STAMPEDE

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

A multi-arm multi-stage randomised controlled trial

Version: 14.0

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Role:	**TRIAL STATISTICIAN**

GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. It describes the STAMPEDE trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), 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 has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Cancer And Other Non-Infectious Diseases Group, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, 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 [where applicable]) and applicable national regulations.

SPONSOR

Medical Research Council, 2nd Floor, David Phillips Building, Polaris House, North Star Avenue, Swindon, SN2 1FL, UK

FUNDING

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

AUTHORISATIONS AND APPROVALS

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

TRIAL REGISTRATION

This trial has been registered with the ClinicalTrials.gov Clinical Trials Register, where it is identified as NCT00268476.

RANDOMISATIONS
To randomise, call MRC CTU at UCL, Monday to Friday 0900-1700
excluding public holidays or dates when notice has been given by the Unit.
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For full details of all trial committees, please see **Appendix M**.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
ACE	Angiotensin-Converting Enzyme
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AR	Androgen receptor
AS	Activity Stage
bid	Twice a day (bis in die)
BP	Blood pressure
BRG	Biological Research Group
BSA	Body surface area
CERES	Consumers for Ethics in Research
CF	Consent Form
CI	Chief Investigator
CI	Confidence interval
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
Cox 2	Cyclooxygenase 2
CRF	Case Report Form
CRUK	Cancer Research UK
CRPC	Castrate Refractory Prostate Cancer
CT	Computerised tomography
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Advisory and Awards Committee
CTC	Common Toxicity Criteria
CTU	Clinical Trials Unit
CTV	Clinical Tumour Volume
CXR	Chest X-ray
DDX	Doctors and Dentists Exemption
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic Acid
DPA	Data Protection Act
ERC	Endpoint Review Committee
ES	Efficacy Stage

Abbreviation	Expansion
ICH	International Conference on Harmonization
ECG	Electro cardiogram
FBC	Full Blood Count
FFS	Failure-Free Survival
GCP	Good Clinical Practice
GP	General Practitioner
GRO	General Register Office
HE	Health Economics
HES	Hospital Episode Statistics
hr	Hour
HR	Hazard Ratio
HRPC	Hormone Refractory Prostate Cancer
HT	Hormone Therapy
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IMRT	Intensity Modulated Radiation Therapy
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Units
IV	Intravenous
LD	Longest diameter
LFTs	Liver Function Tests
LHRH	Luteinising Hormone Releasing Hormone
LREC	Local Research Ethics Committee
m	Month
MHRA	Medicine and Healthcare Products Regulatory Agency
min	Minutes
MRC	Medical Research Council
MREC	Multi-Centre Research Ethics Committee
MRI	Magnetic resonance imaging
M0	Non-metastatic
M1	Metastatic
NCI	National Cancer Institute (USA)
NCRN	National Cancer Research Network

Abbreviation	Expansion
NHS	National Health Service
NSAID	Non-Steroidal Anti-inflammatory Drugs
ONS	Office for National Statistics
OS	Overall Survival
PI	Principal Investigator
PIS	Patient Information Sheet
po	per orum (orally)
PSA	Prostate Specific Antigen
pts	Patients
PTV	Planned Tumour Volume
QALY	Quality-adjusted Life Years
qds	quater die sumendus (4 times each day)
QL	Quality of Life
R&D	Research and Development
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
sc	Sub-cutaneous (under skin)
SNP	Single Nucleotide Polymorphism
SOC	Standard-of-Care
SSA	Site Specific Assessment
STAMPEDE	Systemic Therapy in Advancing and Metastatic Prostate Cancer: Evaluation of Drug Efficacy
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWOG	South West Oncology Group
TMG	Trial Management Group
TMT	Trial Management Team
TURP	Trans-Urethral Resection of Prostate
TSC	Trial Steering Committee
UCL	University College London
ULN	Upper Limit of Normal
U+E	Urea and Electrolytes
WHO	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 treatment) slows the growth of prostate cancers. This type of treatment is called hormone treatment or androgen deprivation therapy (ADT) 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.

There are increasing numbers of treatments available for advanced 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 some of these treatments, given earlier in the course of the disease in combination with the current standard-of-care.

The treatments that have been, or are being, assessed during 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. Recruitment to this treatment has been completed and the results show that the addition of zoledronic acid does not prolong survival.

2. Docetaxel: A drug that stops cells replicating that is currently being used to treat a range of cancers including lung, breast and ovarian cancer as well as prostate cancer. Docetaxel prolongs survival in men with relapsed metastatic prostate cancer. Recruitment to this treatment has been completed and the results show that the addition of docetaxel to hormone treatment does improve survival in men with metastatic disease and delays the time to progression for men with locally advanced and metastatic disease. Docetaxel may now be given as part of standard treatment to all men entering STAMPEDE (from protocol version 14.0).

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 intermediate analysis failed to demonstrate sufficient effect of this drug.

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 anti-hormonal therapies. Abiraterone has been shown to prolonging surival in men with advanced disease when given before and after chemotherapy.

5. Prostate radiotherapy (included from protocol version 9.0)**:** treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory for patients with cancer that is confined to the prostate gland as large trials have shown it improves survival times. We are not certain whether we should give radiotherapy to the prostate if the cancer has already spread and so we are investigating this in STAMPEDE.

6. Enzalutamide (included from protocol version 12.0)**:** This is a blocker of androgen receptors. These stimulate the cancer when hormone therapies have failed. Enzalutamide may be mutually complementary to abiraterone in terms of blocking mechanisms of resistance. 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 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. More than 8,000 patients will join the trial with answers becoming available throughout the trial.

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 commencing long-term Androgen Deprivation Therapy (ADT). Patients can have either newly diagnosed disease, or have been previously treated with radical radiotherapy or surgery but now have signs of progression such as 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 the standard-of-care. The investigational agents are (i) a bisphosphonate, zoledronic acid, (ii) a cytotoxic chemotherapeutic agent, docetaxel and (iii) a cyclooxygenase (Cox-2) inhibitor, celecoxib (iv), abiraterone, a steroid synthesis inhibitor and an androgen receptor signalling inhibitor (v) enzalutamide. Recruitment to the celecoxib arms (D and F) is now closed. An additional arm containing abiraterone was added in protocol version 8.0 which has now completed recruitment. A further comparison arm involving prostate radiotherapy for patients with newly-diagnosed metastatic disease was added in protocol version 9.0, with the addition of an arm considering the combination of enzalutamide and abiraterone added in protocol version 12.0. The trial has multiple arms; the control arm of the trial receives standard therapy alone. When the trial started standard treatment was androgen deprivation therapy (ADT) only, achieved through the use of luteinising hormone releasing hormone (LHRH) analogues e.g. zoledex or LHRH antagonists, or bilateral orchidectomy according to local practice. Since primary results from the trial "original comparisons" have emerged showing a benefit in overall survival for patients receiving docetaxel in addition to ADT, the standard treatment has changed accordingly. Standard treatment may now include docetaxel chemotherapy for all men entering STAMPEDE. Radiotherapy is also mandated for men with node negative non-metastatic disease. The current trial design is shown in **Figure 1;** previous trial designs can be viewed in Protocol version 13.0.

Figure 1: Arms of the STAMPEDE trial from protocol 14.0 (amending the standard of care to permit docetaxel)

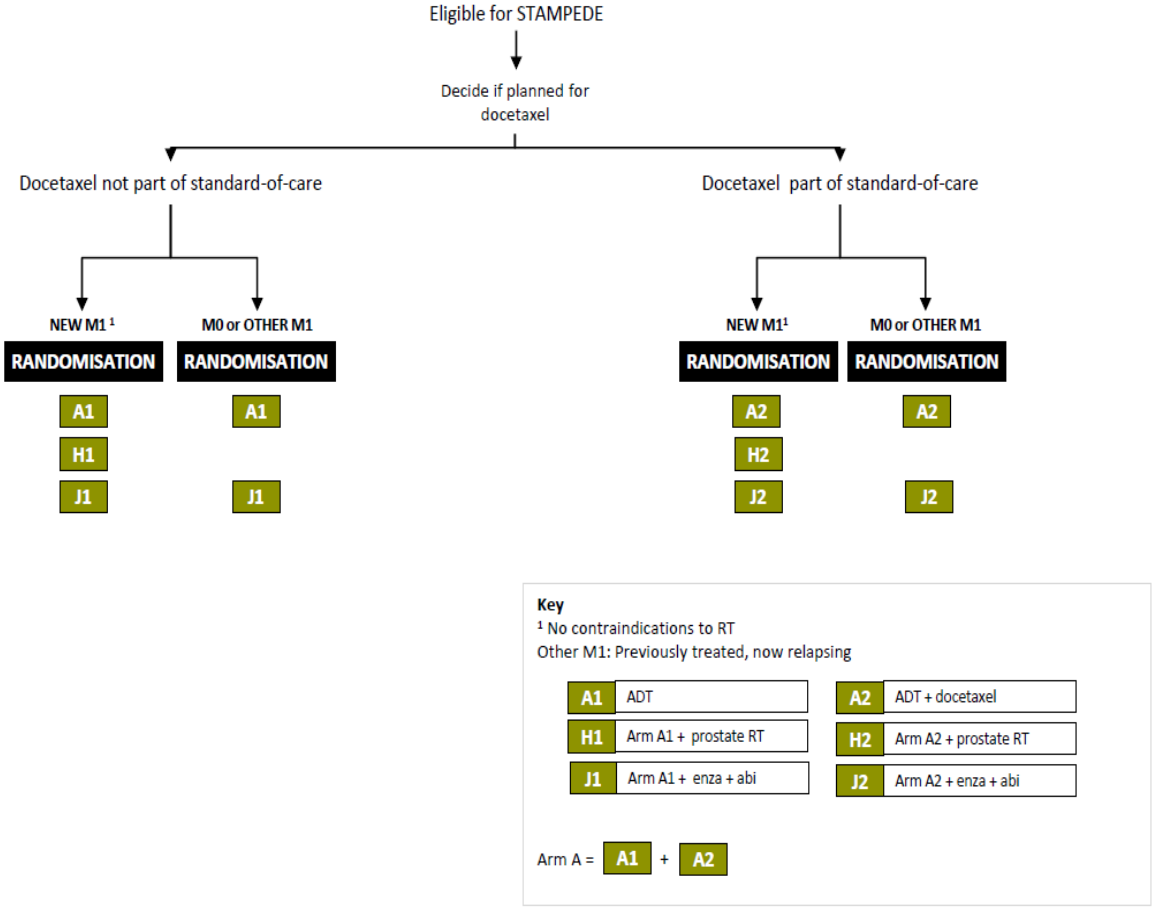
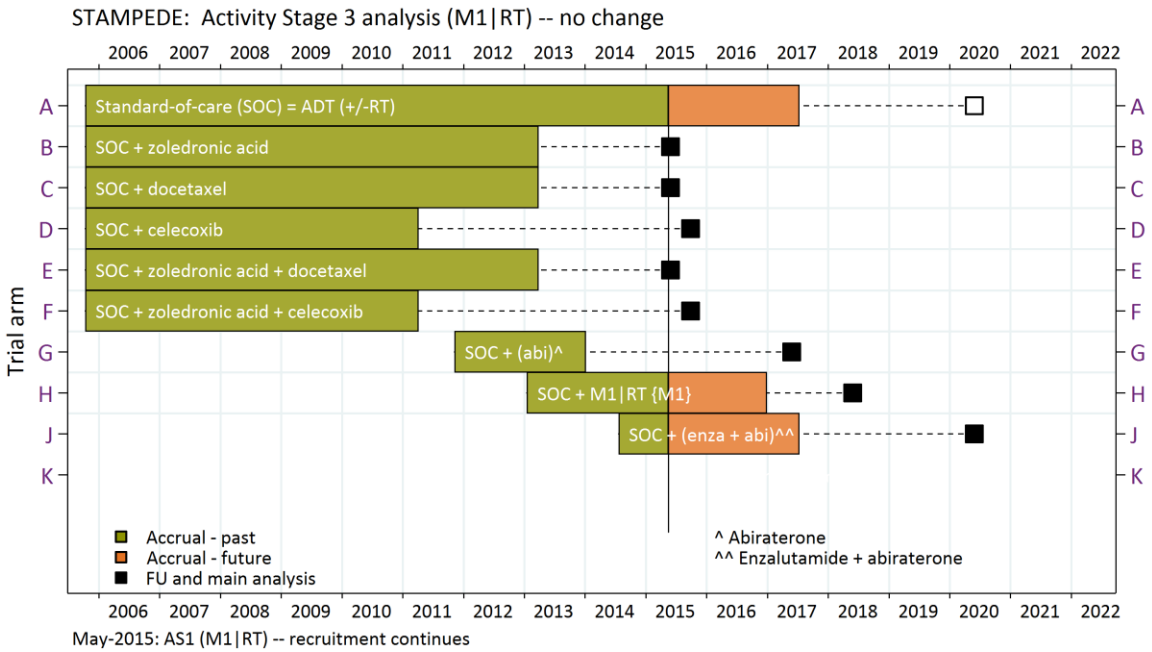


Figure 2: Arms of the STAMPEDE trial open to recruitment over time



For each comparison of research arm against control, the trial will be conducted in a number of stages: a Pilot/Safety Phase, Activity Stages and a final Efficacy Stage. The primary outcome measure of the Pilot/Safety Phase is safety, with 30-50 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 the Activity Stages the primary outcome measure is failure-free survival (FFS). Each Activity Stage is triggered when a pre-specified number of FFS events have been observed in the control arm of the relevant comparison (see **Section 9** for further detail). Recruitment to Arms D (ADT + celecoxib) and F (ADT + zoledronic acid + celecoxib) was stopped in Apr-2011 after the second planned activity analysis when the IDMC and TSC considered the lack-of-benefit guidelines.(1) (See to **Section 9.4** for further information regarding the guidelines for stopping accrual to research arms during the activity stages of the trial).

Some evidence of activity will be required for a research arm to continue past each stage and guidelines are in place for this assessment of activity. The Efficacy Stage will take place when a pre-specified number of deaths are observed amongst the control arm patients for that relevant comparison. This was when around 403 deaths had been reported in the control arm for the "original comparisons" (involving docetaxel and zoledronic acid) and will be when around 267 deaths are reported in the control arm for the "abiraterone comparison", the "M1|RT comparison" and the "enzalutamide+abiraterone comparison". The exact number of patients randomised to, and duration of, the trial will depend on the observed accrual rate, observed event rate and the number of other research arms open to recruitment.

