for high risk patients with no evidence of spread outside the pelvis. Both trials demonstrate an improvement in overall and disease specific survival from the addition of radiotherapy to hormone therapy. The size of this overall survival benefit is substantial (HR 0.68 in SPCG7 and HR 0.77 in PR07). With substantial benefit demonstrated in two mature, large well conducted randomised trials, we now recommend that radiotherapy be considered part of the standard therapy for patients with no nodal or metastatic spread. Patients in this

category will now only be allowed to entry the trial if radiotherapy is planned, with the exception of those for whom radiotherapy is contra-indicated (e.g. inflammatory bowel disease) who should be discussed with the Trials Unit prior to inclusion.

### **3 SELECTION OF INSTITUTIONS AND INVESTIGATORS**

Centres who wish to participate in the STAMPEDE trial should be registered with the Medical Research Council Clinical Trials Unit (MRC CTU) for this purpose. Before any patients are randomised the MRC CTU must receive a completed and signed Investigator Statement. The STAMPEDE investigator statement is signed by the Principal Investigator for that institution (**Appendix M**). R&D approval for the site, along with a fully-signed model agreement are also required before recruitment can begin.

In addition and in compliance with the principles of GCP all institutions participating in the trial will complete a delegation log and forward this to the MRC CTU. Each person working on the STAMPEDE trial must sign off a section of this log indicating their responsibilities. The MRC CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site file at the institution and also at the MRC CTU.

The Clinical Trial Authorisation (CTA) for the STAMPEDE trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating investigators/institutions. Trial staff at the MRC CTU will perform this task; hence, it is vital to receive full contact details for all investigators prior to their entering patients.

Finally, before a patient is entered into the trial written informed consent must be obtained. Approved patient information sheets and informed consent forms are supplied in **Appendix B**.

Only a limited number of centres participated in the initial Pilot Phase of the trial; this was to ensure that safety and feasibility data were collected expediently. The other stages of the trial will be open to any centre that wishes to participate and has fulfilled the requirements described above.

## 4 SELECTION OF PATIENTS

### 4.1 PATIENT INCLUSION CRITERIA

Patients must fulfil both of the criteria in **Section 4.1.1** or the one criterion in **Section 4.1.2** or at least one criteria in **Section 4.1.3**. Additionally, **all** patients must fulfil the criteria in **Section 4.1.4**.

#### **4.1.1 HIGH-RISK NEWLY DIAGNOSED NON-METASTATIC NODE-NEGATIVE DISEASE**

- (i) At least two of: Stage T3/4, PSA $\geq$ 40ng/ml or Gleason sum score 8-10
- (ii) Intention to treat with radical radiotherapy (unless there is a contra-indication; exemption can sought in advance of consent, after discussion with MRC CTU)

OR

#### **4.1.2 NEWLY DIAGNOSED METASTATIC OR NODE-POSITIVE DISEASE**

- (i) Stage T<sub>any</sub> N+ M0 or T<sub>any</sub> N<sub>any</sub> M+<sup>1</sup>

OR

#### **4.1.3 PREVIOUSLY TREATED WITH RADICAL SURGERY OR RADIOTHERAPY, NOW RELAPSING<sup>2</sup>**

At least one of:

- (i) PSA  $\geq$ 4ng/ml and rising with doubling time less than 6 months
- (ii) PSA  $\geq$ 20ng/ml
- (iii) N+
- (iv) M+

<sup>1</sup> Note: From version 8.0, patients with multiple sclerotic bone metastases with PSA $\geq$ 100ng/ml must have histological confirmation

<sup>2</sup> Note: Prior hormone therapy for localised disease must have been completed at least 12 months previously and have been no longer than 12 months in duration. It can have been given as adjuvant or neoadjuvant therapy.

**AND**

#### 4.1.4 FOR ALL PATIENTS

- (i) Histologically confirmed prostate adenocarcinoma
- (ii) Intention to treat with long-term hormone therapy
- (iii) Fit for all protocol treatment<sup>¶</sup> and follow-up, WHO performance status 0-2<sup>♠</sup>
- (iv) Have completed the appropriate investigations prior to randomisation
- (v) Adequate haematological function: neutrophil count  $\geq 1.5 \times 10^9/l$  and platelets  $\geq 100 \times 10^9/l$
- (vi) Estimated creatinine clearance  $\geq 30ml/min$
- (vii) Serum potassium  $\geq 3.5mmol/L$
- (viii) Written informed consent
- (ix) Willing and expected to comply with follow-up schedule
- (x) Using effective contraceptive method if applicable

<sup>¶</sup>The exclusion criteria for patients who have been on a Cox-2-inhibitor for 6+ months has been removed

<sup>♠</sup>For WHO performance status definitions see **Appendix A**

<sup>¶</sup>: Medical contraindications to the trial medications are given in **Appendix G**

## 4.2 PATIENT EXCLUSION CRITERIA<sup>3</sup>

Patients must not fulfil any of the criteria, below.

- (i) Prior systemic therapy for locally advanced or metastatic prostate cancer except as listed in **Section 4.1.3**.
- (ii) Metastatic brain disease or leptomeningeal disease
- (iii) Abnormal liver functions consisting of any of the following:
  - :: Serum bilirubin  $\geq 1.5 \times ULN$  (except for patients with Gilbert's disease, for whom the upper limit of serum bilirubin is  $51.3\mu mol/l$  or  $3mg/dl$ )
  - :: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 2.5 \times ULN$
- (iv) Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
- (v) Patients with active peptic ulceration, gastrointestinal bleeding, inflammatory bowel disease
- (vi) Symptomatic peripheral neuropathy grade  $\geq 2$  (NCI CTC)<sup>4</sup>
- (vii) Any surgery (e.g. TURP) performed within the past 4 weeks
- (viii) Patients with confirmed severe cardiovascular history e.g.:
  - a. Severe/unstable angina
  - b. Myocardial infarction

- c. Severe cardiac failure (NYHA II-IV<sup>5</sup>)
  - d. Cerebrovascular disease (e.g. stroke or transient ischaemic episode)
  - e. Patients with uncontrolled hypertension defined as systolic BP  $\geq$ 160 mmHg or diastolic BP  $\geq$ 95 mmHg).
- (ix) Patients who have been scheduled to have major dental extractions within the next 2 years
- (x) Patients receiving treatment with drugs known to induce CYP3A4 (including phenytoin, carbamazepine, Phenobarbital). A full list is included in **Appendix G**.
- (xi) Prior exposure to abiraterone
- (xii) Prior chemotherapy for prostate cancer
- (xiii) Prior therapy with zoledronic acid other than short-term treatment for hypercalcaemia.

<sup>3</sup> The exclusion criteria for patients who have been on a Cox-2-inhibitor for 6+ months has been removed

<sup>4</sup> See **Appendix G** for common toxicity gradings

<sup>5</sup> NYHA classifications can be found in **Appendix A**

## 4.3 SCREENING PROCEDURES

### 4.3.1 INVESTIGATIONS PRIOR TO RANDOMISATION

All patients should have the following examinations performed the latest available scans should be used:

- CT or MRI of pelvis and abdomen
- Bone Scan
- Chest X-ray (only if chest was not included in CT)
- ECG
- PSA Test

The following blood tests within 8 weeks (56 days) prior to randomisation:

- Testosterone (if available)
- Urea and Electrolytes
- Liver function tests
- Serum creatinine
- Serum corrected calcium
- Phosphates
- Magnesium
- Albumin
- Total Cholesterol
- HDL Cholesterol

- Systolic blood pressure
- Diastolic blood pressure

Patients who initially fail to meet the eligibility criteria can be re-screened at a later date.

#### **4.3.2 HORMONE THERAPY PRIOR TO RANDOMISATION**

It is preferable that patients are not started on hormones prior to randomisation. However, if hormone therapy has already started, the primary hormone therapy should have not have started more than 12 weeks before randomisation, and the baseline PSA measurement must be taken before this was initiated (please report the latest PSA measurement taken before the start of hormone therapy).

Short periods (not exceeding 2 weeks duration) of prior anti-androgens to cover tumour flare are allowed but will not be counted in the 12 week time period mentioned above; but a PSA measurement must be taken before this is initiated.

Note that long-term anti-androgen monotherapy is not permitted in the trial for newly recruited patients from version 8.0 (see **Section 6.1**); patients may change treatment to join the trial, provided that they have not had more than 12 weeks of hormone therapy prior to randomisation.

Note that baseline testosterone measurements will not be required in patients who have already commenced hormone manipulation prior to randomisation.

#### **4.3.3 HYPERCALCAEMIA AT RANDOMISATION**

For patients who are hypercalcaemic prior to randomisation and require treatment, it is recommended that they are treated with a bisphosphonate and that the treatment should be discontinued when they are stabilised.

#### **4.3.4 NSAIDS AND COX-2 INHIBITORS AT RANDOMISATION**

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

For patients who are currently on a Cox-2-inhibitor and who meet the inclusion criteria, please ensure that treatment is discontinued before randomisation. If the patient is allocated to an arm, which does not include celecoxib (arms A, B, C or E), it is advised that the Cox-2 be replaced with a suitable NSAID.

For patients who are taking an NSAID prior to randomisation and are allocated a celecoxib arm (Arm D or F), a clinical decision should be taken as to whether the patient should continue taking the NSAID alongside the celecoxib. This decision should take into account the risk of gastrointestinal problems, and consideration should be given to the co-administration of a proton pump inhibitor

#### **4.3.5 STARTING TRIAL TREATMENT**

Trial treatment should be commenced as soon as possible after randomisation. Investigators should aim that this is at least within 4 weeks post randomisation and within 12 weeks of starting hormone therapy (see **Section 6**).

#### **4.3.6 CONCOMITANT MEDICATIONS**

All concomitant medications should be recorded including any vitamin and mineral supplements the patient is taking, regular consumption of NSAID and/or aspirin and use of other bisphosphonates (see **Section 4.3.1**). All concomitant medications should be continued throughout the trial unless the responsible physician decides otherwise.


### **4.4 ADDITIONAL DETAILS FOR PATIENTS JOINING SUB-STUDIES**

An additional droplet of blood must be taken if the patient has given their consent to participate in the DNA analysis sub-study.

The local pathologist will also be asked to give the remaining tumour sample for tissue micro array analysis to be carried out, if the patient has given consent for his remaining samples to be used for further analyses. In selected centres, patients will also be asked to participate in a bone mineral density sub-study. Full details of all sub-studies and instructions relating to the handling of the blood sample are given in **Section 17** and **Appendix D**.

## **5 RANDOMISATION AND ENROLMENT**

To enter a patient the randomisation form should be completed and the MRC CTU contacted by phone:



**RANDOMISATION**

**To randomise, call MRC CTU, Monday to Friday 0900-1700  
excluding public holidays or dates when notice has been given by  
the CTU.**

**Tel: + 44 (0)20 7670 4777**

A trial number and treatment will be allocated and given over the phone or by return fax. In addition, a letter confirming these details will be sent. The trial number will be the primary way in which the patient will be identified and should be used in all correspondence.

### **5.1 CO-ENROLMENT GUIDELINES**

Ideally, patients should not be participating in any other clinical trial of prostate cancer treatment when they enter STAMPEDE and should not enter any other trials until the patient has had a failure-free survival (FFS) event reported. After this point, the patient may be entered into further, second-line treatment studies. The primary outcome measure of STAMPEDE is overall survival. Participation in post-progression studies should be reported in the co-enrolment CRF.

## 6 TREATMENT OF PATIENTS

### 6.1 TRIAL TREATMENT

Patients will be randomised to the control arm (Arm A) or one of the research arms. All patients will receive HT to achieve castration levels of testosterone. The method of HT is a local choice but must be specified for each patient prior to randomisation. The recommended methods of HT are given in **Section 6.1.1**. All trial treatments should **commence as soon** as practically possible **after randomisation**. Patients having a bilateral orchidectomy should commence any additional treatment with 4 weeks of the operation unless there is a strong clinical reason not to do so. Note that from protocol **version 8.0** onwards, **bicalutamide** monotherapy is **no longer a permitted** trial therapy for new patients (but patients may switch to a permitted to join the trial – see **Section 4.3.2**).

#### 6.1.1 ARM A: HORMONE THERAPY (HT) ALONE OR HT + RADIOTHERAPY (CONTROL ARM)

The standard of care for this patient group is hormone therapy (see **Section 6.1.1.1**). For some patient groups, this should now be supplemented with radiotherapy (see **Section 6.1.1.2**).

##### 6.1.1.A Hormone therapy

The recommended methods of HT are bilateral orchidectomy, LHRH analogues and LHRH antagonists. Anti-androgens alone are not permissible as hormone therapy for patients participating in STAMPEDE, but their use is recommended in the short-term to prevent tumour “flare” which may occur after commencing LHRH analogues. Anti-androgen prophylaxis of tumour flare is not required when using LHRH antagonists. At the time of randomisation, centres will be asked to specify the method of HT for each patient. Other methods of HT should be discussed with the Chief Investigator or the Trial Physician. The planned duration of HT should be at least 2 years.

- **Bilateral orchidectomy:** Operations should be performed by appropriately trained surgeons. A total or subcapsular orchidectomy may be performed.
- **LHRH agonists:** LHRH agonists/analogues used according to local practice. The prophylactic use of anti-androgens to prevent tumour “flare” is recommended.
- **LHRH antagonists:** LHRH antagonists used according to local practice. The use of prophylactic use of anti-androgens to prevent tumour “flare” is not necessary.

### 6.1.1.B Radiotherapy

- **NOMO patients:** Investigators should give radiotherapy (RT) to patients with node negative, non-metastatic disease, in accordance with the recent data from the PR07 and SPCG trials. If there is an intention to omit radiotherapy in patients with NOMO disease this **must be discussed** with the Trials Office before consent. See **Section 6.5** for further details of radiotherapy administration.
- **N+MO patients:** the benefit of radiotherapy in this group is at present uncertain with no firm data to either support or refute its use. However, the PR07 trial included some node positive patients as cross sectional imaging was not a part of the baseline assessment in this trial, which did include whole pelvis radiotherapy. For patients with node positive, non-metastatic disease, radiotherapy is therefore recommended in suitable cases. Investigators will be asked to state their intention with regard to planned radiotherapy in this group at randomisation. Intention to give radiotherapy (or not) for node positive patients must be stated at randomisation to ensure that there is no bias towards particular combinations of systemic therapy with radiotherapy.
- As radiotherapy is not a core part of the trial, we intend to collect only relatively minimal data about the radiotherapy administered. It is accepted that some patients will progress before radiotherapy can be administered and if this occurs the reasons for non-delivery of treatment must be recorded on the radiotherapy form.

### 6.1.2 ARM B: HORMONE THERAPY + ZOLEDRONIC ACID

- **Hormone Therapy (+/- RT)** as described in Section 6.1.1.
- **Zoledronic Acid** 4mg 15min IV infusion every 3 weeks, for 6 treatments followed by zoledronic acid 4mg 15min IV infusion every 4 weeks up to a maximum of 2 years from the start of the treatment or until disease (including PSA) progression (see **Section 7.2**). Patients should also receive an oral supplement of 500mg calcium and 400IU vitamin D daily. These doses are available as a combination tablet. See **Section 6.2.1** for further information.

### 6.1.3 ARM C: HORMONE THERAPY + DOCETAXEL

- **Hormone Therapy (+/- RT)** as described in **Section 6.1.1**.
- **Docetaxel** 75mg/m<sup>2</sup> Day 1 as 1hr IV infusion, plus prednisolone 5mg *bid* daily for 21 days. The cycle should be repeated every 3 weeks for a maximum of 6 cycles. The recommended administration schedule, anti-emetic regimen and dose modifications for docetaxel are given in **Appendix F**. See **Section 6.2.2** for further information.

### 6.1.4 ARM D: HORMONE THERAPY + CELECOXIB

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

- **Hormone Therapy** as described in **Section 6.1.1**.
- **Celecoxib** 400mg *bid* until the sooner of 1 year or disease (including PSA) progression (see **Section 7.2**). See **Section 6.2.3** for further information.

### 6.1.5 ARM E: HORMONE THERAPY + DOCETAXEL + ZOLEDRONIC ACID

- **Hormone Therapy (+/- RT)** as described in **Section 6.1.1**.
- **Docetaxel** 75mg/m<sup>2</sup> Day 1 as 1hr IV infusion, plus prednisolone 5mg *bid* daily for 21 days. The cycle should be repeated every 3 weeks for a maximum of 6 cycles. The recommended administration schedule, anti-emetic regimen and dose modifications for docetaxel are given in **Appendix F**. See **Section 6.2.2** for further information.
- **Zoledronic Acid** 4mg 15min IV infusion every 3 weeks, for 6 treatments followed by zoledronic acid 4mg 15min IV infusion every 4 weeks up to a maximum of 2 years from the start of the treatment or until disease (including PSA) progression (see **Section 7.2**). Patients should also receive an oral supplement of 500mg calcium and 400IU vitamin D daily. These doses are available as a combination tablet. See **Section 6.2.1** for further information.
- **Co-administration of docetaxel and zoledronic acid:** Docetaxel 75mg/m<sup>2</sup> Day 1 as 1hr IV infusion, plus prednisolone 5mg *bid* daily followed by zoledronic acid 4mg 15min IV infusion. There is evidence to suggest that the co-administration of docetaxel and

zoledronic acid is sequence dependent (39). Consequently, docetaxel should be administered **before zoledronic acid**

### **6.1.6 ARM F: HORMONE THERAPY + ZOLEDRONIC ACID + CELECOXIB**

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

- **Hormone Therapy** as described in **Section 6.1.1**.
- **Zoledronic Acid** 4mg 15min IV infusion every 3 weeks, for 6 treatments followed by zoledronic acid 4mg 15min IV infusion every 4 weeks up to a maximum of 2 years from the start of the treatment or until disease (including PSA) progression (see **Section 7.2**). Patients should also receive an oral supplement of 500mg calcium and 400IU vitamin D daily (Calcichew). These doses are available as a combination tablet. See **Section 6.2.1** for further information.
- **Celecoxib** 400mg *bid* until the sooner of 1 year or disease (including PSA) progression (see **Section 7.2**). See **Section 6.2.3** for further information.

### **6.1.7 ARM G: HORMONE THERAPY + ABIRATERONE**

- **Hormone Therapy (+/- RT)** as described in **Section 6.1.1**.
- **Abiraterone** will be administered as a single 1000mg daily oral dose (4 tablets to be taken together once a day) together with prednisolone or prednisone 5mg daily to prevent secondary ACTH excess.

In patients with M1 disease, treatment with abiraterone will continue from randomisation until clinical disease progression, consistent with the COU-AA-301 trial (31) i.e., abiraterone would be given for these patients until a composite of PSA progression (as defined in **Appendix J**), radiological progression (appearance of new lesions or progression of existing lesions) and clinical progression (defined as new cancer-related symptoms). It is accepted that these flexible criteria for stopping treatment with abiraterone are open to the investigator's interpretation and discretion. Patients might continue treatment beyond the first failure-free survival (FFS) event (see **Table 1** in **Section 9.2**); the first FFS event must be reported as per the other arms.

In patients with N0M0 disease or N+M0 disease undergoing radical radiotherapy, treatment would continue for 2 years or disease progression as defined for M1 patients, whichever is the sooner. Hormone therapy can be discontinued in this group at 2 years at the discretion of the local investigator (see **Section 6.1.1.A**).

For patients with N+M0 disease not planned for radical radiotherapy, treatment will continue as for patients with M1 disease until disease progression.

See **Section 6.2.4** for further information for all groups.

## **6.2 ADMINISTRATION AND DOSE MODIFICATIONS**

### **6.2.1 ZOLEDRONIC ACID**

Zoledronic acid will be administered by IV infusion in accordance with the instructions in the summary of product characteristics at a target dose of 4mg (adjusted for renal function, see below) every 3 weeks for the first 6 cycles and every 4 weeks, thereafter.

**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. FBC should be measured at least 3 monthly. Zoledronic acid should be discontinued if there is any evidence of hypersensitivity to the drug. In patients with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In rare cases, zoledronic acid treatment has been associated with the development of osteonecrosis of the jaw, particularly following dental extractions. If a patient develops osteonecrosis of the jaw then the zoledronic acid should be immediately and permanently discontinued. For full details of zoledronic acid administration and dose reductions see **Appendix F**. Contraindications, special precautions, interactions and side effects are listed in **Appendix G**.

### **6.2.2 DOCETAXEL**

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Docetaxel will be administered by IV infusion in accordance with the instructions in the summary of product characteristics at a dose of 75mg/m<sup>2</sup> (up to a maximum dose of 160mg) on day 1 of the study treatment period and then every 3 weeks, thereafter, for a maximum of 6 doses. Patients with a body surface area (BSA) greater than 2.13m<sup>2</sup> should be dosed as though they have a BSA of 2.13m<sup>2</sup>. No ideal weight should be used for BSA calculations. Prednisolone or prednisone 5mg *bid* will be given until completion of chemotherapy. Additional dexamethasone should be given pre- and post-docetaxel infusion to suppress allergic reactions.

Please note that liver function test (LFTs) should be carried out within a week before the first cycle of docetaxel if an anti-androgen has been administered. This is due to an increased risk of neutropenia associated with docetaxel use following anti-androgen administration. Treatment should be delayed if LFTs are abnormal.

For full details of premedication schedule, recommended anti-emetic regimen and dose modifications for docetaxel see **Appendix F**. Contraindications, special precautions, interactions and side effects are listed in **Appendix G**.

Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer. (16, 17)

### **6.2.3 CELECOXIB**

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

Celecoxib should be administered in accordance with the instructions in the summary of product characteristics at a dose of 400mg *bid* orally. Rarely this drug is poorly tolerated and in this instance should be discontinued; particular care should be taken with patients with a history of gastrointestinal disease and patients with significant risk factors for cardiovascular events (see **Appendix G**). Patients with confirmed severe cardiovascular history should not be in STAMPEDE (see exclusion criteria, **Section 4.2**). Contraindications, special precautions, interactions and side effects are listed in **Appendix G**. Dose reductions are not anticipated. **No new patients should be receiving this agent now within the trial.**

## **6.2.4 ABIRATERONE**

Abiraterone absorption is increased by food. The tablets should be taken at least 2 hours after food, swallowed whole with some water. No food should be eaten for 1 hour afterwards. Prednisolone (prednisone in Switzerland) should be taken as a single dose with food in the morning.

If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum alanine aminotransferase (ALT), should be measured immediately. If a rise in transaminases or bilirubin is confirmed, action should be taken as detailed in **Appendix G**.

### **6.2.4.A Steroid Dose Modifications**

Prednisone or prednisolone will be started at 5mg once daily, to prevent secondary mineralocorticoid excess. Prednisone/prednisolone dose increase of up to 10mg/day is permitted to manage mineralocorticoid-related toxicities (e.g., hypokalaemia, hypertension) which are refractory to standard management. Patients experiencing serious Cushingoid symptoms (e.g., weight gain, muscle loss) can decrease or discontinue (temporarily or permanently) steroids at the investigator's discretion. It should be noted that weight gain and muscle loss are also associated with androgen deprivation therapy.

## **6.3 TRIAL PRODUCTS**

Details of the procedures for obtaining the drugs within the trial, dispensing and disposal of unused drug are given in **Appendix E**.

Arrangements for free or discounted drugs are given in the Finance section (**Section 15**).

## **6.4 MEASURES OF COMPLIANCE/ADHERENCE**

Date of treatment, dose, delays and reasons for delays or dose modifications of all study infusions (zoledronic acid and docetaxel) will be recorded. The estimated number of abiraterone tablets taken in a given time period will also be recorded as well as any dose reductions.