In version 8.0 of the protocol a new arm G (ADT + abiraterone) was added. Arm H (ADT+ prostate radiotherapy) was added in protocol version 9.0. The trial stages remain similar to those at trial inception but will be staggered in time compared to the stages for the original arms A-F. Protocol version 10.0 was approved following the completion of recruitment to the remaining original trial arms (B, C and E) and was a "housekeeping" change to remove references to the completed arms

from the information sheets. Protocol version 11.0 was approved following the extension of the recruitment target sample for the “abiraterone comparison” from 1,500 to around 1,800 patients. Protocol version 12.0 added a new combination therapy arm containing abiraterone with enzalutamide; for this comparison we envisage only two pre-planned interim analyses. Protocol 13.0 was approved following the extension of the recruitment target sample for the "M1|RT comparison", from 1,250 to around 1,800 patients, and the introduction of saliva sample collection for DNA analysis. This current protocol amendment (Protocol 14.0) updates the standard-of-care to permit docetaxel in response to the results of the primary analysis of the "original comparisons".

Patients will be assessed 6 weekly for the first 24 weeks after randomisation and then every 12 weeks up to 2 years, 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 their use of health care resources (Health Economics (HE) study). From protocol version 8.0, the QL and HE study has been re-opened to all new patients.

In addition, there are translational sub-studies. Patients willing to participate will be asked at randomisation to donate a saliva sample (previously a droplet of blood), which will be stored for 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 (blood or biopsy samples) for further studies on the causes and nature of prostate cancer. In selected centres patients were previously asked to participate in a bone mineral density sub-study (sub-study now closed). 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

Table 1 presents a summary of the required trial documentation for participating centres

Table 1: Trial documentation required for participating centres

TRIAL DOCUMENTATION	TIMING
R&D approval (including IRMER 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 (or Variation if applicable)	Before centre participation
RTQA accreditation	Before centre participation

2 BACKGROUND

2.1 INTRODUCTION AND SETTING

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 41,000 men are diagnosed with prostate cancer each year and in 2012 over 10,000 men died from the disease.(2)

2.1.1 LONG-TERM ANDROGEN DEPRIVATION THERAPY

The initial (first line) treatment for locally advanced or metastatic prostate cancer is androgen deprivation therapy (ADT) achieved either surgically with bilateral orchidectomy, or medically with LHRH agonists or antagonists (3) Oral anti-androgens are no longer permitted for new patients within the trial from version 8.0.

ADT produces responses in up to 95% of patients but it is not curative and disease recurs in virtually all patients treated with ADT as sole therapy, with a median time to progression of 18-24 months.(3) Data from STAMPEDE has shown progression to be just 12 months in men with newly-diagnosed disease. Such progressive disease is referred to as castrate resistant prostate cancer (CRPC); although this term is unpopular with patient groups due to its perceived pejorative overtones related to castration and hence terminology may yet change again in the future.

2.1.2 ROLE OF RADIOTHERAPY FOR MEN WITH M0 DISEASE

Two randomised trials, SPCG7 (4) and NCIC PR.3 / MRC PR07 (5-7) have tested the question of whether ADT alone combined with radiotherapy is the best treatment for high-risk patients with no evidence of spread outside the pelvis. Both trials demonstrated an improvement in overall and disease specific survival from the addition of radiotherapy to ADT. The size of this overall survival benefit is substantial (hazard ratio 0.68 in SPCG7 and HR 0.77 in PR07). With substantial benefit demonstrated in two mature, large, well conducted randomised trials, we now mandate that radiotherapy be standard for patients with no nodal or metastatic spread. Patients in this category will now only be allowed to enter the trial if standard radiotherapy is planned, with the exception of those for whom radiotherapy is contra-indicated. Such patients should be discussed with the Trials Unit prior to inclusion. For patients with node positive, M0 disease there are no clear data on whether radiotherapy is indicated or not. The NCIC PR.3 / MRC PR07 trial included patients with unknown nodal status who received whole pelvic radiotherapy. Given the large overall benefit observed in this trial, the STAMPEDE TMG recommends that pelvic nodal radiotherapy be considered for patients with node positive, non-metastatic disease at the discretion of the treating clinician [James et all (in press); JAMA Oncology].

2.1.3 ROLE OF DOCETAXEL FOR MEN WITH M0 OR M1 DISEASE

The primary analysis of the "original comparisons" has shown docetaxel to significantly prolong survival (HR 0.78; 95% CI 0.66-0.93). This is in support of the results of the CHAARTED study which showed docetaxel improved survival in men with metastatic disease.(8) There was no evidence of heterogeneity in the treatment effect across patient groups and median survival was improved by 10 months, from 71 to 81 months. In a well powered and pre-planned sub-group analysis of men with metastatic disease at diagnosis the treatment effect was most apparent with the median survival benefit of 15 months. As a result the STAMPEDE TMG recommends that docetaxel should be strongly considered in all men with metastatic disease at presentation who are commencing ADT for the first time and are fit enough to receive chemotherapy.

Survival data for men without metastases at diagnosis is less mature but a statistically significant improvement in failure free survival is seen, therefore, docetaxel may also be considered for men with high-risk non-metastatic disease.

Therefore, docetaxel is now permitted as part of the standard-of-care for all men entering STAMPEDE at the discretion of the treating clinican and patient.

2.2 RATIONALE

There are increasing numbers of treatments which are used post relapse of first-line ADT in patients with CRPC, but there is 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 as first-line treatment. Such treatments include further hormonal manipulations, bisphosphonates, (9), cytotoxic chemotherapy (10), new hormone therapies (11) and palliative radiotherapy. The traditional approach to the testing and introduction of new treatments for prostate cancer is to use them in patients with castrate resistant disease. An alternative approach is to investigate new drugs and new approaches to treatment, as first-line therapy in patients starting ADT. At this point, patients should be fitter and better able to tolerate treatment than when they have CRPC, and there is the possibility of having a larger and longer lasting effect.

2.3 DESIGN

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 long-term ADT for advancing or metastatic prostate cancer. For these questions, each comparison was divided into five stages such that, for each investigational arm, safety and activity data were generated in the first four stages; an investigational arm could only proceed to the fifth and final stage of recruitment, where it would be assessed for effect on overall survival, if shown to be sufficiently safe and active at all prior activity stages. It is important to note, however, that patient data from all arms and all stages are included in the final analyses of the primary outcome measure, even if the investigational arm did not proceed to the final stage.

A second planned interim analysis failed to demonstrate sufficient activity for celecoxib and this agent was removed from trial recruitment in April 2011; patients remaining on celecoxib treatment reverted to standard care. Protocol version 8.0 added a new drug abiraterone to the study as an additional arm (see **Section 2.7**). Protocol version 9.0 added a new comparison arm involving prostate radiotherapy for patients with newly-diagnosed metastatic disease (see **Section 2.8**). Protocol version 10.0 reflected the successful completion of recruitment to three docetaxel- and bisphosphonate-containing arms (Arms B, C and E) and removed references to these agents in the information sheets for new patients. Protocol version 11.0 extended the recruitment target for the "abiraterone comparison" (A vs G) from 1,500 to around 1,800 patients. Protocol version 12.0 added a new comparison involving the combination of abiraterone and enzalutamide. Protocol version 13.0 extended the recruitment target for the M1|RT comparison from 1,250 to around 1,800 patients. Protocol version 14.0 incorporates the permitted use of docetaxel in the standard-of-care.

2.4 RESEARCH TREATMENT: BISPHOSPHONATES

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached.
Treatment has been completed in all patients and the results reported. See Protocol version 13.0 or older for details on the rationale.

2.5 RESEARCH TREATMENT: CHEMOTHERAPY

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached.
Treatment has been completed in all patients and the results reported. See Protocol version 13.0 or older for details on the rationale.

2.6 RESEARCH TREATMENT: CYCLOOXYGENASE-2 INHIBITORS

Note: recruitment completed to both celecoxib-containing arms in Apr-2011 at the end of Activity Stage II of this comparison.
Treatment has been ceased in all patients and the results to be reported in 2016. See Protocol version 13.0 or older for details on the rationale.

2.7 RESEARCH TREATMENT: STEROID SYNTHESIS INHIBITORS

Recent evidence suggests that an important mechanism for escape from tumour control by androgen ablation is the intracellular conversion of steroid 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. (11). Abiraterone acetate (3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene, code CB7630; JNJ-212082) is rapidly converted in vivo to abiraterone (JNJ-589485; formerly code named CB7598). It is a selective, irreversible inhibitor of 17α-hydroxylase/C17,20-lyase (cytochrome P450c17 [CYP17]), an enzyme that is critical in the production of androgens in the testes, adrenal glands and prostate tumor tissue. Inhibition of CYP17 inhibits the conversion of pregnenolone or progesterone into dehydroepiandrosterone (DHEA) or androstenedione, respectively, each of which is a precursor of testosterone. The pharmacodynamic effect is a more effective androgen depletion than can be induced by surgical castration, or medically by gonadotropin releasing (GnRH) hormone analogues used as first line hormone therapy in prostate cancer.

Approximately 2,280 prostate cancer patients participated in the two Phase 3 RCTs (COU-AA-301 and COU-AA-302), with approximately 1,335 patients receiving abiraterone acetate at 1000mg daily dose continuously, in these studies. These studies have demonstrated abiraterone to prolong survival when given post-docetaxel (HR 0.65) and pre-docetaxel (HR 0.82). As a result it is now approved use in the USA and Europe in CRPC.(12, 13)

Side-effects with abiraterone acetate are modest with the main adverse effects being elevated transaminases (usually mild), hypokalaemia and hypertension due to secondary hyperaldosteronism and fluid retention (preventable by low doses of glucocorticoids). In order to prevent 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 side effects of long-term exposure to glucocorticoid. More recent evidence even suggests that for most patients,

no glucocorticoids may be needed. (14) Within the STAMPEDE trial, we suggest prednisolone/ prednisone dose of 5mg daily.

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

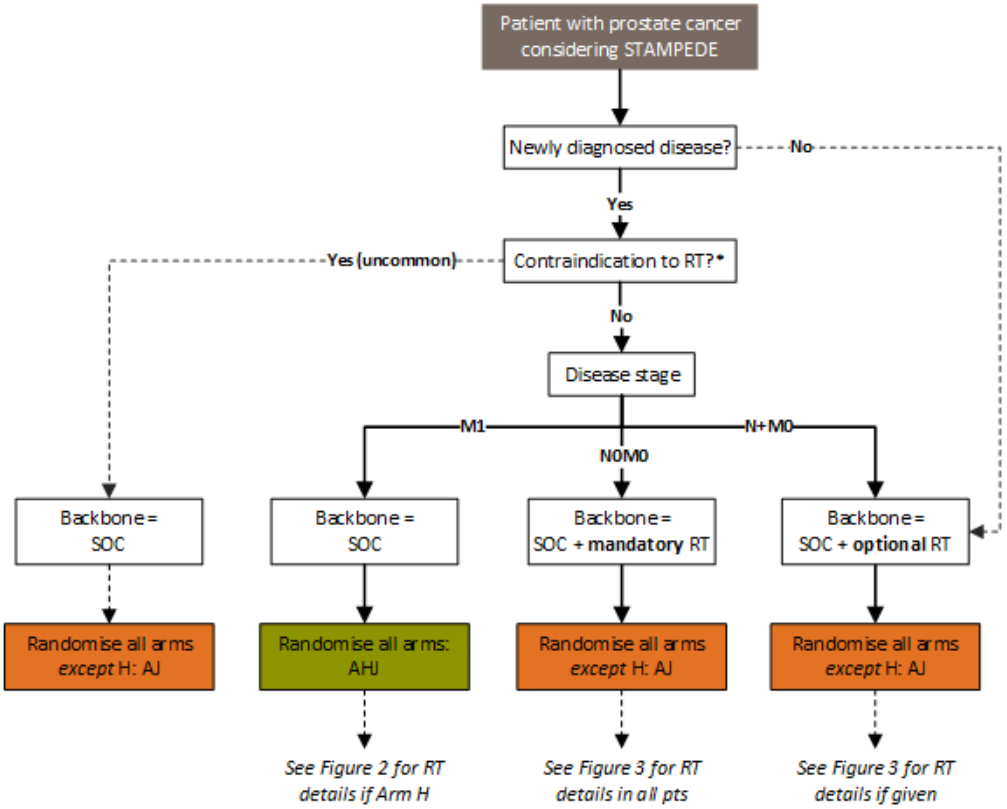
2.8 RESEARCH TREATMENT: RADIOTHERAPY TO THE PROSTATE FOR PATIENTS WITH NEWLY-DIAGNOSED METASTATIC DISEASE

Therapy directed against the primary tumour in the presence of metastatic disease has been evaluated rigorously in only one malignancy to date: renal cell carcinoma. Two cooperative groups ran randomised trials enrolling patients with previously untreated metastatic RCC whose primary tumours were amenable to surgical resection. Patients were randomised to receive the standard systemic therapy of the day, interferon-alpha, either alone or with radical nephrectomy. The combination of nephrectomy and interferon was shown to significantly improve median survival from 7 to 17 months in one trial (15) and from 8 to 11 months in the other.(16) The mechanism by which nephrectomy improves survival remains obscure. In preclinical models, the primary tumour has been found to secrete molecules that prime the microenvironment in which metastases can develop. An implication of this work is that therapy directed at the primary tumour, by abrogating this endocrine signalling, could retard the formation and the growth of distant metastases.

The results of two large-scale randomised trials of prostate radiotherapy are also provocative. The Scandinavian SPCG-7 trial and the MRC PR07 trial randomised men with locally advanced prostate cancer, who were at high risk of possessing occult metastatic disease, to either ADT alone or ADT plus prostate radiotherapy.(4, 17) The addition of radiotherapy dramatically improved 10-year outcomes: mortality from prostate cancer was halved. Interestingly, the benefit of radiotherapy started to emerge as early as three years from the time of randomisation. This seems improbably early if the benefit of local treatment is mediated via the prevention of subsequent disease dissemination. Rather, it is more consistent with the possibility that local treatment has a beneficial impact on the rate of progression of existing micrometastatic disease.

We hypothesise that local therapy to the primary site may retard distant disease progression and prolong survival in patients with newly-diagnosed metastatic prostate cancer.

Figure 3: Use of RT in STAMPEDE



*It is expected that only around 1% of patients will have a contraindication to RT e.g. inflammatory bowel disease. These cases should be discussed with the trials unit prior to randomisation (see Section 2.7).

*It is expected that only around 1% of patients will have a contraindication to RT e.g. inflammatory bowel disease. These cases should be discussed with the trials unit prior to randomisation (see **Section 4.3**).