## 6.5 TREATMENT DATA COLLECTION

Data will be recorded on case report forms (CRFs); the top copy/original should be sent to the MRC CTU for data entry and a copy kept at the local centre. The data to be recorded on these can be viewed in the CRF appendix (**Appendix Q**). The type of data to be recorded is detailed in the Assessments and Procedures section (**Section 7**).

## 6.6 ADMINISTRATION OF RADIOTHERAPY<sup>1</sup>

### 6.6.1 TREATMENT DETAILS

Radiotherapy will be given to appropriate patients in each of the trial arms, following a period of neo-adjuvant HT therapy, as is generally standard in UK practice. For patients receiving docetaxel, this period needs to be a minimum of 6 months after randomisation to ensure that chemotherapy is completed and toxicity resolved before RT begins. To ensure consistency of timing of administration of radiotherapy in all arms, this same 6 months period is recommended for all patients. For patients with negative nodes on axial imaging, clinicians may choose between irradiating prostate and seminal vesicles alone or including the pelvic nodes in addition. Additional staging tests such as pelvic node sampling may be considered in making this decision. Conformal or intensity modulated radiotherapy should be used in all cases. Where patients have good clinical evidence that nodes are free of tumour or patients for whom nodal radiotherapy is contra-indicated (e.g. significant bowel disease), treatment may be given to the prostate gland and seminal vesicles only. The recommended dose is 74Gy in 37 fractions or the equivalent using hypofractionated schedules. These recommendations are summarised **Figure 3. Alternative dosing schedules are permitted but must be agreed** with the STAMPEDE Trial Management Group.

#### 6.6.1.A Radiotherapy Timing

Radiotherapy should be given around 6 to 9 months after randomisation in all trial arms and, if receiving docetaxel, the patient must have recovered from any docetaxel toxicity before RT can begin.

#### 6.6.1.B Type Of Radiotherapy

Conformal or intensity modulated radiotherapy.

#### 6.6.1.C Clinical Target Volume

**CTV1:** Prostate plus seminal vesicles

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<sup>1</sup> Note: this text has been transferred into the protocol from the **Appendices** and updated

**CTV2:** Regional lymph nodes to include internal iliac and the inferior part of the common iliac nodes as used in EORTC trial 22961 (38)

**PTV1:** CTV1 plus 10-15 mm according to local practice

**PTV2:** CTV2 plus 10-20mm according to local practice

#### **6.6.1.D Radiotherapy Dose**

Prostate dose of 74Gy in 2Gy fractions or equivalent, with optional dose to the pelvic nodes of 46-50Gy in 2Gy fractions or equivalent. Higher doses may be considered if using IMRT. Alternative schedules should be agreed with the STAMPEDE Trial Management Group.

#### **6.6.2 DATA COLLECTION, NON-ADMINISTRATION OF RT AND SALVAGE RT**

The RT procedures only apply to patients treated with RT with primary intent, not those receiving salvage RT. There are two CRFs to be completed for patients receiving primary radiotherapy. All radiotherapy and acute side effects details will be recorded on the Radiotherapy Form and any late side effects will be recorded on the Late Toxicity Form.

If it is decided not to give the planned radiotherapy (for example, due to early metastatic progression or patient refusal), this should be stated on the Radiotherapy form together with the reason for non-administration of the treatment.

For patients who receive palliative radiotherapy, a Palliative Radiotherapy CRF should be completed. Details of salvage RT for relapse or palliative will be requested and completed only on the progression form.

### **6.7 NON-TRIAL TREATMENT**

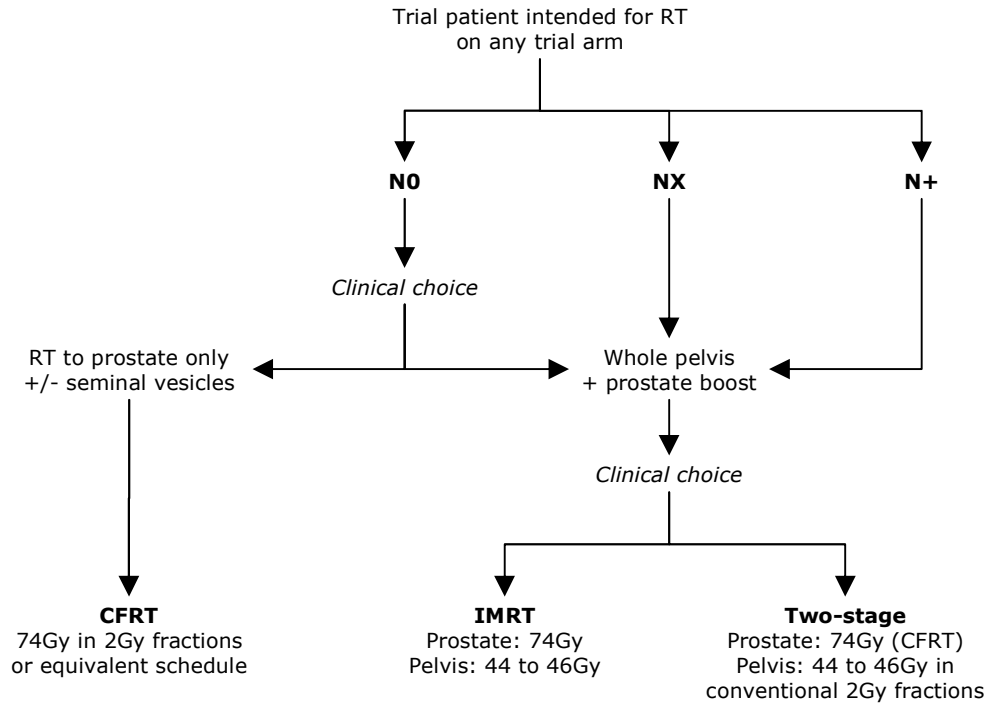
#### **6.7.1 MEDICATIONS PERMITTED**

Any additional treatment that the responsible physician feels is appropriate is permitted.

#### **6.7.2 DATA ON CONCOMITANT MEDICATION**

All concomitant medication will be recorded on the baseline form prior to randomisation and on any subsequent Serious Adverse Event forms. This should include aspirin that may be taken on a regular basis for cardiovascular disease, the use of any Non-Steroidal Anti-inflammatory Drugs (NSAID) as well as any vitamin or mineral supplements the patient is taking.

**Figure 3: Diagram for deciding recommended approach to radiotherapy**



## **7 ASSESSMENTS AND PROCEDURES**

### **7.1 FLOW CHART/SCHEDULE FOR FOLLOW-UP**

A detailed follow-up schedule is given in **Figure 4**.

#### **7.1.1 PSA MEASUREMENTS**

All patients should have PSA measured pre-hormone therapy and at weeks 6, 12, 18 and 24 and every 12 weeks, thereafter, up to 2 years post randomisation. Following this, PSA should be measured every 6 months until 5 years and annually, thereafter. For patients who do not have a scheduled hospital visit, it would be acceptable for arrangements to be made for blood samples to be drawn in a GP's surgery.

#### **7.1.2 ASSESSMENT OF TREATMENT FAILURE (DEFINITION OF PROGRESSION)**

It is not proposed to routinely assess patients for response. However, in order that objective progression can be assessed, it is necessary to have imaging taken at time of best response as judged by the treating clinician. All patients should have baseline radiological examinations as detailed in **Section 4.3.1**. In addition it is recommended that all patients should have scans or X-rays repeated at 24 weeks (and whenever clinically appropriate) if they were abnormal at baseline, particularly if they have a low PSA value on entry in to the trial making biochemical assessment of treatment failure difficult. The following events would constitute a disease progression and should be reported on a progression form:

- Biochemical failure – must be reported alongside castrate levels of testosterone if the patient has received intermittent hormone therapy (see **Appendix J**).
- Local progression
- Lymph node progression
- Progression in distant metastases
- Development of new metastases

Please note that skeletal related events (SREs) may be indicative of disease progression but can have other causes such as osteoporotic fracture. All SREs should be investigated further to establish whether or not the patient has progressed, in which case a progression form should be completed.

#### **7.1.3 ADDITIONAL SAFETY ASSESSMENT**

Due to the risk of liver toxicity and secondary hyperaldosteronism with abiraterone, patients will require **2 weekly** U+Es, LFTs and **blood pressure** measurement for the **first 12 weeks**. It is not proposed to collect the detail of these measurements unless results are

abnormal; in this instance, they should be reported as AEs (on the next Follow-up CRFs) and as an SAEs (see **Section 11**) if appropriate.

Medical review and PSA measurements follow the pattern in the control arm: visits at weeks 6, 12, 18 and 24 and every 12 weeks, thereafter, up to 2 years post randomisation. Following this, PSA should be measured every 6 months until 5 years and annually, thereafter. For patients who do not have a scheduled hospital visit, it would be acceptable for arrangements to be made for blood samples to be drawn either in a GP's surgery or in the patient's home.

#### **7.1.4 FOLLOW-UP SCHEDULES**

An individualised form with a follow-up schedule will be provided for each randomised patient. For patients who are receiving LHRH analogues, it is assumed that any additional treatment will commence within two weeks of randomisation. For patients who are due to have an orchidectomy it is recognised that surgery will have to be scheduled and the scheduling of any additional treatments may be affected by post-operative recovery. It is recommended that all patients who had abnormal radiological investigations at baseline or present with a low PSA on entry into the STAMPEDE trial should have them repeated 24 weeks after randomisation.

### **7.2 FOLLOW-UP**

Every effort should be made to follow-up all patients who have been randomised. Patients should, if possible, remain under the care of an oncologist or urologist for the duration of the trial. If care of a patient is returned to the GP, it is the responsibility of the consultant who obtained the patient's consent to participate in the trial to ensure that the data collection forms are completed. If the patient moves from the local area, arrangements should be made for trial follow-up to be undertaken by their new local centre. Details of other participating centres can be obtained from the MRC CTU. The consent of patients should be obtained for their names to be flagged for survival information through national registries (e.g. ONS in England/Wales and GRO in Scotland). If the clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

**Figure 4a: Summary of timing of case report forms**

Case Report Forms	Timing
Bone Density Risk Factor form	At randomisation
Randomisation Form	At randomisation
Baseline Form	At randomisation
Cardiovascular Assessment Form	At randomisation
Pathology Form	At randomisation. When pathology sample has been taken and sent to UCL laboratory
Pre-18 Week Bisphosphonate Form	Treatment administered every 3. Form holds data for 2 cycles. Form to be sent after 2 <sup>nd</sup> cycle given
Post-18 Week Bisphosphonate Treatment Form	Treatment administered every 4. Form holds data for 3 cycles. Form to be sent after 3 <sup>rd</sup> cycle given
Docetaxel Treatment Form	Treatment administered every 3 weeks Form holds 2 cycles. Form to be sent after 2 <sup>nd</sup> cycle given
Follow-Up Form (see fig 3b below for information on data required at follow-up)	Every 6 weeks for 6 months, then every 12 weeks until 2 years. Every 6 months until 5 years and annually thereafter
Quality of life form	Every 6 weeks for 6 months, then every 12 weeks until 2 years, every 6 months until 5 years and annually thereafter.*
Radiotherapy Form	If applicable, when primary radiotherapy course has finished.
Late Radiotherapy Toxicity Form	If applicable, 6m, 12m 24m and 36m from start of radiotherapy
Palliative Radiotherapy Form	If applicable, when the palliative radiotherapy course is completed
End of Treatment Form	When each treatment is completed (either at end of scheduled treatment or at early cessation of treatment)
Progression & Additional Treatment Form	At the first occurrence of each type of progression and whenever a patient that has progressed receives additional treatment
Serious Adverse Event Form	Following any Serious Adverse Event
Skeletal Related Event Form	Whenever a patient experiences a skeletal related event
BMD Substudy Assessment Forms	At baseline, 6, 12 and 24 months
Co-enrolment Form	When a patient is enrolled in another trial
Death Form	At Death

\*Quality of Life Study is only for first 700 patients entered into the trial and those who were recruited from the implementation of version 8.0 of the protocol . MRC CTU will inform centres of which of their patients this applies to.

**Figure 4b – Data required on follow-up forms**

Timing of follow-up	PSA	Evidence of Progression	Hormone Therapy	Cox-2 treatment	Unscheduled Visits	Toxicities
0-2 years	✓	✓	✓	✓	✓	✓
After 2 years	✓	✓	✓	-	✓	-
After Progression	-	✓	✓	-	✓	-

**Figure 5: Schedule for completion of forms by arm.**

Timing of Assessment	Baseline		Treatment		Outcomes		Freq
	Randomis <sup>n</sup>	Pre-Treatment	Zoledronic acid	Docetaxel	Follow-up <sup>ψ</sup>	QL + HE <sup>‡</sup>	
Yr 0 Wk 0	all	all				all	
Wk 6			BEF <sup>†</sup>	CE <sup>†</sup>	all	all	6 weekly
Wk 12			BEF <sup>†</sup>	CE <sup>†</sup>	all	all	
Wk 18			BEF <sup>†</sup>	CE <sup>†</sup>	all	all	
Wk 24			BEF <sup>‡</sup>		all	all	
Wk 36			BEF <sup>‡</sup>		all	all	12 weekly
Wk 48			BEF <sup>‡</sup>		all	all	
Wk 60			BEF <sup>‡</sup>		all	all	
Wk 72			BEF <sup>‡</sup>		all	all	
Wk 84			BEF <sup>‡</sup>		all	all	
Wk 96			BEF <sup>‡</sup>		all	all	
Yr 2 Month 24 (week 104)			BEF <sup>‡</sup>		all	all	6 monthly
Month 30 (week 130)					all	all	
Yr 3 Month 36 (week 156)					all	all	
Month 42 (week 182)					all	all	
Yr 4 Month 48 (week 208)					all	all	
Month 54 (week 234)							
Yr 5 Month 60 (week 260)					all	all	
annually ...					all	all	

**Key:** all=arms A-F, A=HT alone, B=HT + Zoledronic acid, C=HT + Docetaxel, D=HT + Celecoxib, E=HT + Zoledronic acid + Docetaxel, F= HT + Zoledronic acid + Celecoxib G = HT + Abiraterone

*Note: recruitment completed to both celecoxib-containing arms in April 2011 at the end of Activity Stage II*

<sup>ψ</sup> See **Figure 3** for information required at follow-up

<sup>†</sup> Form records data for two cycles

<sup>‡</sup> Form records data for three cycles

<sup>‡</sup> 1<sup>st</sup> 700 patients and those recruited from protocol version 8.0 onwards only

Radiotherapy, Late RT Toxicity, Palliative Radiotherapy Progression, SAE, End of Treatment, Co-enrolment and Death forms to be completed as required

### 7.3 TRIAL CLOSURE

For the purpose of complying with UK Clinical Regulations introduced on May 2004, the trial will be considered 'closed' when the follow-up point for the primary analysis has been reached. However, further observational follow-up of all patients enrolled in the trial will continue until all randomised patients have died. This will initially be via the hospital, but in the longer term may employ national registers.

## **8 STOPPING OF TREATMENT OR FOLLOW-UP**

Patients should be given every encouragement to adhere to protocol treatment and follow-up schedule, in order to reduce biases. However, a patient has the right to withdraw consent for participation in any aspect of this trial at any time.

### **8.1 STOPPING TRIAL INTERVENTIONS**

A patient may stop trial treatment for the following reasons:

1. Progression whilst on therapy (trial treatment **must** be discontinued in this instance)
2. Unacceptable toxicity
3. Intercurrent illness which prevents further treatment
4. Withdrawal of consent for treatment
5. Any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion
6. Intention to commence a new anti-cancer treatment due to evidence of relapse.

The reason should be recorded on the treatment and/or follow-up forms as well as the End of Treatment form. In the case of abiraterone, the disease event for stopping abiraterone may be after the first reportable failure-free survival event (see **Section 6.1.7**). Unless a patient states otherwise, it should be **assumed that consent is given to continue to record trial data**.

### **8.2 PATIENT TRANSFERS**

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. A copy of the patient's STAMPEDE CRFs will need to be provided to the new site. The patient may need to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre.

### **8.3 WITHDRAWAL FROM THE TRIAL COMPLETELY**

If a patient explicitly withdraws consent to have **any** data recorded their decision must be respected and the MRC CTU must be informed in writing. All communication surrounding the withdrawal should be noted in the patient's records and no further STAMPEDE CRFs should be completed for that patient.

Patients can change their minds about withdrawal at any time and re-consent to participate in the trial. Follow-up data should be collected **only** from the point of when consent was re-instated.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 METHOD OF RANDOMISATION

Patients will be randomised centrally using a computerised algorithm developed and maintained by the MRC CTU. Randomisation will be performed using the method of minimisation over a number of clinically important stratification factors with an additional random element. To decrease determinability, the factors are not listed here but can be found in the Statistical Design Document. From the outset, the trial had 1 control arm (A) and 5 research arms (B, C, D, E and F); from version 8.0, an additional research arm (G) is introduced.

As the control arm is the comparator arm for all the research arms, it is intended to recruit twice as many patients to the control arm as to each of the original research arms as this is the most efficient design. Therefore, the initial randomisation ratio will be 2:1:1:1:1:1. From version 7.0, accrual to the celecoxib-containing arms was halted and the allocation ratio was 2:1:1:0:1:0.

The allocation weighting for the additional arm G (version 8.0 onwards) will be 2, meaning that as many patients will be randomised to arm G as the control arm A: the randomisation ratio will be 2:2 (equivalent to 1:1 control:abiraterone). This gives an overall allocation ratio of 2:1:1:0:1:0:2. When recruitment has been completed to the ongoing original research arms B, C and E (which will be around 2 years before completion of accrual to G), the allocation ratio will be 2:0:0:0:0:0:2 (or 2:2). This is more efficient for this comparison than the 2:1 allocation ratio employed for the original research arms because of the minimal co-recruitment period; it is also anticipated that a 2:2 allocation ratio will be more appealing to patients and will maintain the excellent accrual rates.

### 9.2 OUTCOME MEASURES

The overall, definitive primary outcome measure for the trial for each comparison is overall survival (all cause mortality). The design of the trial is such that it is important to have additional intermediate outcome measures to assess each research arm as the trial progresses. These are listed in **Table 1**. The intermediate primary outcome measure is failure-free survival. The reasons for different emphases in each recruitment stage are explained in **Section 9.3**.

**Table 1: Trial Outcome Measures**

<b>Trials stage</b>	<b>Primary outcome measures</b>	<b>Secondary outcome measures</b>
<b>Pilot phase</b>	Safety*	Feasibility
<b>Activity Stage (AS) I-III</b>	Failure-free survival (FFS) <sup>†</sup>	Overall survival (OS) Toxicity Skeletal related events
<b>Efficacy Stage (ES) IV</b>	Overall survival	Quality of life Cost effectiveness Failure-free survival <sup>†</sup> Toxicity Skeletal related events

\*Based on toxicity

<sup>†</sup>Including biochemical failure (see **Appendix J**)

### 9.3 SAMPLE SIZE: PRINCIPLES AND ASSUMPTIONS

The overall design for this study is a multi-arm, multi-centre randomised controlled trial. There are five stages to the study of each research arm: Pilot Phase, Activity Stages I-III and Efficacy Stage IV. Full details of the methodology underlying the trial design are given by Royston *et al.* (39, 40) The sample size calculations were performed using the `stage2` (version 1.2.0, March 2002) and `stagen` (version 1.1.1, 18 May 2004) programs, both implemented in Stata (Stata Corp, TX) and updated using the later `nstage` program (version 1.0.3, 13-jun-2007; version 2.1.0, 28-jun-2009). (41)

The trial is designed under the assumptions in **Table 2**, and additionally, we assume a slightly higher proportion of non-metastatic than metastatic patients such that the median FFS is two years and median OS four years.

**Table 2: Hazard ratio assumptions under null and alternative hypotheses**

<b>Size of HR</b>	<b>Pilot</b>	<b>AS I-III</b>	<b>ES IV</b>
Under null hypothesis ( $H_0$ )	n/a	HR(FFS) = 1.00	HR(OS) = 1.00
Under alternative hypothesis ( $H_1$ )	n/a	HR(FFS) = 0.75	HR(OS) = 0.75

The HR of 0.75 for any research arm relative to control would translate into an absolute improvement in FFS of 10%, from approximately 50% to 60% at two years and OS of 10%, from approximately 50% to 60% at four years. A beneficial difference of this size would be clinically worthwhile and, indeed, experience tells us it may be unrealistic to expect a larger difference. Therefore, we have adequately powered the trial to detect a HR of 0.75 for overall survival. This design gives 95% power at Activity Stages I-III and 90% power at

Efficacy Stage IV for each comparison. Further details of the sample size calculations are summarised in **Sections 9.4** and **9.5** and detailed in a separate Statistical Design Document which is available on request.

Note that, from version 8.0, radiotherapy will be introduced to the majority of patients with NO M0 disease. This will likely improve the outcomes for this group. Further agents are starting to be licensed for patients with castration-refractory disease which may also improve survival rates. Improved FFS rates would delay the intermediate analyses; improved survival rates would delay the definitive analyses. The Statistical Design Document includes models where median survival is estimated at 5 years rather than 4 years. The trial is powered to detect a difference in relative improvement and the analyses will be performed when a pre-planned number of events has been reported in the control arm, rather than after a certain number of patients have been recruited or a certain amount of time elapsed. **Sections 9.4** and **9.5** provide more detail.

## **9.4 SAMPLE SIZE ISSUES AND TRIAL STAGES: ORIGINAL RESEARCH ARMS (B-F)**

### **9.4.1 PILOT PHASE: ORIGINAL RESEARCH ARMS (B-F)**

It is anticipated that 210 patients will be recruited to the Pilot Phase from a limited number of centres over a one year period. Approximately 60 patients will be randomised to the control arm and 30 patients to each of the five research arms each of which will be assessed for safety and feasibility. If recruitment proves infeasible or any of the research arms prove unsafe or not feasible to administer (e.g., poorly tolerated or unexpected toxicity) recruitment to these arms will be discontinued. There are already considerable safety data on the use of docetaxel and zoledronic acid in patients with malignancies including prostate cancer, and on the use of Cox-2 inhibitors (including celecoxib), although mainly from patients with musculoskeletal disorders. There were fewer data on the combination arms, but it was thought very unlikely that any of the research arms would be discontinued during the Pilot Phase; (indeed, recruitment continued beyond this point). Safety data will continue to be assessed throughout the trial. When 210 patients have been on the trial for a minimum of 18 weeks, the independent Data Monitoring Committee (IDMC) will then review the data from the Pilot Phase. Recruitment will continue to the trial during this period as equipoise will remain.

### 9.4.2 ACTIVITY STAGES I-III: ORIGINAL RESEARCH ARMS (B-F)

In the sample size calculations, we assume that all research arms successfully pass through the Pilot Phase to Efficacy Stage I and that patients will be recruited at a rate of approximately 500 per year. This is faster than in the Pilot Phase because the trial will recruit from additional centres, both in the UK and internationally. The analysis of Activity Stages I, II and III are planned for when around 113, 216 and 334 failure-free survival events have been observed in the control arm, respectively.

The Activity Stage analyses will comprise pairwise comparisons of FFS between the control arm and each of the 5 research arms ( $i=B, C, D, E, F$ ). Let  $HR_i(\text{true})$  represent the hazard ratio (HR) of the  $i^{\text{th}}$  research arm to the control arm, and  $HR_i(\text{observed})$  the observed value. Discontinuation of accrual of further patients will be considered for the  $i^{\text{th}}$  research regimen at each of Activity Stages I-III according to the guidelines in Table 3.