2.9 RESEARCH TREATMENT: COMBINATIONS OF ORIGINAL RESEARCH ARMS

2.9.1 BISPHOSPHONATE AND CHEMOTHERAPY

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 at the end of Activity Stage IV. Treatment has been completed in all patients and the results reported. See Protocol version 13.0 or older for details on the rationale.

2.9.2 BISPHOSPHONATE AND CYCLOOXYGENASE-2 INHIBITORS

Note: recruitment stopped to both celecoxib-containing arms in Apr-2011 at the end of Activity Stage II.

2.10 COMBINATION OF STEROID SYNTHESIS INHIBITORS AND ANDROGEN RECEPTOR SIGNALLING INHIBITOR

The majority of patients with advanced prostate cancer who have disease progression on abiraterone or enzalutamide taken as single agents, have a rise in PSA, suggesting reactivation of androgen receptor (AR), or other steroid signalling pathways resulting in increased PSA transcription, is the pathway to the development of resistance.(18)

The primary pharmacodynamic effect of enzalutamide is inhibition of androgen binding to the AR, AR nuclear translocation in the presence of androgen and AR:chromatin association. In multiple prostate cancer cell lines that specifically model CRPC (LNCaP/AR, VCaP, W741C LNCaP), the consequences of enzalutamide treatment include inhibition of AR-induced gene transcription, reduced cell proliferation, increased cell death by apoptosis and tumor regression.

In a mouse xenograft model of CRPC using prostate cancer cells that overexpress the AR (LNCaP/AR), enzalutamide inhibits tumor growth and reduces tumor size. A major human metabolite of enzalutamide, N-desmethyl enzalutamide, demonstrates key primary pharmacodynamics of similar potency to the parent molecule, while the carboxylic acid derivative metabolite has no known pharmacodynamic effect.

The question under investigation is: can progression be delayed (and survival extended) by using a combination of abiraterone and enzalutamide?

2.10.1 SUPPLEMENTING ABIRATERONE AND PREDNISOLONE WITH ENZALUTAMIDE

Several studies have shown that the AR can become promiscuously activated by very low levels of androgens or other steroid metabolites and drugs that bind the AR.(19-22) It is known that very low levels of androgens can persist in patients treated with abiraterone acetate.(23) Drugs that bind the AR, may include co-administered glucocorticoids. Furthermore, AR mutations of the sort previously described in CRPC, can be activated by cortisol and other glucocorticoids at levels much lower than those reported in patients treated with abiraterone and prednisolone at a dose of 5mg bid.(22, 24) Moreover, abiraterone binds the AR and, although weak antagonism of wild-type and most previously described AR mutations are observed,(24) a similar mechanism to that described with classical anti-androgens, such as bicalutamide, could lead to change-of-function AR mutations associated with AR activation following abiraterone binding. Therefore, concomitant treatment with an androgen receptor signalling inhibitor could prevent “promiscuous” AR activation in patients treated with abiraterone. Enzalutamide is a androgen receptor signalling inhibitor and has gained recent approval for use on its own in the treatment of advanced CRPC,(25) and there is evidence of activity for hormone-naïve prostate cancer.(26)

2.10.2 SUPPLEMENTING ENZALUTAMIDE WITH ABIRATERONE AND PREDNISOLONE

Enzalutamide in combination with ADT is both effective and well tolerated in CRPC.(25) However, recent studies have suggested that intra-tumoral testosterone levels increase in patients treated with enzalutamide.(27) The implications of this finding are that the increase in intra-tumoral testosterone could be associated with up-regulation of enzymes involved in steroid biosynthesis.(28) Although enzalutamide has a high affinity for the AR, this is several-fold lower than both the natural ligands testosterone and DHT,(29) which means that enzalutamide would be out-competed at the AR ligand-binding domain if and when androgen levels rise. In vitro, a ten-fold rise in intra-cellular androgen was sufficient to prevent inhibition of AR by 30uM of enzalutamide;(24) these levels are

representative of the plasma levels of enzalutamide active metabolites, which can be achieved with enzalutamide 160mg po daily.(30)

A strategy for preventing the rise in intra-cellular androgens in patients treated with enzalutamide would be inhibition of CYP17A1. Abiraterone is currently the only CYP17A1 inhibitor with proven efficacy. It therefore seems logical to use the combination of enzalutamide and abiraterone to both block a rise of intra-cellular androgens and prevent promiscuous activation of the AR.

2.10.3 Summary Of Rationale For This Combination

To date, investigation has focussed on patients with CRPC but there is a strong rationale for the combination of enzalutamide and abiraterone in the hormone treatment-naïve setting in which STAMPEDE is focused.

STAMPEDE is already evaluating abiraterone plus conventional ADT but we will not assess the combination of conventional ADT plus enzalutamide; other trials by industry and other cooperative groups will address that question. The inclusion of an arm with ADT and enzalutamide in STAMPEDE was therefore considered to be a duplication of effort and was not supported by the Trial Management Group.

The combination of enzalutamide and abiraterone is a novel approach and offers considerable promise in delaying progression – it therefore represents an attractive addition to the comparisons under investigation in STAMPEDE, and one that is unlikely to be replicated in other planned trials of this size.

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 at University College London (MRC CTU at UCL) 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 (download from www.stampedetrial.org). 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 as templates.

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

3.1 RADIOTHERAPY ACCREDITATION

The introduction of the "M1|RT comparison" in Protocol 9.0 introduced the need for RTQA accreditation in sites giving radiotherapy. The detail of RTQA accreditation is in **Appendix K**. However, centres that have been RTQA accredited for another multi-centre prostate radiotherapy trial in the UK (e.g. RADICALS or CHHIP) will be automatically granted STAMPEDE RTQA accreditation.

4 SELECTION OF PATIENTS

4.1 PATIENT INCLUSION CRITERIA

Patients must fulfil both of the criteria in **Section 4.1.1** **or** one criterion in **Section 4.1.2** **or** at least one criterion 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

Both:

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

OR

4.1.2 NEWLY-DIAGNOSED METASTATIC OR NODE-POSITIVE DISEASE

At least one of:

- Stage T_{any} N+ M0
- Stage T_{any} N_{any} M+

OR

4.1.3 PREVIOUSLY TREATED WITH RADICAL SURGERY AND/OR RADIOTHERAPY, NOW RELAPSING[1]

At least one of:

- PSA ≥4ng/ml and rising with doubling time less than 6 months
- PSA ≥20ng/ml
- N+
- M+

AND

4.1.4 FOR ALL PATIENTS

I. Histologically confirmed prostate adenocarcinoma
II. Intention to treat with long-term androgen deprivation therapy
III. Treating clinician and patient must have decided if docetaxel is to be part of the standard-of-care prior to randomisation
IV. Fit for all protocol treatment[2] and follow-up, WHO performance status 0-2[3]
V. Have completed the appropriate investigations prior to randomisation
VI. Adequate haematological function: neutrophil count >1.5x10^9/l and platelets >100x10^9/l
VII. Estimated creatinine clearance >30ml/min
VIII. Serum potassium ≥3.5mmol/L
IX. Written informed consent
X. Willing and expected to comply with follow-up schedule
XI. Using effective contraceptive method if applicable

[1] Courses of 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.
[2] Medical contraindications to the trial medications are given in **Section 6.11.4 and 4.3**
[3] For WHO performance status definitions see **Appendix A**

4.2 PATIENT EXCLUSION CRITERIA[4]

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 ≥1.5 x ULN (except for patients with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
IV. Any other previous or current malignant disease which, in the judgement of the responsible clinician, is likely to interfere with STAMPEDE treatment or assessment
V. Patients with contra-indications to prednisolone, including active peptic ulceration or a history of gastrointestinal bleeding
VI. Patients with active inflammatory bowel disease
VII. Symptomatic peripheral neuropathy grade ≥2 (NCI CTC)[5]
VIII. Any surgery (e.g. TURP) performed within the past 4 weeks
IX. Patients with significant cardiovascular disease such that, in the investigator's opinion, the patient is unfit for any of the study treatments. This might include:
   - Severe/unstable angina
   - Myocardial infarction less than 6 months prior to randomisation
   - Arterial thrombotic events less than 6 months prior to randomisation
   - Clinically significant cardiac failure requiring treatment (NYHA II-IV)[6]
   - Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 2 years prior to randomisation
   - Patients with uncontrolled hypertension defined as systolic BP greater or equal than 160 mmHg or diastolic BP greater or equal than 95 mmHg
X. Patients receiving treatment with drugs known to interact with CYP3A4 and CYP2C9 (please see **Table 11 and Table 12** for more details on drug interaction)
XI. Prior exposure to abiraterone
XII. Prior exposure to enzalutamide
XIII. Prior chemotherapy for prostate cancer (excluding patients receiving docetaxel as part of the new SOC)
XIV. Prior therapy with zoledronic acid or other bisphosphonates other than treatment for hypercalcaemia or low bone density
XV. Prior exposure to long-term hormone therapy before randomisation (unless as described in **Section 4.4.2**)
XVI. History of seizure including any febrile seizure, brain injury with loss of consciousness, or transient ischaemic attack within the 12 months prior to randomisation or any history of prior conditions that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation)
XVII. Unexplained history of loss of consciousness within 12 months of randomisation
XVIII. Operation of heavy machinery during treatment

[4] The exclusion criteria for patients who have been on a Cox-2-inhibitor for 6+ months has been removed
[5] See **Appendix I** for common toxicity grading
[6] NYHA classifications can be found in **Appendix A**

4.3 SELECTION CRITERIA FOR COMPARISON OF RESEARCH RT FOR METASTATIC DISEASE (M1|RT)

All patients meeting criteria in **Section 4.1** and **4.2** are eligible for the trial, but not all can be allocated to the research (M1) radiotherapy arm. The selection criteria for this "RT to the prostate" comparison are:

- Newly-diagnosed prostate cancer
- Demonstrable M1 disease
- No contraindication to radiotherapy e.g. no previous pelvic radiotherapy and no history of inflammatory bowel disease
- No previous radical prostatectomy

Any patients meeting these criteria will have a chance to be allocated to Arm H. For those rare cases where radical RT is planned for a newly-diagnosed M1 patient, the TMT and TMG will need to review and approve the inclusion of the patient for randomisation only between Arm A and J.

4.4 SCREENING PROCEDURES

4.4.1 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 (or equivalent e.g. whole body MRI)
- 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
- Waist circumference measure

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

Prior to randomisation:

- Check details of any prior treatments for prostate cancer
- Check any contraindications to radiotherapy

4.4.2 Androgen Deprivation Therapy Prior To Randomisation

If ADT has already started prior to randomisation, the primary therapy should have not have started more than 12 weeks before randomisation. If a short course of anti-androgens (e.g. bicalutamide) was used to prevent tumour flare, this will not be counted in the 12 week period, but the PSA level must have been taken before this was started. The start date of anti-androgens cannot be more than 14 weeks before randomisation and patients will not be eligible if time since starting anti-androgen monotherapy has exceeded 14 weeks.

Note that long-term anti-androgen monotherapy is not permitted in the trial for newly recruited patients from protocol version 8.0; patients may change treatment to join the trial, provided that they have not had more than 12 weeks of ADT prior to randomisation. Further details on hormone therapies allowed prior to randomisation are discussed in **Appendix L**.

Any relapsing patients treated with adjuvant or neo-adjuvant hormone therapy alongside their radical surgery or radiotherapy must have completed that period of hormone therapy at least 12 months before joining STAMPEDE and it must have been no longer than 12 months in duration.

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

4.4.3 Choice About Standard-Of-Care Docetaxel

The treating clinician and patient must have decided, prior to randomisation, whether docetaxel is to be given as part of standard-of-care. Docetaxel treatment must start within 12 weeks after starting ADT, preferably within 8 weeks. Patients can have already started docetaxel treatment when randomised providing this is within 12 weeks after starting ADT.

4.4.4 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.

4.4.5 NSAIDs And Cox-2 Inhibitors At Randomisation

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

4.4.6 Starting Trial Treatment

Patients not receiving docetaxel as part of the standard-of-care should start allocated trial treatment 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 ADT (see **Section 6**).

Radiotherapy for patients allocated to Arm H should be commenced within 4 weeks from randomisation and continued according to the predefined scheduled unless toxicity is reported. Any delays in starting research radiotherapy should be discussed with the STAMPEDE team and recorded as appropriate in the relevant CRF.

Docetaxel-treated patients should aim to start allocated trial treatment within 3-4 weeks after the last administration of docetaxel, preferably within a maximum of 6 weeks. Should any docetaxel-related toxicities occur during treatment these need to have recovered to grade 1 before the allocated research treatment begins. Please discuss with the trial team if any docetaxel-related

toxicities of greater severity than grade 1 persist (this excludes alopecia, nail changes and neuropathy, which do not need to have resolved prior to starting research treatment).

Investigators should discuss with the trial team any patient who may not start their allocated trial treatment or where a delay of 6 or more weeks, between last administration and starting research treatment is expected.

4.4.7 CONCOMITANT MEDICATIONS

Before randomising all patients, please check **Table 11 and 12** for drug interactions.

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 4.2**). Of particular interest in this are herbal preparations such as PC-SPES, Prostasol, Saw Palmetto and St John's Wort.

All concomitant medications should be continued throughout the trial unless the responsible clinician decides otherwise. If patients continue to require medication for the management of docetaxel-related toxicities, please discuss this with the trial team. Please see **Section 6** for more information on concomitant medications and their use with abiraterone and enzalutamide.

4.5 ADDITIONAL DETAILS FOR PATIENTS JOINING SUB-STUDIES

If the patient has given their consent to participate in the DNA analysis sub-study, a saliva sample will be collected. This replaces the droplet of blood collected in previous versions of the protocol. An additional element of DNA analysis will involve the collection of plasma samples for patients in the "enzalutamide + abiraterone comparison".

The local pathologist will also be asked to make the tissue block from the tumour sample remaining after primary interrogation available 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. Full details of all sub-studies and instructions relating to the handling of the saliva and blood sample are given in **Section 17** and **Appendix D**.

5 RANDOMISATION AND ENROLMENT

Patients will be allocated to any of the open research arms for which they are suitable. Patients with non-metastatic disease or who have had previous local therapy to the prostate or who have a contraindication to radiotherapy will not be allocated to Arm H (see **Section 4.3**).

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

RANDOMISATIONS
To randomise, call MRC CTU at UCL, 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 a failure-free survival (FFS) event has been experienced and 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 must be reported on the Co-enrolment CRF.

Data sharing agreements with “down-stream” trials are encouraged to improve data quality in both trials and to reduce costs to both organisations.