**Table 3: Guidelines for stopping accrual to the  $i^{\text{th}}$  original research arm**

Activity Stage	Number of control arm events	Consider discontinuation if $HR_i(\text{observed})$ is...
I	~113	>1.00
II	~216	>0.92
III	~334	>0.89

### 9.4.3 EFFICACY STAGE IV: ORIGINAL RESEARCH ARMS (B-F)

The analysis of Efficacy Stage IV for the original research arms will be performed when around 403 deaths have been observed in the control arm. This would give 90% power to detect the targeted hazard ratio of 0.75 at one-sided significance level of 0.025. The actual length of this stage, balancing continued accrual with just follow-up, depends on the number of arms passing through to further recruitment from Activity Stages I-III and the observed accrual and event rates.

### 9.4.4 SAMPLE SIZE FOR ORIGINAL RESEARCH ARMS (B-F)

Assuming an accrual rate of 500 patients/year, between 2800 and 3600 patients are planned to be entered into the original research comparisons of the trial over a period of 5½ and 7 years. The exact number of patients to be entered depends on the observed accrual rate<sup>2</sup> and the observed event rate, which is, in itself, dependent on the mix of patients joining the trial from the broad spectrum of eligibility. The primary analysis on overall survival requires around 403 deaths to be observed on the control arm. Accrual will continue until the main

analysis can be foreseen so that the overall duration of the trial is as short as possible (longer accrual facilitates this) and so that few, if any, patients remain on treatment when the main results are released. The statistical team will monitor and project the timelines using the `artpep` command in Stata.

## 9.5 SAMPLE SIZE ISSUES AND TRIAL STAGES: ADDITIONAL RESEARCH ARM G

### 9.5.1 PILOT PHASE: ADDITIONAL RESEARCH ARM G

A similar approach will be followed for the additional research arm G as detailed for the original research arms in **Section 9.4.1**. The IDMC will review safety data, in the context of data from the control arm, when the first 30 patients allocated to arm G have been on trial for 18 weeks.

Furthermore, an additional review of safety will be performed when 30 patients with newly diagnosed non-metastatic disease have been allocated to arm G and have been on trial for 18 weeks.

### 9.5.2 ACTIVITY STAGES I-III: ADDITIONAL RESEARCH ARM G

The same principles will be applied to the new comparison as to the previous comparisons. The notable difference will be in the accrual rate to this comparison which is anticipated to be higher. There are two reasons for this. First, STAMPEDE started to recruit slowly in only a limited number of pilot sites. As more sites have been activated, including internationally, accrual has increased. At the time of version 8.0 of the protocol, monthly accrual to the study was averaging around 60 patients/month (over 700 patients/year). Second, there is an equal allocation ratio for the abiraterone arm compared to the control arm. It is this different allocation ratio which means that the number of control arm events required to trigger the intermediate analyse is different for the assessment of abiraterone to the assessment of the original research arms. This is shown in **Table 4**.

**Table 4: Guidelines for stopping accrual to the additional research arm G**

Activity Stage	Number of control arm events	Consider discontinuation if $HR_G(\text{observed})$ is...
I	~75	>1.00
II	~142	>0.92
III	~221	>0.89

<sup>2</sup> Note in version 8.0: accrual has been exponential rather than constant.

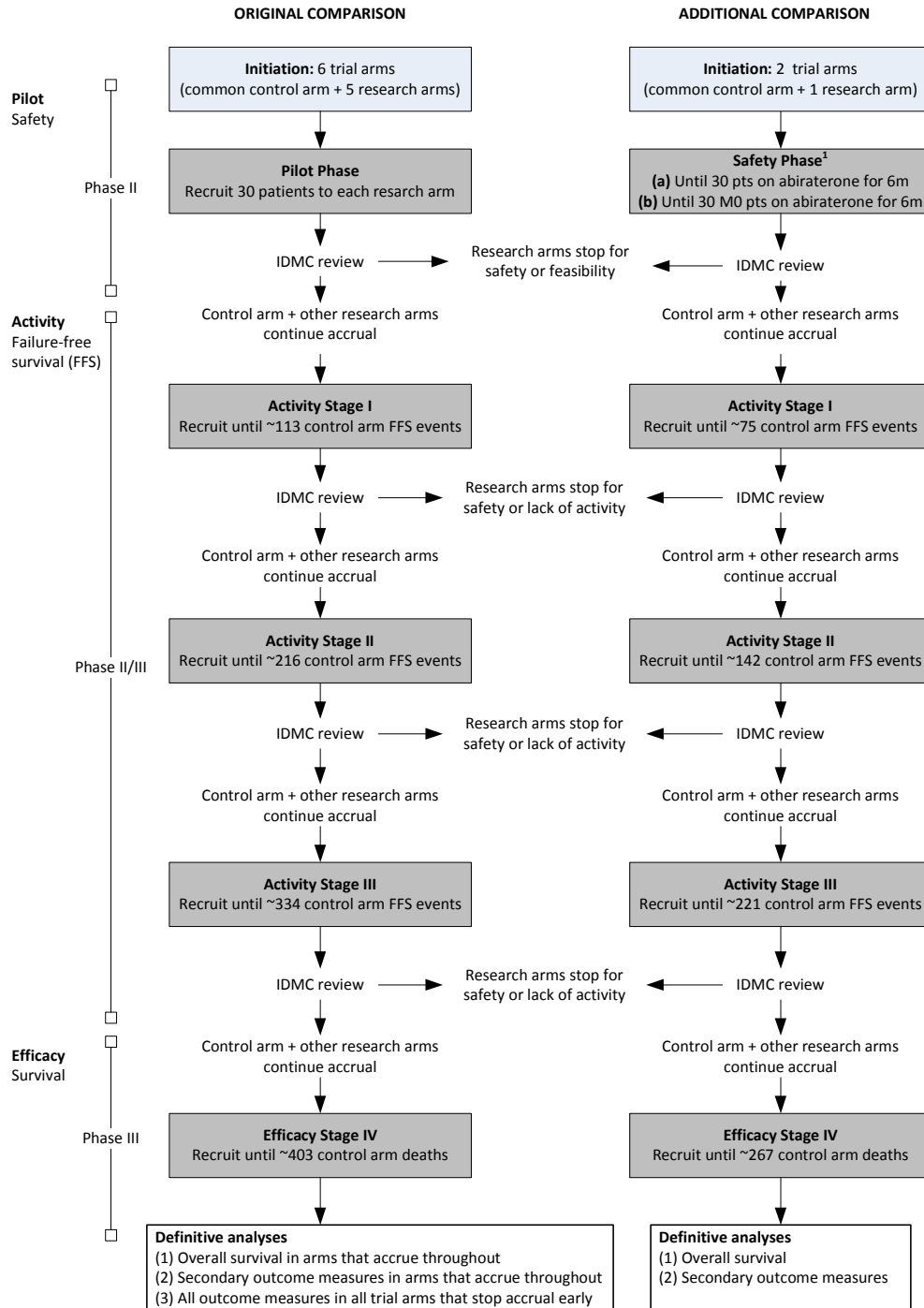
### **9.5.3 EFFICACY STAGE IV: ADDITIONAL RESEARCH ARM G**

The analysis of Efficacy Stage IV for the additional comparison will be performed when around 267 deaths have been observed in the control arm. This would give 90% power to detect the targeted hazard ratio of 0.75 at one-sided significance level of 0.025.

### **9.5.4 SAMPLE SIZE FOR ADDITIONAL RESEARCH ARM G**

Accrual will stop early if arm G is not showing sufficient evidence of activity, just as for research arms B to F. Up to around 1500 patients will join the abiraterone comparison with half allocated to the research arm. Providing the accrual rate remains above 50 patients/months, accrual will be halted when 1500 patients have been recruited or after 3 years, whichever is the sooner. The total number of patients joining this comparison depends on the same issues as for the original comparisons (notably, observed accrual and event rates) but also the length of time that the original research arms co-recruit alongside the additional research arm. It is assumed that this will be for around 1 year. The sample size calculations and projected durations are fairly robust to changes in the co-recruitment with the original research arms and future co-recruitment of any further research arms which the Trial Management Group may introduce. This is detailed in the Statistical Design Document.

**Figure 6: Progress Of STAMPEDE Through The Trial Stages**



**Notes**  
<sup>1</sup> (a) ~9 months, (b) ~12 months

## **9.6 FURTHER NOTES ON TRIAL DESIGN**

### **9.6.1 OVERALL SAMPLE SIZE**

There is no formal overall sample size target, but the numbers of patients required for each comparison are detailed in **Sections 9.4** and **9.5**. It is expected that around 4,000 patients will likely be recruited overall.

### **9.6.2 FACTORIAL DESIGN**

We note here that we have not employed a factorial design in this trial because we anticipate the possibility of synergy between hormone therapy, zoledronic acid and docetaxel and between hormone therapy, zoledronic acid and celecoxib. It would not be possible to assess any such interactions reliably in a factorial trial (see the Statistical Design Document for further details).

## **9.7 INTERIM MONITORING AND ANALYSES**

Formal interim analyses of the accumulating data will be performed at regular intervals (approximately annually) for review by an Independent Data Monitoring Committee (IDMC) (see also **Section 16**). These analyses will be performed by the trial team at the MRC CTU. Only patients randomised contemporaneously will be included in the comparison of each research arm against control ie patients allocated to the control arm prior to version 8.0 will *not* contribute to the comparison of abiraterone (A vs G).

The IDMC will be asked to give advice on whether the accumulating data from the trial with the guidelines for discontinuation of accrual for Activity Stages I-III, together with results from any other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including those entering patients into the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the Trial Steering Committee (TSC, see **Section 16**) as to whether the trial should continue in its present form. While the trial is ongoing the accumulating data will remain confidential.<sup>3</sup>

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<sup>3</sup> At the end of the second Activity Stage for arms D and F, the IDMC recommended and the TSC agreed to stop recruitment to both celecoxib-containing arms, and to recommend stopping further treatment with celecoxib.

## 9.8 OUTLINE ANALYSIS PLAN

Analyses will be performed on an intention-to-treat basis. The standard unadjusted log-rank approach will be applied to analyses of FFS and OS. The impact of potential confounders including the stratification factors used at randomisation will be considered in a Cox proportional hazard model; restricted mean survival methods will be used preferentially if the proportional hazards assumptions required for Cox models cannot be supported. The  $\chi^2$  test or Mann-Whitney test will be implemented for categorical data comparisons, including toxicity, as appropriate. The primary outcome measures in **Table 1** (see **Section 9.2**) will be considered for all arms of the trial at each phase, but the main emphasis will be placed on the comparison of the research arms that have continued to recruit throughout the trial.

### 9.8.1 PILOT / SAFETY PHASES

The Pilot Phase randomised patients between all the trial arms so that the results from these patients can be included in the main trial. Feasibility is considered in terms of the acceptability of the trial randomisation and reported toxicities and adherence to trial medication. Centres participating in the Pilot Phase for the original research arms were required to keep an anonymised log of all patients assessed for trial eligibility (see protocol version 2.0) so that the number of patients who did not participate in the study and the number of eligible patients who choose to not participate in the study could be summarised (reasons for non-participation were collected where the patients was willing). This will not be repeated for new research arms like arm G introduced in version 8.0.

On the patients who are randomised, we shall describe the incidence of expected and unexpected severe toxicities and adverse events/reactions (see **Section 11**) to decide whether to continue with research arms beyond the Pilot Phase. As indicated above, we do not anticipate that recruitment to the research arms will be discontinued after the Pilot Phase, as there is considerable experience with zoledronic acid and docetaxel when combined with HT, while Cox-2 inhibitors generally have a good toxicity profile. Although there are limited data on the combinations, we do not expect severe toxicity.

### 9.8.2 ACTIVITY AND EFFICACY STAGES

The approach to analysis of these stages is summarised within the sample size calculations (see **Section 9.4.3**). Each research arm will be compared in a pairwise fashion against the control arm.

Full details are available in the Statistical Analysis Plan.

## **10 MONITORING & QUALITY ASSURANCE**

### **10.1 MONITORING AT MRC CTU**

Data provided to the MRC CTU will be checked for missing or unusual values (range checks) and consistency over time. If missing or questionable data are identified, staff at the MRC CTU will request that the data be clarified. The exact procedures for data clarification and the amendment of CRFs will be described in the trial specific SOPs and instructions will be sent to all STAMPEDE institutions as soon as they have been approved to participate in the trial. The MRC CTU will also send reminders for any overdue data.

### **10.2 DIRECT ACCESS TO DATA**

Collaborating institutions should be aware that direct access to patient data by MRC CTU staff may be required for trial-related monitoring or audit. Patient consent for this will be obtained as part of the general trial consent process.

### **10.3 VISITS TO INVESTIGATOR SITES**

A selection of institutions will be visited at least once during the course of the STAMPEDE trial. The MRC CTU will give the responsible investigator adequate notice of the monitoring visit to allow adequate time, space and staff for these visits. The standard operating procedures (SOP) for monitoring are available from the MRC CTU.

After the monitoring visit the monitor will complete a site visit report. This report will be circulated to the TMG for comment. Once the TMG have reviewed the report and agreed on any recommendations the monitor will finalise the report and send a copy to the Principal Investigator (PI) at the site. A copy will also be sent to the CI for the trial and another copy will be kept in the MRC CTU STAMPEDE trial master file.

### **10.4 CONFIDENTIALITY**

All information collected during the course of the research will be kept strictly confidential. In addition, all procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998. No individual patients will be identified when the results of the trial are published.

Patients will be asked for permission for information about their health status to be obtained from the Office of National Statistics (ONS) or via the NHS Strategic Tracing Service or

similar by the Medical Research Council, if necessary. In addition, patients will be asked for permission to inform their GP of their involvement in the STAMPEDE trial.

## 11 SAFETY REPORTING

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

### 11.1 DEFINITIONS

The safety reporting definitions from ICH GCP apply in this trial protocol. These definitions are given in **Table 4**.

**Table 4: Event Terms and Definitions**

Term	Definition
<b>Adverse Event (AE)</b>	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
<b>Adverse Reaction (AR)</b>	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
<b>Unexpected Adverse Reaction (UAR)</b>	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
<b>Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none"> <li>• results in death</li> <li>• is life-threatening*</li> <li>• requires hospitalisation or prolongation of existing hospitalisation**</li> <li>• results in persistent or significant disability or incapacity</li> <li>• consists of a congenital anomaly or birth defect</li> <li>• Other important medical condition***</li> </ul>

#### Clarifications and Exceptions

\*The term 'life-threatening' in the definition of 'serious' 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 which hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

\*\*\*Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Pregnancy occurring in a STAMPEDE patient's partner during the patient's participation in the trial, must be reported to the MRC CTU within the same timelines as an SAE and classified as an 'other important medical condition' on the SAE form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome to the mother or child should be reported.

### **11.1.1 TRIAL-SPECIFIC EXEMPTIONS**

Disease progression or death as a result of disease progression are not considered to be SAEs and should be reported on the STAMPEDE Progression Form or Death Form.

The following situations that fulfill the definition of an SAE are excluded from expedited notification on an SAE form and should be reported only on the STAMPEDE follow-up form

- Elective hospitalisation and surgery for treatment of locally advanced or metastatic prostate cancer or its complications
- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment

## **11.2 INSTITUTION/INVESTIGATOR RESPONSIBILITIES**

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity (symptoms) section of the Follow-up CRF and sent to the MRC CTU within one month of the form being due. SAEs/SARs should be notified to the MRC CTU as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (<http://ctep.cancer.gov/reporting/index.html>). A flowchart is given in **Appendix O** to help explain the notification procedures. Any questions concerning this process should be directed to the MRC CTU in the first instance.

### **11.2.1 INVESTIGATOR ASSESSMENT**

#### **11.2.1.A Seriousness**

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is **serious** using the definitions given in Table 4. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the MRC CTU notified.

### 11.2.1.B Causality

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 5. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

**Table 5: Assigning type of SAE through causality**

Relationship	Description	Event Type
<b>Unrelated</b>	There is no evidence of any causal relationship	Unrelated SAE
<b>Unlikely</b>	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 treatment).	Unrelated SAE
<b>Possible</b>	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after 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 treatments).	SAR
<b>Probable</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
<b>Definitely</b>	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

### 11.2.1.C Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event. Please see **Appendix G (Table G.2)** for a list of expected toxicities associated with the drugs being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR.

### 11.2.1.D Notification

Investigators must notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU indefinitely (i.e. no matter when they occur after randomisation).

### **11.2.2 NOTIFICATION PROCEDURE:**

1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.
2. Send the SAE form by fax to the MRC CTU. **Fax Number: + 44 (0) 20 7670 4818**
3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

### **11.3 MRC CTU RESPONSIBILITIES**

Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the research ethics committees as appropriate.

The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

## **SAE REPORTING**

**Fax to 020 7670 4818 within 24 hours of becoming aware of the event**

## **12 ETHICAL CONSIDERATIONS AND APPROVAL**

### **12.1 ETHICAL CONSIDERATIONS**

This is a randomised trial therefore neither the patients nor their physicians will be able to choose the patients' treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of patients receiving each of the different treatments are similar.

Hormone therapy alone is the standard treatment for these forms of prostate cancer. Patients will be randomised to one or two of the newer treatments in combination with hormone treatment. The trial employs an unequal allocation ratio for efficiency, these are explained in detail in the patient information sheet.

The newer combined treatment options are being assessed in a detailed and systematic fashion in this trial. There is some evidence to suggest that the newer treatment options *may* have advantages over standard treatment (hormone therapy) alone with regards clinical outcome, but this is not confirmed and toxicity may be increased. This trial will follow a large group of men who have been randomly allocated to either the standard treatment (hormone therapy alone) or the newer combined treatment options in order to measure the benefits of the new treatments. The patients will also be followed-up for toxicity and safety issues, so that any benefits can be weighed against any negative aspects.

Patients participating in the trial will have some additional hospital visits and some extra blood samples taken compared to patients who are not participating in the trial, with the amount varying according to the allocated treatment. Sometimes the blood samples can be taken when the patient is attending hospital for treatment, anyway. On some of the trial arms, the patient may have to make additional visits to the hospital for the blood sample to be taken, although in some cases it may be possible for the blood sample to be taken in the GP's surgery. The additional visits and blood samples are to ensure that follow-up of patients is comparable in all the treatment groups. The blood samples will also be used for genetic and serum marker studies, where this information will be considered with clinical data. Blood samples will be link-anonymised. There will be no feedback to individual patients.

If new information emerges during the course of the trial which may affect the treatment or follow-up of patients who have joined the trial, information will be provided through the study doctor.

## **12.2 ETHICAL APPROVAL**

The protocol has a Favourable Opinion from an appropriate Research Ethics Committee, according to national guidelines. Additionally, each site must also obtain management permission for research (R&D approval) from the relevant host organisations before patients can be entered into the trial. The patient's informed consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Patient information sheets and patient consent forms are given in **Appendix B**.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his further treatment.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (<http://www.mrc.ac.uk>).

## **13 REGULATORY APPROVAL**

This trial has been approved in the UK by the MHRA and will be conducted under a CTA (Ref: 00316/0026/001-0001) in the UK.

The trial has been approved in Switzerland by Swissmedic (Ref: 2009 DR 3235).

## **14 INDEMNITY**

The MRC and NHS are both publicly funded bodies and are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury.

The MRC will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of trial or other work supported by MRC. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. The MRC acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in MRC-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in an MRC-supported study. MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not.

The Swiss Group for Clinical Cancer Research (SAKK) have provided trial-specific insurance to provide indemnity for Swiss sites against claims relating to non-negligent harm.

## **15 FINANCE**

STAMPEDE is funded by the Clinical Trials Advisory Awards Committee (CTAAC) (on behalf of Cancer Research UK, Medical Research Council, and other charities). The trial has National Cancer Research Network (NCRN) approval and, therefore, local NCRN funds may be available at each centre to support entry of patients into this trial.

Zoledronic acid is manufactured by Novartis. Novartis have agreed to provide an educational grant to support the conduct of this study. Novartis have also agreed to supply the study drug, zoledronic acid free of charge for patients participating in the study.

Docetaxel is manufactured by Sanofi-Aventis Pharma. They have agreed to supply the study drug, docetaxel at a discounted rate for patients that are participating in the trial and to provide an educational grant to support the conduct of the study. The Department of Health has agreed to provide a central subvention as follow: £1,787 per patient randomised to arms C and E of the trial and prescribed docetaxel. This amount is payable in respect of a hospital trust randomising more than 3 patients. For more details contact the STAMPEDE Trial Manager.

Celecoxib is manufactured by Pfizer. They agreed to supply free drug and provide funds to distribute drug to participating sites.

Abiraterone is manufactured by Janssen Pharma PV (pharmaceutical companies of Johnson & Johnson). They have agreed to provide free drug and funds to distribute drug to participating sites and to help support the conduct and management of the trial.

## **16 TRIAL COMMITTEES**

### **16.1 TRIAL MANAGEMENT GROUP (TMG)**

A Trial Management Group (TMG) has been formed comprising the Chief Investigator, other co-investigators and members of the MRC CTU. The membership of the TMG may be expanded if other groups of trialists wish to participate. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference at least 3 monthly and in person as needed. The TMG members are detailed in **Appendix K**.

Further details of TMG functioning are provided in the TMG charter (available on request)

### **16.2 TRIAL STEERING COMMITTEE (TSC)**

A Trial Steering Committee (TSC) has been formed to provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet regularly.

Further details of TSC functioning are provided in the TSC charter (available on request)

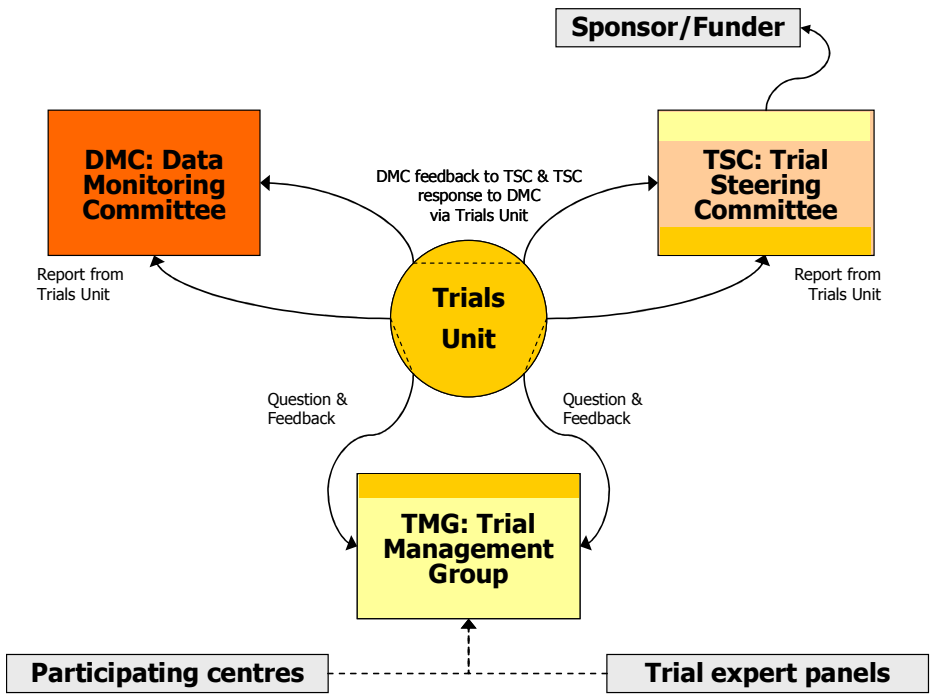
### **16.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)**

An Independent Data Monitoring Committee (IDMC) has been formed. The IDMC will be the only group who sees the confidential, accumulating data to the trial. Reports to the IDMC will be produced by the MRC CTU. The IDMC will meet within 6 months of the trial opening with the frequency of meetings dictated by the IDMC. The IDMC will consider data in accordance with the analysis plan (see **Section 9.5**) and will be advisory to the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued.