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 androgen deprivation therapy (ADT) to achieve castration levels of testosterone. The method of ADT is a local choice but must be specified for each patient prior to randomisation. The recommended methods of ADT are given in **Section 6.2.1**. Note that from protocol version 8.0 onwards, bicalutamide monotherapy is no longer permitted as a trial therapy for new patients but patients may switch to a permitted therapy to join the trial.

6.1.1 REQUIRED TIMELINES WHEN STARTING TRIAL TREATMENT

Allocated treatment should start promptly after randomisation. In patients having docetaxel as part of standard-of-care, this will be within 3-4 weeks after the last docetaxel cycle, preferably within a maximum of 6 weeks. In patients not having docetaxel trial treatment should start as soon as possible after randomisation.

6.2 ARM A: ADT ALONE OR ADT + STANDARD-OF-CARE (M0) RT OR ADT +/- DOCETAXEL +/- (M0) RT

The standard-of-care for this patient group is **androgen deprivation therapy** (see **Section 6.2.1**). For some patient groups, this should now be supplemented with standard radiotherapy (see **Section 6.2.2**). From Protocol 14.0 onwards the standard-of-care includes permitted use of docetaxel for patients joining STAMPEDE (see **Section 6.2.3**)

6.2.1 HORMONE THERAPY

The permitted methods of ADT are bilateral orchidectomy, LHRH analogues and LHRH antagonists. Patients having a bilateral orchidectomy are required to adher to the same timelines as specified in **Section 4.4.2.** unless there is a strong clinical reason not to do so. Other methods of ADT should be discussed with the Chief Investigator or the Trial Surgeon. The planned duration of ADT should be at least 2 years.

Bilateral orchidectomy: Operations should be performed by appropriately trained surgeons. A total or sub-capsular 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.

6.2.2 STANDARD-OF-CARE (M0) RT

N0M0 patients: Investigators should give standard radiotherapy (RT) to patients with node negative, non-metastatic disease (N0M0), in accordance with data from the PR07 and SPCG trials. If there is an intention to omit radiotherapy (e.g. contraindications) in patients with N0M0 disease this must be discussed with the Trials Office before consent. See **Section 6.16** for further details of radiotherapy administration.

N+M0 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 [James et all (in press); JAMA Oncology].

Investigators will be asked to state their intention with regards 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.

Standard-of-care radiotherapy is not a core part of the trial, therefore we intend to collect minimal data about the radiotherapy administered. It is accepted that some patients will develop progressive disease before radiotherapy can be administered and if this occurs the reasons for non-delivery of treatment must be recorded on the radiotherapy detail form.

6.2.3 STANDARD-OF-CARE DOCETAXEL

Investigators are strongly encouraged to consider giving docetaxel as part of the standard-of-care for patients with newly-diagnosed metastatic disease based on the survival benefit demonstrated by both STAMPEDE in the primary analysis of the "original comparisons" and CHAARTED.(8) Investigators may also consider giving docetaxel to patients with high-risk locally advanced disease given both the significant improvement in failure-free-survival and consistency of effect for prostate cancer-specific survival shown by STAMPEDE.

The treating clinician and patient must have decided if docetaxel is to be given prior to randomisation and treatment may have started when the patient is randomised. As with standard radiotherapy, minimum data collection will be required however the start and end dates of treatment are needed to ensure the appropriate timelines are met (see **Section 6.1.1**). A confirmation whether the treatment with docetaxel has started or not as planned will also need to be sent to the trial team.

Docetaxel is given according to local protocols as a standard non-trial treatment. The regime used previously within STAMPEDE was 75mg/m2 Day 1 as 1hr IV infusion, plus prednisolone 5mg bid daily for 21 days repeated every 3 weeks for a maximum of 6 cycles.

The STAMPEDE TMG would suggest prednisolone could be omitted and data on the use of co-prescribed steroid will be collected on the relevant CRF (please see **Table 13** for more details)

6.3 ARM B: ADT + ZOLEDRONIC ACID

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached. Please see Protocol version 13.0 for information on the administration of this trial drug

6.4 ARM C: ADT + DOCETAXEL

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached. Please see Protocol version 13.0 for information on the administration of this trial drug

6.5 ARM D: ADT + CELECOXIB

Note: recruitment completed to both celecoxib-containing arms in Apr-2011 at the end of its Activity Stage II. Please see Protocol version 13.0 for information on the administration of this trial drug

6.6 ARM E: ADT + DOCETAXEL + ZOLEDRONIC ACID

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached. Please see Protocol version 13.0 for information on the administration of this trial drug

6.7 ARM F: ADT + ZOLEDRONIC ACID + CELECOXIB

Note: recruitment completed to both celecoxib-containing arms in Apr-2011 at the end of its Activity Stage II. Please see Protocol version 13.0 for information on the administration of this trial drug

6.8 ARM G: ADT + ABIRATERONE

Note: recruitment to the "abiraterone comparison" completed in Jan-2014. Please note that some patients will continue treatment until all types of disease progression or up to a maximum of 2 years. Please see sections below for more information

Androgen deprivation therapy (+/- standard-of-care M0 RT) as described in **Section 6.2.**

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 mineralocorticoid excess. 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.

In patients with M1 disease, treatment with abiraterone will continue from randomisation until all types of progression have occurred, consistent with the COU-AA-301 trial (31) i.e., abiraterone would be given for these patients until a composite assessment based on:

- 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; the first FFS event must be reported as per the other arms; all types of progression (PSA, radiological and clinical) need to be reported once.

In patients with N0M0 disease or N+M0 disease undergoing radical radiotherapy, treatment would continue for 2 years or all types of disease progression as defined for M1 patients, whichever is the sooner. ADT can be discontinued in this group at 2 years at the discretion of the local investigator (see **Section 6.2.1**).

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

If a patient allocated to Arm G develops only biochemical failure, the responsible clinician might switch from abiraterone + prednisolone 5mg od to abiraterone and dexamethasone 0.5mg od.

Trial treatment must stop if other systemic treatments are initiated at any time for disease progression control (including chemotherapy, radium 223 etc). Anti-androgens (i.e. bicalutamide) should not be given in combination with abiraterone due to the risk of toxicity.

See **Section 7.1.2** for further information on the trial definition of progression.

6.9 ARM H: ADT + PROSTATE RADIOTHERAPY IN M1 PATIENTS

Standard-of-care: androgen deprivation therapy +/- docetaxel (as described in **Sections 6.2.1** and **6.2.3**)

Radiotherapy will commence as soon as practicable. For non-docetaxel treated patients, this should ideally be within 4 weeks after randomisation. Docetaxel-treated patients should aim to start trial treatment within 3-4 weeks after the last administration of docetaxel, preferably within 6 weeks (see **Section 6.9.1**)

Treatment will be according to the guidelines in **Section 6.9.1**. Two radiotherapy dose-fractionation schedules are permitted:

- 36Gy in 6 fractions of 6Gy, administered weekly over 6 consecutive weeks
- 55Gy in 20 fractions of 2.75Gy, administered daily, five days per week, over 4 consecutive weeks

Details of the recommendations for outlining, CTV and PTV are in **Section 6.9.1**.

6.9.1 RESEARCH (M1) PROSTATE RADIOTHERAPY TREATMENT ADMINISTRATION

A treatment planning CT scan will be acquired with the patient supine, with empty rectum and comfortably full bladder.

Megavoltage equipment is required with effective photon energies ≥6MV. Minimum source-to-axis distance is 100cm. Field arrangement is at the clinician's discretion: acceptable treatment techniques (field arrangement) include a 3-field (anterior, right lateral, and left lateral), 4-field (anterior, posterior, right lateral, and left lateral), or 6-field (right and left anterior oblique, right and left posterior oblique, and right and left lateral) or equivalent coplanar technique with multi-leaf collimation for all fields to adequately protect normal structures.

The Clinical Target Volume (CTV) will consist of the prostate gland alone as visualized on the treatment-planning CT scan. The base of the seminal vesicles may also be included if they are macroscopically involved. Inclusion of pelvic lymph nodes in the CTV is not permitted. The Planning Target Volume will have a 0.8 cm margin posteriorly and 1.0 cm margin in all other directions around the CTV to account for prostate gland motion and uncertainty in daily treatment setup.

Critical normal tissues should be delineated on the treatment-planning CT scan by the treating clinician:

- Rectum – inferior limit: level of ischial tuberosities; superior limit: sigmoid flexure
- Bladder – entirety

Two radiotherapy dose-fractionation schedules are permitted. In either case, radiotherapy is prescribed such that the PTV receives at least 95% of the prescribed dose:

- 36Gy in 6 fractions of 6Gy, administered weekly over 6 consecutive weeks
- 55Gy in 20 fractions of 2.75Gy, administered daily, five days per week, over 4 consecutive weeks

Dose-volume objectives for each dose-fractionation schedule are shown in **Tables 2** and **3** below. Values have been calculated using the formula BED = D[1+d/(alpha-beta ratio)] assuming an alpha-beta ratio of 3 for rectum and bladder. These are provided for guidance only.

Portal imaging to verify accuracy of treatment delivery may be done according to the participating centre's local guidelines. Image-guidance technology (e.g., gold seed intraprostatic fiducial markers, cone-beam CT scanning) will be permitted according to clinician preference but is not required. Further illustration on the research radiotherapy arm schedule is shown in **Figure 4**.

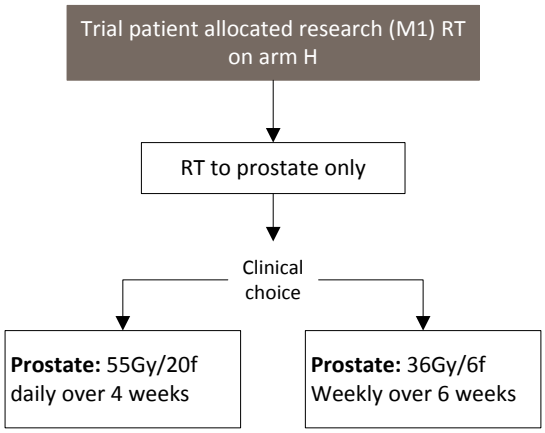
Table 2: Rectal dose volume objectives

55Gy/20f	36Gy/6f	Max Vol (%)
52.5 Gy	33.3 Gy	50%
43.5 Gy	27.8 Gy	60%
26.1 Gy	16.7 Gy	80%

Table 3: Bladder dose-volume objectives

55Gy/20f	36Gy/6f	Max Vol (%)
52.2	33.3	25%
43.5	27.8	50%

Figure 4: Diagram for deciding approach to research (M1) RT to the prostate



6.10 ARM J: ADT + ABIRATERONE + PREDNISOLONE + ENZALUTAMIDE ADMINISTRATION

Standard-of-care: androgen deprivation therapy +/- docetaxel and +/- M0 RT (as described in **Section 6.2**)

Abiraterone as described in **Section 6.8**.

Prednisolone as described in **Section 6.8**.

Enzalutamide will be administered as a 160mg oral dose (four capsules), taken together at the same time every day, with or without food.

Trial treatment must stop if other systemic treatments are initiated at any time for disease progression control (including chemotherapy, radium 223 etc). Anti-androgens (i.e. bicalutamide) should not be given in combination with enzalutamide due to the risk of toxicity.

In patients with M1 disease, treatment with both abiraterone and enzalutamide will continue until all types of progression have occurred, consistent with the approach taken for abiraterone (see **Section 6.8**) i.e., abiraterone and enzalutamide will be given 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 and enzalutamide are open to the investigator's interpretation and discretion. Patients may continue treatment beyond the first failure-free survival (FFS) event ; 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 all types of disease progression as defined for M1 patients, whichever is the sooner. ADT can be discontinued in this group at 2 years at the discretion of the local investigator (see **Section 6.2.1**).

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

If a patient has had PSA progression before commencing abiraterone and enzalutamide (i.e. on or shortly after completing docetaxel), they should still start trial treatment and should continue until radiological and/or clinical progression occurs. In the rare instances of a patient commencing abiraterone and enzalutamide having had biochemical **and** radiological progression, they should continue trial treatment whilst there is perceived evidence of benefit as judged by the local investigator. If a patient develops PSA progression only whilst on abiraterone and enzalutamide, the local investigator might consider switching from from abiraterone + prednisolone 5mg od to abiraterone and dexamethasone 0.5mg od.

See **Section 7.1.2** for further information on the definition of progression.

6.11 ADMINISTRATION, DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITIES

6.11.1 ZOLEDRONIC ACID

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached.
Please see Protocol version 13.0 for information on the administration of this trial drug

6.11.2 DOCETAXEL

Note: recruitment stopped to the zoledronic acid and docetaxel-containing arms in Mar-2013 as recruitment target sample was reached.
Please see Protocol version 13.0 for information on the administration of this trial drug

6.11.3 CELECOXIB

Note: recruitment completed to both celecoxib-containing arms in Apr-2011 at the end of Activity Stage II. No new patients should be receiving this agent as first-line within the trial.
Please see Protocol version 13.0 for information on the administration of this trial drug

6.11.4 ABIRATERONE OR ENZALUTAMIDE + 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.

Enzalutamide can be taken with or without food.

6.11.4.A Abiraterone Contraindications

- Unusual or allergic reaction to past abiraterone acetate treatment
- Uncontrolled hypertension
- Uncontrolled heart failure
- Abnormal liver function or active or chronic liver disease

6.11.4.B Abiraterone Special Warnings and Precautions For Use

Timing of administration compared with meals
Administration of abiraterone acetate with food significantly increased the absorption of abiraterone acetate. Administration of 1000mg dose of abiraterone acetate tablets in fed conditions increased systemic exposure to abiraterone compared with the fasted state. Abiraterone mean Cmax and AUC values increased approximately 7- and 5-fold, respectively, when administered immediately after a low-fat meal. Abiraterone mean Cmax and AUC values increased approximately 17- and 10-fold, respectively, when administered immediately after a high-fat meal. It is, therefore, recommended that abiraterone acetate is taken on an empty stomach.

Cardiovascular history
Abiraterone acetate should be used with caution in patients with a history of cardiovascular disease. The safety of abiraterone acetate in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure has not been established. Before treatment with abiraterone acetate, hypertension must be controlled and hypokalemia must be corrected.

Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, e.g. those with heart failure, recent myocardial infarction, or ventricular arrhythmia.

Blood pressure management
Blood pressure should be monitored every 2 weeks until week 12 and at every follow-up visit after week 12 whilst the patients remain on treatment. For the management of abiraterone induced hypertension see **Table 5.**

Hepatic Impairment
The pharmacokinetics of abiraterone was examined in patients with pre-existing mild or moderate hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control patients. Systemic exposure to abiraterone acetate after a single oral 1000mg dose increased by approximately 11% and by 260% in patients with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone was prolonged to approximately 17.7 hours in patients with mild hepatic impairment and to approximately 18.6 hours in patients with moderate hepatic impairment. No dosage adjustment was necessary for patients with pre-existing mild hepatic impairment. Abiraterone acetate should not be used in patients with pre-existing moderate or severe hepatic impairment.

Hepatotoxicity
Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies. Serum transaminase and bilirubin levels should be measured prior to starting treatment with abiraterone acetate, every 2 weeks for the first 3 months of treatment, and monthly thereafter.

If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum alanine aminotransferase (ALT), should be measured immediately. See **Table 4** for the management of abiraterone induced hepatotoxicty.

Renal Impairment
The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable hemodialysis schedule versus matched control patients with normal renal function. Systemic

exposure to abiraterone after a single oral 1000mg dose did not increase in patients with end-stage renal disease on dialysis.

6.11.4.C Abiraterone Undesirable Effects

The safety profile of abiraterone acetate across studies in CRPC was distinct from the safety profile typically associated with myelosuppressive cytotoxic agents. The most common adverse drug reactions observed in the integrated safety data for those patients who received 1000mg abiraterone acetate plus prednisone or prednisolone in clinical studies (n=1,070) were fatigue, arthralgia, peripheral oedema, back pain, bone pain, nausea, constipation, hypokalemia and anaemia.

The adverse events graded as 3 or 4 and which occurred in more than 5% of patients were fatigue, peripheral oedema, anaemia and back pain see **Appendix G**.

6.11.4.D Abiraterone Overdose

There have been no reports of overdose of abiraterone acetate during clinical studies. There is no specific antidote to abiraterone acetate. In the event of an overdose, administration of abiraterone acetate should be stopped and general supportive measures undertaken, including monitoring for cardiac arrhythmias. Liver function should also be assessed.

6.11.4.E Enzalutamide Contraindications

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Monitoring should continue for at least the first month of treatment and dose adjustments considered. Given the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

6.11.4.F Enzalutamide Special Warnings and Precautions For Use

History of seizures

Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medications that may lower the seizure threshold. Enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

Hepatic impairment

A hepatic impairment study showed that the composite AUC of enzalutamide plus N-desmethyl enzalutamide after administration of a single dose of enzalutamide was similar in patients with baseline mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C respectively) relative to patients with normal hepatic function, and no starting dose adjustment is needed.

Renal impairment

Based on population pharmacokinetics modeling the factors of age, weight and renal function (Creatinine clearance ≥ 30 mL/min) do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are needed.. Clinical data are insufficient to assess the

potential effect of severe renal impairment (Creatinine clearance < 30 mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

6.11.4.G Enzalutamide Overdose

There is no antidote for enzalutamide. In the setting of an overdose, stop treatment with enzalutamide and initiate general supportive measures taking into consideration the t1/2 of 5.8 days. Patients may be at increased risk of seizures following an overdose.

6.11.4.H Management of specific toxicities due to abiraterone and enzalutamide

The safety monitoring and toxicity management plan described below takes into account AEs based on the reported clinical safety data of abiraterone and enzalutamide given separately. There are limited reported data on the safety and toxicity of the combination of enzalutamide and abiraterone however the recommendations summarised here have been updated in light of the experience gained in STAMPEDE as recommended by the STAMPEDE TMG.

Seizures

If any patient suffers a seizure whilst on treatment, enzalutamide should be discontinued immediately. Abiraterone and prednisolone can be continued providing there are no abiraterone-specific toxicities.

Table 4: Management of Abnormal Liver Function Tests (LFTs)

TOXICITY EVENT	ACTION
Grade 1 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN)	The frequency of LFT monitoring should be increased to at least weekly, if the investigator judges that the laboratory abnormalities are potentially related to study medication. No dose reduction is required.
Grade 2 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN)	Withhold abiraterone, enzalutamide and all other concomitant medications that are potentially hepatotoxic. The frequency of LFT monitoring should be increased to at least weekly until the liver function tests return to baseline value or grade 1 when all trial medication can be re-started. No dose reduction is required after one episode providing this resolved within 4 weeks but should be considered if Grade 2 derangements recurs.
Grade 3 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >5X ULN; increase in total bilirubin to >3X ULN),	Withhold abiraterone and enzalutamide and all other concomitant medications that are potentially hepatotoxic. At least weekly monitoring is required until the LFTs return to baseline value or grade 1. Enzaluatmide can be re-started with no dose reduction. See below for abiraterone re-challange.
Grade 4 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >20x ULN; increase in total bilirubin to >10x ULN)	Patients must discontinue abiraterone and enzalutamide immediately. At least weekly monitoring is required until the LFTs return to baseline value or grade 1 and then prednisone can be discontinued and the investigator can consider restarting enzalutamide. Abiraterone should not be re-introduced.
RE-CHALLENGE AFTER GRADE 3 TOXICITY	**ACTION**
If study treatment resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin	Resume study treatment with abiraterone dose reduction to 750mg when grade 3 toxicities resolve to grade 1 or baseline.
If Grade 3 or higher increases in AST, ALT or bilirubin recur after the first dose reduction	Hold study medication and all other concomitant medications that are potentially hepatotoxic. At least weekly LFT monitoring is required, starting immediately regardless of study schedule and continued until a return to baseline values or Grade 1.
If study treatment resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction	Resume study treatment with abiraterone dose reduction to 500mg when AST, ALT or bilirubin returns to baseline value or Grade 1.

An opinion from a hepatologist should be considered if there are any concerns or liver function derangement shows no improvement within 2 weeks of discontinuation of abiraterone.

Table 5: Management of hypertension

TOXICITY EVENT	ACTION
Grade 1-2	Management as per investigator with anti-hypertensive treatment and increase frequency of blood pressure monitoring to at least weekly. Follow local guidance for selection of anti-hypertensives but avoid thiazide diuretics to minimise risk of serum potassium derrangment. Calcium channel antagonists of beta blockers are often preferred. As with other symptoms of minerlocorticoid excess, consider increasing prednisolone dose to 5mg BID.
Grade 3-4	Withhold abiraterone and enzalutamide. Adjust or add anti-hypertensive medications to mitigate the toxicity. When hypertension resolves to Grade ≤1, resume both enzalutamide and abiraterone at full dose with prednisolone 5mg bid.

An opinion from a cardiologist should be considered if blood pressure control is not achieved within 4 weeks.

Table 6: Management of hypokalaemia

TOXICITY EVENT	ACTION
Grade 1* (LLN- 3.0nM)	Supplement with oral potassium and monitor closely and increase prednisolone dose to 5mg BID. Exclude and manage other causes of hypokalemia.
Grade 3 (<3.0mM–2.5mM) or life-threatening Grade 4 (<2.5mM)	Abiraterone will be permenently discontinued and the patients will be hospitalized for intravenous potassium replacement and cardiac monitoring. After the return of serum potassium to normal, prednisolone will be discontinued. The patient can continue on enzaluatamide alone. If hypokalaemia persists consider a dose reduction of enzalutamide to 120mg once a day.

*No Grade 2 definition in CTCAE v3.0

Table 7: Management of fluid retention/oedema

TOXICITY EVENT	ACTION
Grade 1-2	Increase prednisolone dose to 5mg bid.
Grade 3-4	Withhold abiraterone. Consider addition of mineralocorticoid receptor antagonist eplerenone until resolution of symptoms. Enzalutamide can be continued. When fluid retention/oedema returns to baseline or resolves to ≤Grade 1, resume abiraterone at full dose with prednisone 5mg bid, if symptoms do not resolve abiraterone should not be re-started and enzalutamide should be dose reduced to 120 mg per day.

Table 8: Management of diarrhoea

TOXICITY EVENT	ACTION
Grade 1-2	Symptomatic management.
Grade 3-4	Withhold abiraterone. If no improvement reduce dose of enzalutamide to 120 mg per day. Once resolved to Grade 1, recommence abiraterone at 750 mg per day.

Table 9: Management of arthralgia & muscle Pain

TOXICITY EVENT	ACTION
Grade 1-2	Symptomatic management.
Grade 3-4	Reduce dose of enzalutamide to 120 mg per day

Table 10: Management of fatigue

TOXICITY EVENT	ACTION
Grade 1-2	No change in treatment
Grade 3-4	Patients who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with enzalutamide for 1 week or until the toxicity grade improves to grade 2 or lower severity. Subsequently, study drug dosing may be re-started at the original dose (160 mg/day) or at a reduced dose (120mg/day or 80mg/day) in consultation with the study team.

6.11.4.I Management of Specific Toxicities from Prednisolone

Prednisolone/prednisone will be started at 5mg once daily, to prevent secondary mineralocorticoid excess.

Prednisolone/prednisone 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 symptoms of cushings syndrome (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 ADT.

6.12 CONCOMITANT MEDICATIONS AND DRUG INTERACTION

6.12.1 ABIRATERONE: INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Details on drug interactions are described in **Appendix G.** The table below provides a summary on the main interactions.

Anti-androgens

Abiraterone is steroid synthesis inhibitor and should not be given together with any other anti-androgens given the risk of toxicity. Cyproterone acetate should be discontinued 10 days and

finasteride stopped 48 hours before commencing enzalutamide. Concommitent use of dutasteride, bicalutamide and flutamide are all contraindicated.

Table 11: Drugs which may interact with Abiraterone

DRUGS WHICH MAY INCREASE ABIRATERONE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP3A4 inhibitors	Macrolide antibiotics	Clarithromycin	Avoid or hold abiraterone if short term use unavoidable given increased risk of abiraterone toxicity
	Anti-fungals	Ketoconazole Itraconazole Voriconazole	Avoid or hold abiraterone if short term use unavoidable given increased risk of abiraterone toxicity
DRUGS WHICH MAY REDUCE ABIRATERONE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP3A4	Anti-epileptics*	Phenytoin Carbamazepine Phenobarbital Primadone	Contraindicated
	Anti-depressants	St Johns Wart	Contraindicated
	Anti-TB	Rifampicin Rifabutin	Contraindicated
	Anti-retroviral	Atazanavir Saquinavir Ritonavir Indinavir Nelfanavir	Contraindicated
DRUGS WHICH MAY ACCUMULATE WHEN GIVEN WITH ABIRATERONE			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2D6	Cardiac	Metoprolol Propranolol Propafenone Flecanide	Monitoring required as drug levels may increase with abiraterone use
	Anti-depressants	Desipramine Venlafaxine Citalopram	Monitoring required as drug levels may increase with abiraterone use
	Anti-psychotics	Haloperidol Risperidone	Monitoring required as drug levels may increase with abiraterone use
	Analgesia	Tramadol Codeine Oxycodone	Monitoring required as drug levels may increase with abiraterone use
	Alpha blockers	Tamsulosin	Monitoring required as drug levels may increase with abiraterone use
	Anti-diabetic	Repaglinide	Monitoring required as drug levels may increase with abiraterone use

*Please note that any hisotry of epilepsy is an exclusion criteria.

6.12.2 ENZALUTAMIDE: INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Details on drug interactions are described in **Appendix G.** The table below provides a summary on the main interactions

Anti-androgens

Enzalutamide is potent androgen receptor antagonist and should not be given together with any

other anti-androgens given the risk of toxicity. Cyproterone acetate should be discontinued 10 days and finasteride stopped 48 hours before commencing enzalutamide. Concommitent use of dutasteride, bicalutamide and flutamide are all contraindicated.

Table 12: Drugs which may interact with Enzalutamide

DRUGS WHICH MAY INCREASE ENZALUTAMIDE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C8 inhibitors	Lipid-lowering	Gemfibrozil	Avoid, if no alternatives, reduce enzalutamide dose to 80mg
DRUGS WHICH MAY DECREASE ENZALUTAMIDE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C8 inducers	Anti-TB	Rifampicin Rifabutin	Avoid and switch to an alternative if possible
CYP3A4 inducers	Anti-epileptics	Phenytoin Carbamazepine Phenobarbital	Contraindicated
	Anti-depressant	St Johns Wart	Contraindicated
	Anti-retrovirals		Contraindicated
ENZALUTAMIDE MAY REDUCE DRUG LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C19	Gastric protection	Omeprazole	Omeprazole AUC reduced by 70% Consider increasing dose of omeprazole for same therapeutic effect
CYP3A4	Analgesia	Fentanyl* Alfentanil* Tramadol	Monitor closely and consider alteratives
	Immunosuppressants	Sirolimus* Tacrolimus* Cyclosporine*	Monitor closely
	Anti-migraine	Ergotamine	Monitor closely
	Cardiac	Nifedipine Ivabradine	Monitor closely, consider alternatives
CYP2C9	Anti-epileptics	Phenytoin*	Contraindicated
	Anti-coagulants	Warfarin*	Warfarin AUC reduced by 56% Consider switching to low molecular heparin, increase INR monitoring if this is not possible
DRUGS WHICH MAY ACCUMULATE WHEN GIVEN WITH ENZALUTAMIDE			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
p-gp		Colchicine* Dabigatran* Digoxin*	Monitor closely

*narrow therapeutic index

6.13 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**).

6.14 MEASURES OF COMPLIANCE/ADHERENCE

Date of treatment, dose, delays and reasons for delays or dose modifications of all trial treatments will be recorded. The estimated number of abiraterone tablets and enzalutamide capsules taken in a given time period will also be recorded as well as any dose reductions.

6.15 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. Up-to-date versions of all CRFs can be found on the trial website (http://www.stampedetrial.org/) and centres will be notified of any changes throughout the course of the trial. The type of data to be recorded is detailed in the Assessments and Procedures section (**Section 7**).

6.16 ADMINISTRATION OF STANDARD RADIOTHERAPY TO NON-METASTATIC PATIENTS

6.16.1 TREATMENT DETAILS

Standard radiotherapy will be given to appropriate patients in each of the trial arms, following a period of neo-adjuvant ADT therapy, as is generally standard in UK practice. 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 patients. 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 to the prostate and seminal vesicles or the equivalent using hypo-fractionated schedules. These recommendations are summarised in **Figure 5**. Alternative dosing schedules are permitted but must be agreed with the STAMPEDE Trial Management Group.

6.16.1.A Standard-of-care RT Timing in M0 patients

Radiotherapy should be given around 6 to 9 months after randomisation in all trial arms and, if receiving docetaxel as part the standard-of-care (permitted from Protocol 14.0), the patient must have sufficiently recovered from any docetaxel toxicity before RT can begin.

6.16.1.B Type Of standard-of-care RT in M0 patients

Conformal or intensity modulated radiotherapy.