From version 8.0 onwards, any recommendation from the IDMC to stop recruitment to one or more trial arms will be acted upon immediately, pending ratification from the TSC. As this period between meetings should be very short, sites would not be notified until after the TSC have made a decision. IDMC recommendations based on emerging safety issues would be discussed with sites promptly.

Further details of IDMC functioning and the procedures for interim analysis and monitoring are provided in the IDMC charter (available on request).

**Figure 7: Diagram of relationships between trial committees**



## **17 ANCILLARY STUDIES**

### **17.1 QUALITY OF LIFE**

A quality of life (QL) study is being performed to assess the impact of each treatment arm on the quality of patient's lives and participation in this study was limited to the first 700 patients recruited (this was reached in September 2008) patients. The QL study re-opened from the implementation of version 8.0 of the protocol. The EORTC QLQ-C30 with the prostate-specific module QLQ PR25 will be used. Key items for assessment are pain reduction for patients with metastatic disease and urinary symptoms for patients with locally advanced disease. In addition specific hypotheses will be generated for each of the research arms. The EuroQol (EQ-5D) (42) will be used in the study as a generic measure of health-related quality of life which can be linked to public preferences. These data will be used to calculate quality-adjusted life-years as part of the economic evaluation (see **Section 17.2**). Patients who were recruited into the QL study, should continue on the study throughout the trial. Questionnaires should be self-administered, although it is recommended that a key person (e.g. research nurse) at each centre be responsible for the data collection to optimise compliance and completeness of the data.

The QL and the HE questionnaires should be completed without conferring with friends or relatives and all questions should be answered even if the patient feels them to be irrelevant.

The responsible person should check each questionnaire for its completeness, ensuring that the correct date of completion and patient identifiers are present. The research nurse should approach patients at appropriate clinical visits to complete a questionnaire. If no clinical visit is scheduled for the patient (with a window of 4 weeks around the expected date) the nurse should organise the completion of the questionnaire, by post or by a visit to the patient at home (or in a hospice).

### **17.2 HEALTH ECONOMICS**

A health economics (HE) sub-study will be performed. Core resource use information will be collected, using CRFs on days in hospital (by speciality) and outpatient visits. Data being collected on concomitant medication will also be used in the economic analysis. Information on patients' use of primary care and community-based services will be collected as additional questions in the QL questionnaire. Costs will be calculated on the basis of representative UK unit costs at the point of analysis. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs). Quality adjustments will be based on patients' responses to the

EQ-5D health status measure which will be administered at baseline and each point of follow-up as part of the QL questionnaire. A cost-effectiveness analysis will compare all regimens in Activity Stage IV.

## **17.3 TRANSLATIONAL SUB-STUDIES**

### **17.3.1 DNA ANALYSIS**

Blood samples from as many patients as possible will be collected for future research. With patient consent, an additional droplet of blood sample will be collected and stored for DNA and protein analysis in order to try to identify molecular features of clinical significance.

Blood samples should be sent directly to the central laboratory on the FTA elute cards provided. Patient information sheets and consent forms which highlight this research are given in **Appendix B**, while details of specimen collection, posting and contact details are given in **Appendix D**.

### **17.3.2 TISSUE MICROARRAY**

Patient consent will be sought to utilise paraffin embedded tissue for the construction of tissue microarrays from needle cores. One needle biopsy will be selected for microarray and the remaining tissue will be returned to the originating histopathologist. Given the entry criteria for the trial, the majority of patients will have extensive disease in the diagnostic needle core biopsies, in contrast to men with localised, low grade disease. Consequently, removal of one core is unlikely to compromise any subsequent histopathological assessment. Details regarding transfer of samples will be issued at the time of construction of the micro array.

### **17.3.3 BONE MINERAL DENSITY**

In selected centres, patients will be asked to participate in a bone mineral density sub-study. The aim of this sub-study will be to evaluate the long-term effects of the treatments used in STAMPEDE on bone health. Further details in regard to this study can be found in the Patient information sheets and consent forms (different versions for use when a centre is participating in the Bone Mineral Study) in **Appendix B** and in the Bone Mineral Density sub-protocol in **Appendix O**.

In addition, a number of sub-studies are being proposed using blood or urine samples from selected centres. We will ask patients to consent to the collection of material on the basis

that separate Ethical Approval will be obtained for each sub study prior to any use of the samples.

## **18 PUBLICATION**

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the TMG has published its report. The TMG together with the STAMPEDE collaborators will form the basis of the writing committee and decide on the nature of publications. Any release, of efficacy or safety data, presentation or publication will be agreed with the TSC according to the terms of their charter.

All publications will acknowledge the participating centres and clinicians, and these will be detailed in an appendix to the main report. Papers will have named authors determined by the TMG according to the following principles:

- (1)** To be as inclusive as possible where this is practicable
- (2)** To ensure that there is justification for anyone to be named as an author
- (3)** Reasons for nomination for authorship may include: trial design; grant holding; day-to-day trial oversight (TMG membership); analysis; discussion and interpretation of data; representation for key groups; active participation at large recruiting sites. It should be accepted that the people qualifying for authorship will vary over time. In addition, key positions will vary depending on the nature of the publication: clinical lead for clinical papers, statistician lead for methodology papers, translational papers may be lead by authors not on the main TMG if appropriate (e.g., the bone sub-study). In the event of any dispute related to authorship or data release, the TSC will be responsible for making the executive decision.

In the manuscript, a full list of sites and the number of patients recruited will be provided. In the presentations, this list of sites will also be shown. The term "the STAMPEDE investigators" will clearly be stated and relevant names included in the presentation credits.

## **19 PROTOCOL AMENDMENTS**

### **19.1 PROTOCOL**

#### **19.1.1 AMENDMENTS MADE TO SECTIONS IN PROTOCOL VERSION 1.0 (MAY 2004)**

1. Administrative changes such as typos, word change etc.
2. Name additions/changes to:
  - TMG members
  - TSC members
  - IDMC members
3. 'General Information' Section – additional information re. Abridged version of protocol
4. Section 1.2 – Figure 1, Celecoxib duration amended
5. Section 1.3 – Figure 2, addition of cardiovascular assessment form, name and timings amended
6. Section 2.3 – Docetaxel information updated
7. Section 2.4 – Additional text re dose and duration justification for Celecoxib use.
8. Section 3 – Title change and content updated
9. Section 4.2 – New exclusion criteria added
10. Section 4.3.1 – New investigations added and additional text re testosterone measurements and additional text re. prior celecoxib treatment
11. Section 6.1.4 – Celecoxib duration amended
12. Section 6.1.5 – Additional text re. Co-administration of docetaxel and bisphosphonates
13. Section 6.1.6 – Celecoxib duration amended
14. Section 6.2.2 – additional docetaxel information
15. Section 6.2.3 – addition of CV event history
16. Section 11 – Safety reporting updated
17. Section 12.1 – Additional text re. the collection of blood for genetic and serum marker studies
18. Section 15 – Additional information re. Central Subvention for docetaxel arms

#### **19.1.2 AMENDMENTS MADE TO SECTIONS IN PROTOCOL VERSION 1.1 (MAY 2005)**

1. Section 6.2 Administration and Dose Modifications, subsection 6.2.1 Zoledronic Acid

#### **19.1.3 AMENDMENTS MADE TO SECTIONS IN PROTOCOL VERSION 2.0 (JUN 2005)**

1. General Information section – SAE reporting fax number and timeframe added.
2. Section 1.2 – Addition of anti-androgen use for M0 patients as a method of HT
3. Section 1.2 – Increase in amount of blood needed & addition tissue sample request.

4. Section 1.3 Trial Documentation updated to include new table detailing trial documentation ahead of accreditation, the inclusion of the radiotherapy forms and correct case report form timings
5. Section 2.1 – Addition of anti-androgen use for M0 patients as a method of HT
6. Section 4.1.3 – Inclusion criteria Vii “Normal testosterone prior to hormone treatment” removed.
7. Section 4.1.3 - ¶note has been omitted and moved to section 4.2 (see number 8)
8. Section 4.2 – Exclusion criteria added to exclude patients with active peptic ulceration, gastrointestinal bleeding and inflammatory bowel disease.
9. Section 4.2 – Exclusion Criteria added to exclude patients with planned major dental work
10. Section 4.3.1 - All blood test timelines changed from 14 days to 28 days.
11. Section 4.3.1 – Hormone Therapy pre-randomisation deadline extended from 4 weeks to 12 weeks.
12. Section 4.3.1 – Additional information regarding the use of NSAIDs and cox-2-inhibitors before coming on to the STAMPEDE study and once commenced on study treatment
13. Section 4.3.2 – Updated to ask for all vitamins and minerals the patient is taking to be recorded.
14. Section 4.3.3 – Updated to include the extra blood required and the request for consent of patients’ tissue samples.
15. Section 6.1.1 – Addition of anti-androgen use for M0 patients as a method of HT
16. Section 6.1.6 – Addition of the calcium & vitamin name “calcichew”.
17. Section 6.6.2 – asking also to collect vitamins and minerals under concomitant medication.
18. Section 6.6.3 – New section to inform investigators that patient’s, who they wish to give radiotherapy to, are also eligible for STAMPEDE
19. Section 6.6.4 – New section to detail what data is being collected on the radiotherapy given to patients.
20. Section 7.1; figure 4 – Addition of radiotherapy form and in note, addition of AA alone
21. Section 7.1.2 – omission of repeated scans and x-rays at 24 weeks, also omitted in note under figure 4.
22. Chapter 11 – Safety reporting section updated
23. Section 17.3 – Increase in amount of blood needed & additional tissue sample request.

#### **19.1.4 AMENDMENTS MADE TO SECTION IN PROTOCOL VERSION 3.0 (JUL 2006)**

Front Cover - NCRN logo added for accuracy

Front Cover - Clafication that protocol developed with NCRI rather than on behalf of

Front Cover - Clarification the it is a 6 arm trial

General Information section - MRC CTU staff section updated

Section 1.2 – Statistics section updated.

Section 1.2 - Additional research paragraph updated to reflect additional studies and for clarification of terms

Section 1.2 - Blood collection volume changed to reflect new technique used

Section 1.3 (figure 3) - Table showing case report form schedule updated to reflect clarification of follow-up schedule and addition of new CRF (End of Treatment)

Section 2.2 - AS changed to HT (clarification of terms)

Section 2.3 - Updated in information in regard to use of docetaxel added to reflect up to date practice

Section 2.5 - Sub-headings numbered for consistency

Section 3.0 - Information in regard to the Pilot Phase now written in past tense as Pilot Phase has now been completed

Section 4.1.1 - Inclusion criteria extended so that patients who fulfil 2 out of the three of the first inclusion criteria can be eligible.

Section 4.3.1 - Change in time scales by which baseline investigations need to be completed.

Section 4.3.1 - Clarification that chest X-ray is only required if chest is not included in the CT

Section 4.3.1 - Removal of 12 week timeline for baseline PSA test to be performed. (Stipulation that it must be performed before start of HT)

Section 4.3.2 – Information added in regard to time allowed from randomisation to start of treatment

Section 4.3.3 - Additional research paragraph updated to reflect additional studies and for clarification of terms

Section 4.3.3 - Blood collection volume changed to reflect new technique used

Sections 6.1.2-6.1.6 - Androgen Suppression replaced with Hormone Therapy for consistency of terms

Section 6.2.2 - '(Taxotere)' Removed for consistency

Section 6.2.2 \_ information added in regard to the need to closely monitor liver function prior to docetaxel administration

Section 7.1 - Page number reference updated

Section 7.1.1 - PSA measurement timings updated to accurately reflect follow-up schedule

Section 7.3 (Table 4) - Table and key updated to accurately reflect follow-up schedule and to include information about new CRFs and removal of withdrawal CRF

Section 8 - Rewording for clarification of definition of trial withdrawal

Section 8.1 - Instruction that withdrawal from trial treatment should be recorded on End of Treatment Form rather than withdrawal form

Section 8.1 - Information updated to emphasise that trial treatment must be discontinued following a progression

Section 8.2- Information added in regard to patient transfers

Section 8.3 - Instruction that withdrawal from trial completely must be notified in writing to the MRC CTU rather than included on withdrawal form

Section 9 and Summary – Target event numbers updated to reflect the slightly revised numbers obtained by using -nstage- which is the new, recommended program for MAMS trials

Sections 11.1 and 11.2 - Form numbers removed to allow for future changes in numbering

Section 11.2 – Reference to toxicity grading website added

Section 11.2.1 - Reference to table in appendix G added

Section 12.2 - 'Suggested' removed from 'Suggested patient information sheets'

Section 13 - CTA reference added

Section 17.3 - Information added to reflect new blood collection method for DNA analysis and in regard to additional translational studies for which funding has recently been approved

### **19.1.5 AMENDMENTS MADE TO PROTOCOL VERSION 4.0 (DEC 2007)**

General Information Section - Randomisation and SAE reporting details sections clarified

Section 1.2 and throughout protocol - Efficacy Stages 1-111 renamed to Activity Stages 1-111 for accuracy and clarity

Section 1.2 - Follow schedule corrected

Section 4.1.2 - Inclusion criteria widened to include high risk relapsing patients, that would not have met the previous PSA based criteria

Section 4.1.3 - Note added to reference location of WHO performance status definitions

Section 4.2 - Notes added to reference locations of toxicity gradings and NYHA classifications

Section 4.3.1 - Timings of baseline scan information changed to accurately reflect most common current practice

Section 6.1.1 - Information about use of LHRH antagonists to ensure that the protocol accurately reflects current and future practice

Section 6.1.1 - Information about suggested duration of hormone therapy added to ensure that the protocol accurately reflects current practice

Section 6.2.2 - Additional information added about the timing of liver function tests prior to docetaxel administration added for clarity

Section 6.6.4 - Information on radiotherapy data collection added

Section 7.1.1 - Erroneous information about the timing of PSA measurements removed

Figure 3 - Moved to new section in protocol for clarity and extended to include current information on data collection

Figure 3b - Added to describe how extent of data collection during follow-up should change, post treatment and post progression

Figure 4 - Notes added to explain the changes in data collected at follow-up and to information that the quality of life study will be applicable to the first 700 patients randomised only

Figure 4 - Note added to include palliative radiotherapy CRF

Section 11.3 - SAE reporting information updated

Section 19 - Protocol amendments list updated

### **19.1.6 AMENDMENTS MADE TO PROTOCOL VERSION 5.0 (AUG 2008)**

1. General Information Section – Randomisation phone line number updated – non UK extension added
2. Section 3 – Information about QL study removed to reflect closure of QL study after first 700 patients
3. Section 4.2 – Exclusion criteria clarified to explain that only patients with severe poor cardiovascular history should be excluded
4. Section 4.3.1 – Information on co-administration of NSAIDS with celecoxib changed based on clinical advice.
5. Section 5 - Randomisation phone line number updated – non UK extension added
6. Section 6.2.1. – Information added to clarify that patients who develop an osteonecrosis of the jaw should stop zoledronic acid treatment
7. Section 6.2.3 – ‘severe’ text added to accurately reflect which patients should be excluded based on their cardiovascular history
8. Section 7.1.2 – Definition of disease progression extended for clarity
9. Figure 3 – Updated to include reference to newly created skeletal related event form
10. Figure 4 – Previous error in table amended to show that the 4<sup>th</sup> Zoledronic Acid form that is submitted contains information about 3 cycles rather than 2 as previously indicated
11. Table 4 – ‘Other important medical condition’ added to definition of serious in the SAE section, to accurately reflect SAE form and current practice
12. Section 11.1 – Information added on reporting or pregnancies
13. Section 17 - Information about QL study removed to reflect closure of QL study after first 700 patients

### **19.1.7 AMENDMENTS MADE TO PROTOCOL VERSION 6.0 (JUL 2009)**

1. General Information Section – Trial Pharmacist removed and changes of:

- Co-Investigator
  - Patient Representatives
  - Trial Manager
  - Data Manager
2. General Information Section - Coordinating Centre – address change
  3. General Information Section – change of Sponsor address
  4. Section 1.1 – ratio of patients randomised to the investigational arms updated
  5. Section 1.2 – figure 1b added to clarify trial design from April 2011 onwards
  6. Section 1.2 – paragraph added to explain trial changes after the second activity analysis
  7. Section 1.2 – wording added to clarify that QL data only collected for first 700 patients randomised
  8. Section 1.3 – SSA Favourable Opinion removed from list of trial documentation required ahead of site accreditation
  9. Section 2.1 – Amount of men diagnosed with prostate cancer annually updated
  10. Section 2.4 – note added to explain completion of recruitment to celecoxib- containing arms
  11. Section 2.5.2 - note added to explain completion of recruitment to celecoxib- containing arms
  12. Section 3 – SSA Favourable Opinion removed
  13. Section 4.2 – Exclusion criterion xiii greyed out
  14. Section 4.3.1 – paragraph removed regarding potential randomisation to celecoxib- containing arms
  15. Section 5 – Randomisation instructions expanded to exclude public holidays or dates when notice has been given by the CTU
  16. Section 6.1.4 – formatting changed to grey font to reflect recruitment completion for arm D
  17. Section 6.1.6 - formatting changed to grey font to reflect recruitment completion for arm F
  18. Section 6.2.3 – recruitment note added
  19. Section 6.6.3 – radiotherapy statement changed to reflect data from recent trials
  20. Section 7.1.2 – removal of reference to SRE- specific CRF
  21. Section 7.3 – Figure 3 - Addition of Bone Density Risk Factor Form and BMD sub-study assessment forms to summary of timing table
  22. Section 7.3 – Figure 4 – Weeks added to timings of assessments post 2 years
  23. Section 7.3- Figure 4 – note added to explain recruitment completion for arms D and F
  24. Section 12.1 – Wording changed to reflect change to randomisation allocation ratio

- 25. Section 12.1 – Addition of statement regarding new information emerging during the trial
- 26. Section 12.2 – Reference to SSA removed
- 27. Section 16.3 – Statement added regarding actioning IDMC recommendation ahead of TSC ratification

#### **19.1.8 AMENDMENTS MADE TO PROTOCOL VERSION 7.0 (JUL 2011)**

- 1. General Information Section- SAE reporting fax number corrected
- 2. Section 11- SAE reporting fax number corrected

#### **19.1.9 AMENDMENTS MADE TO PROTOCOL VERSION 7.1 (JUL 2011)**

Throughout protocol – numbering has been updated in some sections new accommodate new information that has been added.

General Information Section – contact details updated

General Information Section – Funding information updated to include involvement from additional company

General Information Section – Wording on compliance and regulations updated to reflect current MRC CTU standard wording

General Information Section – Abbreviations list updated

Section 1.1 – The number of investigational agents being studied updated from three to four

Section 1.1 – Information regarding celecoxib updated to reflect that recruitment to these arms was discontinued in April 2011

Section 1.1 – Information about new IMP, Abiraterone inserted

Section 1.1 – Sample size and trial duration information updated to reflect changes brought about by additional trial arm

Section 1.2 – Summary information updated to reflect the discontinuation of recruitment to celecoxib arms and the addition of abiraterone

Figures 1a, b and c - Updated to reflect the discontinuation of recruitment to celecoxib arms and the addition of abiraterone

Section 1.2 – Information on trial stages updated to reflect changes brought about by additional trial arm

Section 1.2 – Information updated regarding the re-opening of the quality of life sub-study from implementation of protocol version 8.0

Section 2.1 – Wording related to hormone therapy updated for clarity

Section 2.1 - Updated to reflect the discontinuation of recruitment to celecoxib arms and the addition of abiraterone

Section 2.2 – Updated references added

Section 2.3 – Updated references added

Section 2.5 – Section added to give background information on new IMP, abiraterone

Section 2.6.1 – Updated references added

Section 2.7 – Section added to give information regarding radiotherapy which is to be given as part of standard care following recently published trial data.

Section 3 – Wording updated regarding selection of investigators to reflect current MRC CTU practice

Section 4.1 – Inclusion criteria updated with new criterion regarding radiotherapy use

Section 4.1 - Inclusion criteria updated with new criterion regarding contraceptive use

Section 4.1 – Wording of inclusion and exclusion criteria updated for clarity

Section 4.1 – Exclusion criteria updated with new criterion regarding acceptable liver function for trial entry

Section 4.1 – Exclusion criteria updated with specifics related to blood pressure levels

Section 4.1 - Exclusion criteria updated with new criterion regarding concomitant medications

Section 4.1 - Exclusion criteria updated with new criterion regarding prior treatment with abiraterone

Section 4.1 - Exclusion criteria updated with new criterion regarding prior treatment with chemotherapy

Section 4.1 - Exclusion criteria updated with new criterion regarding prior treatment with zoledronic acid

Section 4.3 – Wording updated to reflect that patients who initially fail screening can be re-screened at a later date

Section 4.3.2 – Wording updated regarding prior anti-androgen and LHRH use updated for clarity

Section 5.1 – Co-enrolment guidelines information updated to describe newly created co-enrolment CRF

Section 6.1 – Trial treatment information updated to reflect the fact that anti-androgens alone will be no longer permitted as hormone therapy

Section 6.1.1 – Updated to describe patients for whom radiotherapy should be given as standard practice

Section 6.1.1 a and b - Sections added to give information regarding radiotherapy treatment

Section 6.1.1-6.1.6 – References to further sections updated

Section 6.1.7 – Section added to describe abiraterone treatment

Section 6.2.4 - Section added to describe abiraterone treatment

Section 6.6 - Section added to give information regarding radiotherapy treatment

Section 7.1.1 – Reference to blood being taken at patient’s home removed as this does not occur in practice

Section 7.1.2 – Wording updated regarding the reporting of biochemical failures for clarity

Section 7.1.2 – Wording updated regarding skeletal related events for clarity

Section 7.1.3 – Section added to describe additional assessments required related to abiraterone treatment

Section 7.1.4 – Section added to provide information on when treatment should commence

Figure 4 – Updated for clarity regarding return of BMD sub-study forms, the addition the co-enrolment CRF and the description of the re-opening of the QoL Sub-study.

Figure 5 – Updated with reference to abiraterone and co-enrolment form

Section 7.3 - Wording on trial closure updated to reflect current MRC CTU standard wording

Section 8.1 – Additional criteria for definition of progression added for clarity

Section 8.1 – Definition of progression for abiraterone patients added.

Section 9 – Statistical information updated to describe the addition of the new trial arm

Section 11 – Safety reporting wording updated for clarity

Section 11 – SAE reporting fax number updated

Section 12 – Ethical information updated to describe the unequal randomisation allocation ratio

Section 12 – Ethical information updated to describe that the visit schedule will vary according to trial arm

Section 12.2 – Wording updated to reflect international participation in the trial

Section 13 – Wording updated to reflect international participation in the trial

Section 14 – Wording updated to reflect international participation in the trial

Section 15 - Updated to reflect the discontinuation of recruitment to celecoxib arms and the addition of abiraterone

Section 16 – Reference to trial committee charters added for information

Section 17.1 – Information added to reflect re-opening of quality of life sub-study

Section 17.2 – Timing of health economics analysis updated to previous error

Section 18 – Information on publication policy expanded for clarity

Section 19 – Information regarding amendments to protocol appendices moved to the separate appendices document

Section 20 – References extensively updated

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