6.16.1.C Standard Clinical Target Volume in M0 patients

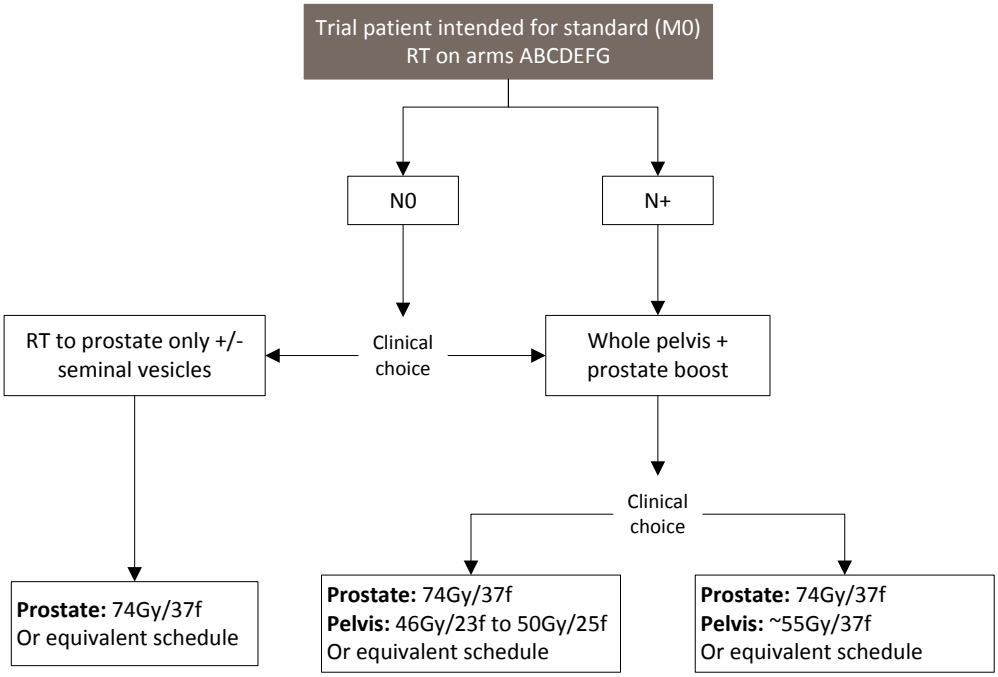
- **CTV1:** Prostate plus seminal vesicles
- **CTV2:** (Node positive patients) Regional lymph nodes to include internal iliac and the inferior part of the common iliac nodes as used in EORTC trial 22961 (32)
- **PTV1:** CTV1 plus 10-15 mm according to local practice

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

6.16.1.D Standard-of-care RT Dose in M0 patients

Prostate dose of 74Gy in 2Gy fractions or equivalent, with optional dose to the pelvic nodes of 55-60Gy in 2Gy fractions or equivalent using IMRT to deliver the treatment over 37 fractions, suggested dose is 55Gy in 37 fractions with IMRT in line with CHHIP trial. Higher doses may be considered if the department is experienced in using IMRT for nodal radiotherapy, particularly as data emerges from the PIVOTAL trial of nodal IMRT in high-risk node negative patients where a nodal dose of 60Gy in 37 fractions is being evaluated. Alternative schedules should be agreed with the STAMPEDE Trial Management Group.

Figure 5: Diagram for deciding recommended approach to standard-of-care (M0) RT in non-metastatic patients



6.17 NON-TRIAL TREATMENT

6.17.1 MEDICATIONS PERMITTED

Guidance on concomitant medications and drug interaction is detailed in **Section 6.12**.

6.17.2 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.

Please see **Section 6.12** for further details on drug interactions for abiraterone and enzalutamide.

7 ASSESSMENTS AND PROCEDURES

7.1 SCHEDULE FOR ASSESSMENTS

A detailed follow-up schedule is given in **Table 13, 14 and 15**.

7.1.1 PSA MEASUREMENTS

All patients should have PSA measured pre-androgen deprivation 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 4.4.1**. 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 should be reported on a progression form & additional treatment form:

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

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. All SREs are reported on the Progression and Additional Treatment CRF to confirm whether this represents disease progression.

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

Medical review and PSA measurements follow the same 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 DATA COLLECTION FOR STANDARD DOCETAXEL

The decision to use docetaxel as part of the standard-of-care must be made before randomisation and should be recorded on the randomisation CRF. The date of the first cycle should be recorded at the time of randomisation; this can be a planned date when randomisation occurs prior to docetaxel commencing but must be within 12 weeks of starting ADT (see **Section 4.4.3**). All further details should be recorded on the standard-of-care docetaxel CRF.

If a patient does not receive the planned docetaxel this must also be recorded on the standard docetaxel CRF together with the reason why.

7.1.5. DATA COLLECTION AND NON-ADMINISTRATION OF STANDARD RADIOTHERAPY

There are CRFs to be completed for patients receiving primary radiotherapy whether this is standard radiotherapy for M0 patients on any arm or prostate radiotherapy for Arm H patients. All radiotherapy and acute side effects details will be recorded on the Radiotherapy Detail and Acute Toxicity Forms; any late side effects will be recorded on the follow up 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 Detail form together with the reason for non-administration of the treatment.

7.1.6. DATA COLLECTION PALLIATIVE RADIOTHERAPY

For patients who receive palliative radiotherapy as part of first line treatment, a Palliative Radiotherapy CRF should be completed.

The progression and additional treatment CRF is used to record details of any further palliative radiotherapy given at progression. This includes palliative RT for SREs e.g. bone pain and spinal cord compression, as well as salvage RT to the prostate. For SRE's an additional assessment is required to determine if this represents progression.

7.1.7 DATA COLLECTION RESEARCH (M1) RADIOTHERAPY

All RT data should be reported on the RT Detail CRF; acute toxicity data should be reported once the primary course of RT has been completed. Adverse events such, TURPs, SREs should be reported on the FU form.

7.1.8. 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 radiological investigations 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 all relevant 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, for example NHS Information Centre/Office of National Statistics (ONS) in England/Wales and General Register Office in Scotland, Hospital Episode Statistics (HES). If the clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

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 of the final comparison 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.

Table 13: Summary of timing of case report forms

CASE REPORT FORMS	TIMING OF ASSESSMENT AND CRF
Baseline	
Bone Density Risk Factor	At randomisation
Randomisation	At randomisation
Baseline	At randomisation
Cardiovascular Assessment	At randomisation
Pathology	At randomisation. When pathology sample has been taken and sent to Sponsor's designated laboratory.
Treatment	
Standard-of-care docetaxel	Complete for all patients 20 weeks after randomisation
Hormone Therapy	Form to be sent with corresponding follow-up form if there is a change in hormone therapy to report
Abiraterone and Enzalutamide Treatment	Treatments administered daily; form to be sent at week 6 and with corresponding follow-up form if there is a change in treatment to report
RT detail	• When standard-of-care radiotherapy is completed or if planned RT is no longer to be given • Arm H when research RT completed • Arm A (M1) at 3 months Once primary RT is completed for Arm H patients or those receiving RT as standard-of-care For patients who did not receive primary RT (since Protocol 9.0 regardless of being planned) this should be completed 10 months after randomisation or 3 months for newly-diagnosed M1 patients to confirm RT was not given
RT Acute Toxicity	For all patients who receive primary RT.
Assessments	
Follow-Up	Every 6 weeks for 6 months, then every 12 weeks until 2 years, then every 6 months until 5 years and annually thereafter. (See **Table 7** for more information.)
Palliative Radiotherapy	If applicable, when a palliative radiotherapy course is completed.
End of Treatment	When each treatment is completed (either at end of scheduled treatment or at early cessation of treatment).
Progression & Additional Treatment	At the first occurrence of each type of progression, including skeletal-related events and whenever a patient that has progressed receives additional treatment for progression. All SREs requiring additional treatment should be recorded on this form and an assessment made as to whether this constitutes progression.
Additional Treatment Update	Whenever a patient who has previously progressed received additional treatment but has not experienced a new type of progression
Serious Adverse Event	Following any Serious Adverse Event
Death	At Death
Administration	
Patient Transfer	When a patient is transferred to a different hospital for the administration of trial treatment and follow up
Co-enrolment	When a patient is co-enrolled in any other clinical trial. Please see **Section 5.1** for more information

Table 14: Data required on follow-up forms

TIMING OF FOLLOW-UP	PSA	EVIDENCE OF PROGRESSION	ANDROGEN DEPRIVATION THERAPY	TREATMENT	UNSCHEDULED VISITS	TOXICITIES
Follow-up Form	✓	✓	✓	✓	✓	✓
Follow-up Form (Post-Progression)	✓	✓	✓	x	✓	X*

* Toxicity information will be collected for Arm G and J patients if progression has occurred but trial treatment continues

Table 15: Schedule for completion of treatment and outcome forms by arm.

Timing From Randomisation			Treatment Forms		Outcome forms	
Years	Months	Weeks	ABI and/or ENZA	RT	Follow-up[Ψ]	QL + HE[¥]
6-Weekly						
-	-	6	G, J	-	All arms	All arms
-	-	12	G, J	M1: A,H	All arms	All arms
-	-	18	G, J	-	All arms	All arms
-	6	24	G, J	-	All arms	All arms
12-Weekly						
-	9	36	G, J	-	All arms	All arms
1	12	48	G, J	M0: A,B,C,E,G, J	All arms	All arms
-	15	60	G, J	-	All arms	All arms
-	18	72	G, J	-	All arms	All arms
-	21	84	G, J	-	All arms	All arms
-	-	96	G, J	-	All arms	All arms
6-Monthly						
2	24	104	G, J	-	All arms	All arms
	30	130	G, J	-	All arms	All arms
3	36	156	G, J	-	All arms	All arms
	42	182	G, J	-	All arms	All arms
4	48	208	G, J	-	All arms	All arms
	54	234	G, J	-	All arms	All arms
5	60	260	G, J	-	All arms	All arms
Annual						
6	72	-	G, J	-	All arms	All arms
7	84	-	G, J	-	All arms	All arms
Etc	-	-	G, J	-	All arms	All arms

Key:

A = SOC
B = SOC + zoledronic acid
C = SOC + docetaxel
D = SOC + celecoxib
E = SOC + zoledronic acid + docetaxel
F = SOC + zoledronic acid + celecoxib
G = SOC + abiraterone
H = SOC + M1 research RT to the prostate
J = SOC + enzalutamide + abiraterone

Notes:

Ψ See Table 6 for information required at follow-up
† Form records data for two cycles
‡ Form records data for three cycles
¥ 1st 700 patients and those recruited from protocol version 8.0 onwards only

Note: Radiotherapy Detail & Acute Toxicity, Late RT Toxicity, HT and Abiraterone & Enzalutamide Treatment, Palliative Radiotherapy Progression, SAE, End of Treatment, Co-enrolment and Death forms to be completed as required.

Note: Docetaxel forms are no longer shown on the table as all patients will have completed treatment with docetaxel

Note: Recruitment was stopped to Arms D and F in April 2011 and completed to Arms B, C and E in March 2013; Arm G in January 2014

8 STOPPING OF TREATMENT OR FOLLOW -UP

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

8.1 STOPPING RESEARCH INTERVENTIONS

A patient may stop trial treatment for the following reasons:

- Progression whilst on therapy (trial treatment must be discontinued in this instance). For patients randomised to Arm G or J, please refer to **Section 6.8** for criteria to stop treatment
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Withdrawal of consent for treatment
- Any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion
- Intention to commence a new anti-cancer treatment due to evidence of relapse.

The reason should be recorded on the relevant treatment and the End of Treatment form. In the case of abiraterone or enzalutamide and abiraterone, the disease event for stopping treatment may be after the first reportable failure-free survival event (see **Section 6.8**). In the event of PSA progression whilst on standard docetaxel, allocated trial treatment may be still initiated and continued until evidence of radiological and/or clinical progression. If a patient commences trial treatment having already progressed (biochemical and/or radiological) this should be recorded on a progression form but trial treatment should start and continue whilst there is perceived evidence of benefit as judged by the local investigator.

Unless a patient states otherwise, consent is assumed for continued recording 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. To document the transfer process the main contact person at both the current and receiving hospitals should complete and sign the Patient Transfer Confirmation form. A fully completed form must be returned to the CTU prior to the patient transfer and ideally any outstanding data queries for the patient should be completed prior to transfer.

On receipt of the completed transfer form a member of the STAMPEDE team will confirm the database has been updated and request confirmation of the name of the patient's new Clinician. Photocopies of the following documents may then be sent to the new hospital to complete the transfer and copies must be also retained at the original site for monitoring purposes:

- Consent form
- Completed CRFs

- Any documentation relating to the patient's participation in STAMPEDE (patient names must be removed from any documentation).

8.3 EARLY CESSATION OF TRIAL PARTICIPATION

If a patient explicitly withdraws consent to have any further trial data recorded their decision must be respected and the MRC CTU must be informed in writing. All communication surrounding the early cessation of trial participation should be noted in the patient's records. Please note data prior to this decision will still be required.

In the majority of cases, patients give permission for their data and information on their health to continue to be collected via clinical notes and national registries. Any information on the follow-up status, however minimal, would be helpful.

Early stopping of follow-up should not be undertaken lightly and the site must consider the implications for the trial and the patient in reaching such a decision. Without long-term data, the efficacy of trial treatments would be less reliable and could lead to inconclusive results. The early stopping of trial treatment should not lead to the early cessation of trial participation and in such cases follow-up assessments should be continued as per trial protocol.

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.

Table 8 shows the allocation weighting for each arm by protocol version. The relative weighting within each pairwise comparison remains constant throughout.

9.1.1 VERSION 7

From the outset, the trial had 1 control arm (A) and 5 research arms (B, C, D, E and F).

As the control arm is the comparator arm for all the research arms, twice as many patients were recruited to the control arm as to each of the original research arms as this is an efficient design where there are multiple comparisons to be made. Therefore, the initial randomisation ratio will be 2A:1B:1C:1D:1E:1F. From version 7.0, accrual to the celecoxib-containing arms was halted and the allocation ratio was 2A:1B:1C:0D:1E:0F.

9.1.2 VERSION 8

From version 8.0, an additional research arm (G) was introduced. The allocation weighting for the additional Arm G is 2, meaning that as many patients are contemporaneously randomised to Arm G as the control Arm A: the randomisation ratio is 2:2 (equivalent to 1:1, control:abiraterone). This gave an overall allocation ratio of 2A:1B:1C:0D:1E:0F:2G. 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 arm G), the allocation ratio will be 2A:0B:0C:0D:0E:0F:2G (or 2A:2G). 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.

9.1.3 VERSION 9

Version 9.0 introduced a "M1|RT comparison" for men with newly-diagnosed metastatic disease which is irrelevant to a subset of men joining STAMPEDE. This could only be achieved by splitting the randomisation system so that newly-diagnosed patients with M1 disease, no planned RT and no contraindication to RT are randomised 2A:1B:1C:0D:1E:0F:2G:2H and other men are randomised 2A:1B:1C:0D:1E:0F:2G:0H. Note that the allocation ratio for each pairwise comparison in unaffected, only the rate at which comparisons accrue.

9.1.4 VERSION 10 AND 11

Version 10.0 followed the successful completion of recruitment to Arms B, C and E. Therefore, the allocation ratio will be 2A:0B:0C:0D:0E:0F:2G (or 2A:2G) for M0 patients and A2:B0:C0:E0:D0:F0:G2:H2 for M1 radiotherapy arm patients (2A:2G:2H).The equal allocation ratio is suitable with fewer research arms open.

Version 11.0 then followed the successful completion of recruitment to Arm G, therefore for a short period of time STAMPEDE was only open to recruitment of newly-diagnosed M1 patients eligible for the "M1|RT comparison". Therefore the allocation ratio was A:H.

9.1.5 VERSION 12

Version 12.0 introduces a further allocation, Arm J: HT + abiraterone + enzalutamide. This allocation will be available to all patients. Accounting for Arm H still recruiting, this can only be achieved by keeping the randomisation system split so that newly-diagnosed patients with M1 disease and no contraindication to RT will be randomised 2A:0B:0C:0D:0E:0F:0G:2H:2J and other men will be randomised 2A:0B:0C:0D:0E:0F:0G:0H:2J. This can be simplified to equal allocation in these groups to A:H:J and A:J respectively.

Table 16: Allocation to each arm by protocol version

PROTOCOL	NEWLY-DIAGNOSED M1 PATIENTS									OTHER PATIENTS								
VERSION	A	B	C	D	E	F	G	H	J	A	B	C	D	E	F	G	H	J
V1	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V2	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V3	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V4	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V5	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V6	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-	**2**	**1**	**1**	**1**	**1**	**1**	-	-	-
V7	**2**	**1**	**1**	*0*	**1**	*0*	-	-	-	**2**	**1**	**1**	*0*	**1**	*0*	-	-	-
V8	**2**	**1**	**1**	*0*	**1**	*0*	**2**	-	-	**2**	**1**	**1**	*0*	**1**	*0*	**2**	-	-
V9	**2**	**1**	**1**	*0*	**1**	*0*	**2**	**2**	-	**2**	**1**	**1**	*0*	**1**	*0*	**2**	0	-
V10	**2**	*0*	*0*	*0*	*0*	*0*	**2**	**2**	-	**2**	*0*	*0*	*0*	*0*	*0*	**2**	0	-
V11	**2**	*0*	*0*	*0*	*0*	*0*	*0*	**2**	-	**2**	*0*	*0*	*0*	*0*	*0*	*0*	0	-
V12	**2**	*0*	*0*	*0*	*0*	*0*	*0*	**2**	**2**	**2**	*0*	*0*	*0*	*0*	*0*	*0*	0	**2**
V13	**2**	*0*	*0*	*0*	*0*	*0*	*0*	**2**	**2**	**2**	*0*	*0*	*0*	*0*	*0*	*0*	0	**2**
V14	**2**	*0*	*0*	*0*	*0*	*0*	*0*	**2**	**2**	**2**	*0*	*0*	*0*	*0*	*0*	*0*	0	**2**

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 activity in each research arm as the trial progresses. These are listed in **Table 17**. 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 17: Trial Outcome Measures by Comparison Stage

TRIALS STAGE	PRIMARY OUTCOME MEASURES	SECONDARY OUTCOME MEASURES
Pilot phase	Safety*	Feasibility
Activity Stage (AS) I-III	Failure-free survival (FFS)†	Overall survival (OS) Toxicity Skeletal-related events
Efficacy Stage (ES) IV	Overall survival	Quality of life Cost effectiveness Failure-free survival† Toxicity Skeletal-related events

*Based on toxicity
†Including biochemical failure (see **Appendix J**)

9.3 SAMPLE SIZE: PRINCIPLES AND ASSUMPTIONS

The overall design for this study is a multi-arm multi-stage, multi-centre randomised controlled trial. There are a number of stages for each research arm: a Pilot Phase, several Activity Stages and a final Efficacy Stage. Full details of the methodology underlying the trial design are given by Royston et al. (33, 34) 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). (35)

The trial was designed under the assumptions in **Table 18**, and additionally, we assume a slightly higher proportion of non-metastatic than metastatic patients joining the trial such that median FFS is two years and median OS four years for the whole cohort.

Table 18: Hazard ratio assumptions under null and alternative hypotheses

SIZE OF HR	PILOT	AS I-III	ES IV
Under null hypothesis (H0)	n/a	HR(FFS) = 1.00	HR(OS) = 1.00
Under alternative hypothesis (H1)	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 Documents which are available on request.

Note that, from protocol version 8.0, standard-of-care RT was introduced to the majority of patients with N0 M0 disease. This is likely to improve the outcomes for this group. Further agents are starting to be licensed for patients with castrate-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, 6 and 7 years rather than just 3and 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, including some variations on these assumptions.

Throughout recruitment to protocol version 12.0, at least, the proportion of metastatic men joining the trial has been fairly constant, at around 60%. From protocol version 9.0, we introduced an allocation, Arm H, only for men with (newly diagnosed) M1 disease. This means that further comparisons for the whole patient group will have proportionately fewer metastatic patients and, therefore, fewer events at any given moment in time. This will affect contemporaneously-recruiting comparisons, such as the "enzalutamide + abiraterone comparison" introduced in protocol version 12.0. Median survival may therefore be higher in that comparison, at around 7 years.

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

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

It was anticipated that 210 patients would be recruited to the Pilot Phase from a limited number of centres over a one year period. Approximately 60 patients would be randomised to the control arm and 30 patients to each of the five research arms, each of which were assessed for safety and feasibility. If recruitment proved unfeasible or any of the research arms proved unsafe or not feasible to administer (e.g., poorly tolerated or unexpected toxicity) recruitment to these arms would have been discontinued. There were 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. When 210 patients had been on the trial for a minimum of 18 weeks, the Independent Data Monitoring Committee (IDMC) reviewed the data from the Pilot Phase and continued to the trial during this period as equipoise remained. Recruitment continued beyond this point. Safety data are assessed throughout the trial.

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

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

The Activity Stage analyses 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(true) represent the hazard ratio (HR) of the i^{th} research arm to the control arm, and HRi(observed) the observed value. Discontinuation of accrual of further patients was considered for the i^{th} research regimen at each of Activity Stages I-III according to the guidelines in **Table 19**.

Table 19: Guidelines for stopping accrual to the original research arm

ACTIVITY STAGE	NUMBER OF CONTROL ARM EVENTS	CONSIDER DISCONTINUATION IF HR_i(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 was planned for when around 403 deaths have been observed in the control arm. This gave 90% power to detect the targeted hazard ratio of 0.75 at one-sided significance level of 0.025. The actual timing of this analysis, balancing continued accrual with just follow-up, depended 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 2,800 and 3,600 patients were planned to be entered into the original research comparisons of the trial over a period of between 5½ and 7 years. The exact number of patients entered depended on the observed accrual rate and the observed event rate, which was, in itself, dependent on the mix of patients joining the trial from the broad spectrum of eligibility. The primary analysis on overall survival required around 403 deaths to be observed on the control arm. Accrual continued until the main analysis could be foreseen so that the overall duration of the comparisons would be as short as possible (longer accrual facilitates this) and so that few, if any, patients remained on treatment when the main results are released. The statistical team have monitored and projected the analysis timelines using the `artpep` command in Stata. Results were presented in May-2015. Further information is available in the Statistical Master File.

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

9.5.1 PILOT PHASE: ADDITIONAL RESEARCH ARM G

A similar approach is being followed for the additional research Arm G, as detailed for the original research arms in **Section 9.4.1**. The IDMC reviewed safety data, in the context of data from the control arm, when the first 30 patients allocated to Arm G had been on trial for at least 18 weeks.

Furthermore, an additional review of safety was performed when 30 patients with newly-diagnosed non-metastatic disease allocated to Arm G had been on trial for at least 18 weeks. Both of these milestones were successfully completed.

9.5.2 ACTIVITY STAGES I-III: ADDITIONAL RESEARCH ARM G

The same principles are 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 first started recruitment 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 analyses is lower for the assessment of abiraterone to the assessment of the original research arms. This is shown in **Table 20**.

Table 20: Guidelines for stopping accrual to additional research Arms G and H

ACTIVITY STAGE	NUMBER OF CONTROL ARM EVENTS	CONSIDER DISCONTINUATION IF HR_G(OBSERVED) IS…
I	~75	>1.00
II	~142	>0.92
III	~221	>0.89

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 will give 90% power to detect the targeted hazard ratio of 0.75 at a one-sided significance level of 0.025.

9.5.4 SAMPLE SIZE FOR ADDITIONAL RESEARCH ARM G

Up to around 1,800 patients will join the abiraterone comparison, with half allocated to the research arm. Consideration was given to ceasing further randomisations to Arm G if it was not showing sufficient evidence of activity at the interim analyses, just as was done for research Arms B to F.

The original plan intended for accrual to be halted either when 1,500 patients had been recruited or after 3 years, whichever was the sooner, providing the accrual rate remained above 50 patients/months.

The total number of patients joining this comparison depended not just on the same issues as the "original comparisons" (notably, observed accrual and event rates), but also the length of time that the original research arms co-recruited alongside this additional research arm; it was originally assumed that this would be for approximately 1 year, but it was closer to 1.5 years. The sample size calculations and projected durations are fairly robust to changes in the length of co-recruitment with the original research arms and future co-recruitment with any further research arms which the Trial Management Group may introduce. Many scenarios are detailed in the Statistical Design Document.

In Sep-2013, the target sample size for the "abiraterone comparison" was increased from around 1,500 patients to around 1,800 patients, with note that the efficacy analysis remains unchanged and is still to be triggered by around 267 control arm deaths. This increase in sample size was primarily because of an increase in the proportion of non-metastatic patients joining the comparison; this related to the activation of Arm H which only recruits patients with newly-diagnosed metastatic disease and thereby reduces the numbers of metastatic patients randomised to the "abiraterone comparison". Non-metastatic patients have a lower event rate than the metastatic patients and maintaining the same overall sample size would lead to a delay in time to the primary analysis. The increase in sample size was achievable because recruitment rates to the trial had been substantially higher than 50 patients/month for the preceding 6 months.

9.6 SAMPLE SIZE ISSUES AND TRIAL STAGES: ADDITIONAL RESEARCH ARM H

9.6.1 PILOT PHASE: ADDITIONAL RESEARCH ARM H

A similar approach will be followed for the additional research Arm H as detailed for the original research arms in **Section 9.4.1**. The IDMC reviewed safety data, in the context of data from the control arm, when the first 30 patients allocated to arm H had been on trial for around six months.

9.6.2 ACTIVITY STAGES I-III: ADDITIONAL RESEARCH ARM H

The same principles will be applied to the new comparison as to previous comparisons and an equal allocation ratio of control arm patients to patients allocated to Arm H will be employed, as for Arm G. The number of control arm events required to trigger the intermediate analyses will be the same as for the abiraterone comparison (see **Table 20**).

9.6.3 EFFICACY STAGE IV: ADDITIONAL RESEARCH ARM H

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 will give 90% power to detect the targeted hazard ratio of 0.75 at one-sided significance level of 0.025.

9.6.4 SAMPLE SIZE FOR ADDITIONAL RESEARCH ARM H

Consideration was given to ceasing further randomisations to Arm H if it was not showing sufficient evidence of activity on the intermediate primary outcome measure (FFS), just as for the other research arms. This research comparison is relevant to around 60% of patients joining STAMPEDE. At the point of the scientific approval, accrual was averaging around 80 patients per month to the trial. If accrual to the trial was slower at 70 patients per month, then accrual to this comparison could be between 18 and 42 patients per month, depending on which other trial arms are open to recruitment at the time.

We are targeting a 25% relative improvement in overall survival following local radiotherapy to the prostate in this patient group. This is the same size of effect targeted with the other research arms in STAMPEDE. This relative improvement can be further justified in the light of MRC PR07 which demonstrated an improvement of this magnitude for adding radiotherapy to ADT in locally advanced disease, with a hazard ratio for overall survival of 0.77 (95% CI 0.61 to 0.98). In that trial, fewer than half of the deaths were from prostate cancer, whereas in newly-diagnosed metastatic patients nearly all men will die of their disease. Therefore, it is relevant to note the relative benefit of radiotherapy in PR07 in terms of prostate cancer-specific survival, where the hazard ratio was 0.54 (95% CI 0.27 to 0.78). Long-term survival-based data, with a median follow-up of ~10 years, were presented orally at the American Society of Clinical Oncology 2012 which confirmed these findings.(7)

We anticipated that around 1250 patients were required over 4 years to observe 267 control arm deaths after 5.25 years. This assumed that (i) recruitment was constantly 70 pts/m to the trial overall; (ii) the original research arms stopped accrual within 6 months after activation of the RT arm; (iii) the abiraterone arm stops accrual around 24 months after activation of the RT arm; and (iv) a further new research arm with an equal allocation ratio was introduced 18 months after activation of the RT arm.

In protocol version 13.0, we reflect on these four points: (i) recruitment to the trial has been faster; (ii) the original research arms completed accrual 2 months after activation of the RT arm; (iii) the

abiraterone arm stopped accrual 12 months after activation of the RT arm; and (iv) Arm J was activated 18 months after activation of the RT arm, Arm H.

Of patients joining STAMPEDE during this time, 60% have been eligible for the "M1|RT comparison". Prior to randomisation, a RT schedule must be nominated: Weekly or Daily (see **Section 6.9**). We have observed that around half of patients in the comparison are nominated for RT with the Daily schedule and half for the Weekly schedule, primarily chosen by trial site with patient groups nominated for each schedule observed to be comparable at baseline. There will likely be interest to know the effect of each RT schedule when the main results are reported. This will be explored by "within schedule" comparisons of patients randomised to research vs control (arms H vs A) within each nominated RT schedule.

Therefore, in protocol version 13.0, the target sample size was increased from 1,250 patients up to around 1,800 patients, resulting in an approximate increase in the split by planned RT schedule from 625 to 900 in each "within schedule" analysis. A FFS analysis "within schedule" will be carried out at the time of the "main analysis"; predicted to have ~300 control arm FFS events by schedule (FFS "within schedule" analysis parameters: target HR=0.75, power 90%, 1-sided α=0.015). For either of the RT schedules showing evidence of an effect on FFS, a comparative "within schedule" analysis will be carried out on survival when ~199 control arm deaths are observed in that schedule comparison. This is a closed test with OS only formally compared within schedule if there is an advantage in FFS for that RT schedule at the main analysis. Thus, extending recruitment enables a secondary analysis of the impact of RT on survival by planned "RT schedule" to happen within around 18 months from the first main analysis.

All sample scenarios are documented in the Trial Master File.

All patients joining the trial will be starting long-term ADT for the first time. The focus of this comparison will be on the newly-diagnosed, metastatic patients (with no contraindications to RT), which is the largest subgroup of patients in the trial and the group of patients at highest risk of death from prostate cancer. Patients with non-metastatic disease will be excluded from this particular comparison as there are already randomised data demonstrating the survival benefit from radiotherapy in patients with locally advanced disease. Radiotherapy is now mandatory in node negative patients; it is also recommended in the node-positive, non-metastatic (N+ M0) group. Relapsing patients are also excluded from this comparison.

For the control arm of the whole trial, we constructed sample size scenarios median failure-free survival being 18, 24 or 30 months and constructed sample size scenarios around each of these options; the event rate would depend on the patient mix. We now know that around 60% of patients have M1 disease at trial entry and we have reported that FFS at 24 months is 51% across the whole of the control arm.(1)

For the sample size calculation for this new planned comparison, we have based our estimates on the subgroup of patients with newly-diagnosed M1 disease in the control arm. Therefore, we estimate median FFS to be 1 year and estimate that median overall survival will be around 3.5 years.

9.7 SAMPLE SIZE ISSUES AND TRIAL STAGES: ADDITIONAL RESEARCH ARM J

9.7.1 PILOT PHASE: ADDITIONAL RESEARCH ARM J

A similar approach will be followed for the additional research Arm J as detailed for the original research arms in **Section 9.4.1**. The IDMC first reviewed safety data for this combination when the first 50 patients allocated to Arm J had been on trial around 6 weeks (i.e. to the first follow-up visit).

The IDMC reviewed safety data again when 50 patients were 6 months out from randomisation. Additional safety reviews will be performed if the IDMC raises any concerns over safety and routinely reviewed at regular intervals.

Direct comparison will be available with contemporaneously randomised patients on Arm A (hormones alone). Contextual data will be provided from Arm G (hormones plus abiraterone). Indicative safety data may also be available on the combination from other studies in CRPC.

9.7.2 ACTIVITY STAGES I-II: ADDITIONAL RESEARCH ARM J

The principles of intermediate analyses will be applied to this new comparison, but some of the details will be different. Owing to the expected accrual rate (>100 pts/m) and the expected slower event rate, only two activity stages are planned before accrual is completed. These are set out in **Table 21**.

Table 21: Guidelines for stopping accrual to the additional research Arm J

ACTIVITY	SIG LEVEL	POWER	TARGETED	NUMBER OF CONTROL	CONSIDER DISCONTINUATION
I	0.40	95%	0.70	~66	>0.957
II	0.12	95%	0.70	~139	>0.869

9.7.3 EFFICACY STAGE III: ADDITIONAL RESEARCH ARM J

The analysis of the final Efficacy Stage for this 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 a one-sided significance level of 0.025.

9.7.4 SAMPLE SIZE FOR ADDITIONAL RESEARCH ARM J

Consideration will be given to ceasing further randomisations to Arm J if it is not showing sufficient evidence of activity on the intermediate primary outcome measure (FFS), just as for the other research arms.

The patient mix for this comparison is likely to represent a more favourable prognosis on average than in the original research trial's other arms, due to concurrent recruitment of M1 but not M0 patients, to Arm H.

We anticipate that around 1800 patients are required within 3.5 years to observe ~267 control arm deaths within 6 years. This time will be dependent on the observed overall survival. The default scenario assumes that (i) recruitment is constantly 70pts/m to the trial overall, (ii) the M1|RT arm accrues throughout and (iii) a further new research arm with an equal allocation ratio is introduced 18 months after activation of Arm J. The stopping date for Arm G is no longer an assumption.

Variations on these factors are documented in a Statistical Design Document. If accrual rates to the trial are at 150pts/m (as observed during Summer 2013), accrual of around 1,800 patients to the comparison could be achieved within 2 years. These sample scenarios will also be documented in the Trial Master File.

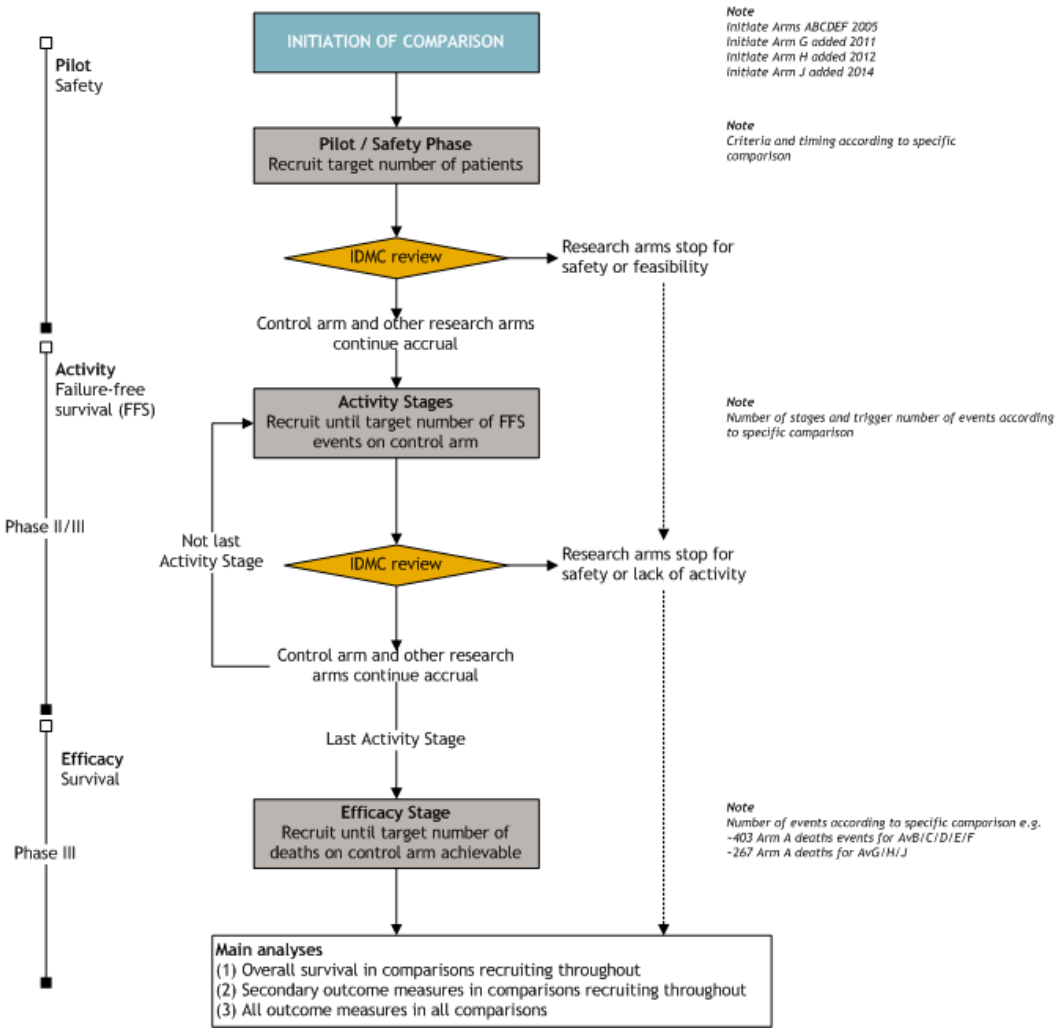
Updating the standard-of-care to include docetaxel has minimal impact on the projected time to maturity of the “enzalutamide + abiraterone comparison”. Within 3 months after this protocol version is activated, the TMG will review the mix of patients that do and do not include docetaxel as part of their standard-of-care. The TMG will consider whether changes are provoked, based on these administrative, patient characteristic data, with reference, if necessary, to the published events rates of similar patient groups from the “original comparisons”.

9.7.5 Further Sample Size Issues For Additional Research Arm J

Careful consideration will be given to the emerging data from the "abiraterone comparison" (Arm A vs Arm G) and whether this arm continues to recruit throughout. It is anticipated that recruitment to this Arm J comparison will be completed *before* survival data emerge from the "abiraterone comparison".

Indirect comparisons to understand the contribution from each agent may be possible if this research arm is demonstrably superior to the standard-of-care. These plans will be developed and documented elsewhere, but a higher number of patients will help with the power to the indirect comparison.

Figure 6: Schema of progress of STAMPEDE through the trial



Key
FFS: Failure-free survival
HR: Hazard ratio
IDMC: Independent Data Monitoring Committee
Pts: Patients

Notes
Exact accrual depends on many factors including accrual rate, event rate and arms recruiting in each stage

9.8 FURTHER NOTES ON TRIAL DESIGN

9.8.1 OVERALL SAMPLE SIZE

Given the adaptive nature of the study, there is no formal overall sample size target, but the numbers of patients required for each comparison are detailed in **Sections 9.4** to **9.7**. To date, more than 7,000 patients have been recruited overall.

9.8.2 FACTORIAL DESIGN

We note here that we have not employed a factorial design in this trial because we anticipate the possibility of synergy between ADT, zoledronic acid and docetaxel and between ADT, 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).

9.9 INTERIM MONITORING AND ANALYSES

The accumulating data will be reviewed at regular intervals (approximately annually) by an Independent Data Monitoring Committee (IDMC), including pre-specified formal intermediate analyses of activity data (see also **Section 16**). These analyses will be performed by the trial team at the MRC CTU. Only patients randomised contemporaneously, and eligible for that comparison, will be included in the comparison of each research arm against control e.g. patients allocated to the control arm prior to protocol version 12.0 will not contribute to the "enzalutamide + abiraterone comparison" (Arm A vs Arm J).

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up; guidelines for discontinuation of accrual for the relevant Activity Stages, together with results from any other relevant trials will aid them in this. 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. The intermediate stopping guidelines apply to the intermediate primary outcome measure. To stop accrual early for benefit in any comparison would require convincing data in terms of the definitive primary outcome measure, overall survival. For example, this could be $p<0.001$ as proposed by Haybittle-Peto.(36, 37) The use of such a guideline for stopping for benefit has a minimal impact on the operating characteristics.

If a decision is made to continue without change, 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 generally remain confidential, unless the TSC and IDMC agree that the data should be made public.

9.10 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. Flexible parametric models will be used to calculate the absolute differences between the arms to show treatment differences over time and to estimate restricted mean “survival” times (RMST). The estimated difference in restricted means survival time (RMST) will be used preferentially to compare treatment arms if the proportional hazards assumptions required for hazard ratios cannot be supported. The χ^2 test or Mann-Whitney test will be implemented for categorical data comparisons, including toxicity, as appropriate. The primary outcome measures (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.

9.10.1 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 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 chose to not participate in the study could be summarised (reasons for non-participation were collected where the patients was willing). The anonymised logs will not be needed for new research arms after Protocol version 8.0.

For 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.

9.10.2 Activity And Efficacy Stages

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

Full details are available in the Statistical Analysis Plan. See **Figure 6** for an overview of the schema of progress.

10 MONITORING AND 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 may be circulated to the TMG for comment. Once the TMT 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 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 results from 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. Further information on the expected toxicities for the trial interventions (docetaxel, zoledronic acid, abiraterone and radiotherapy) can be found in **Appendix G**.

11.1 DEFINITIONS

The safety reporting definitions from ICH GCP apply in this trial protocol. These definitions are given in **Table 22**.

Table 22: Event Terms and Definitions

TERM	DEFINITION
Adverse Event (**AE**)	Any untoward medical occurrence in a patient or clinical trial patient to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (**AR**)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (**UAR**)	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.
Serious Adverse Event (**SAE**) or Serious Adverse Reaction (**SAR**) or Suspected Unexpected Serious Adverse Reaction (**SUSAR**)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • Other important medical condition***

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 patient 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.

Patients who develop any new primary carcinomas should have the event reported on a SAE CRF as "other important medical condition".

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 only.

The following situations that fulfil 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 should be graded using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (ctep.cancer.gov/reporting/index.html). 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 22**. 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 23**. 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 23: Assigning type of SAE through causality

RELATIONSHIP	DESCRIPTION	EVENT TYPE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	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
Possible	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
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	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 **Table 6** 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 for any research arm in the trial, including standard-of-care treatments, HT and docetaxel. Similarly, SAEs occurring in patients randomised to Arm A must be reported until 30 days after last injection or progression (whichever is sooner). SARs and SUSARs must be notified to the MRC CTU indefinitely for all research arms (i.e. no matter when they occur after randomisation).

11.2.2 NOTIFICATION PROCEDURE

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.

Send the SAE form by fax to the MRC CTU. Fax Number: + 44 (0) 20 7670 4818. The STAMPEDE trial team will confirm receipt of the SAE report to the main point of contact via email. Contact the STAMPEDE trial team If receipt is not received within 24 hours.

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 can be updated on the originial 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 as similar as possible.

All patients will receive standard treatment which will include ADT and may include radiotherapy and/or docetaxel. Patients may be randomised to one (or two; dependent on allocated arm) of the newer treatments in combination with hormone treatment. The trial has employed an unequal allocation ratio for some comparisons to maximise efficiency; this was 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 alone with regards to 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 (androgen deprivation 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 by the trial team to all Principal Investigators. PIs therefore have the duty to inform the patients in their care of any new information emerging using any appropriate channel (e.g. letter, communication at follow up clinic, etc).

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

University College London holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the managing organisation's Insurers, via the managing organisation's office.

Hospitals selected to participate in this clinical trial must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.

15 FINANCE

STAMPEDE is funded by the Clinical Trials Advisory Awards Committee (CTAAC) on behalf of Cancer Research UK; it is also funded by the MRC through the MRC Clinical Trials Unit. The trial has National Institute for Health Research Clinical Research Network (NIHR CRN) approval and, therefore, local NCRN funds may be available at each centre to support entry of patients into this trial.

M1|RT will be administered as per trial protocol using NHS RT equipment following successful RTQA by trial team.

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.

Enzalutamide is manufactured by Astellas Pharma. 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. It will also be amended during the trial if other circumstances require e.g. retirement.

The TMG will be responsible for the day-to-day running and management of the trial. They will meet by teleconference at least 3-monthly and in person as needed. The TMG members are detailed in **Appendix M**.

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).

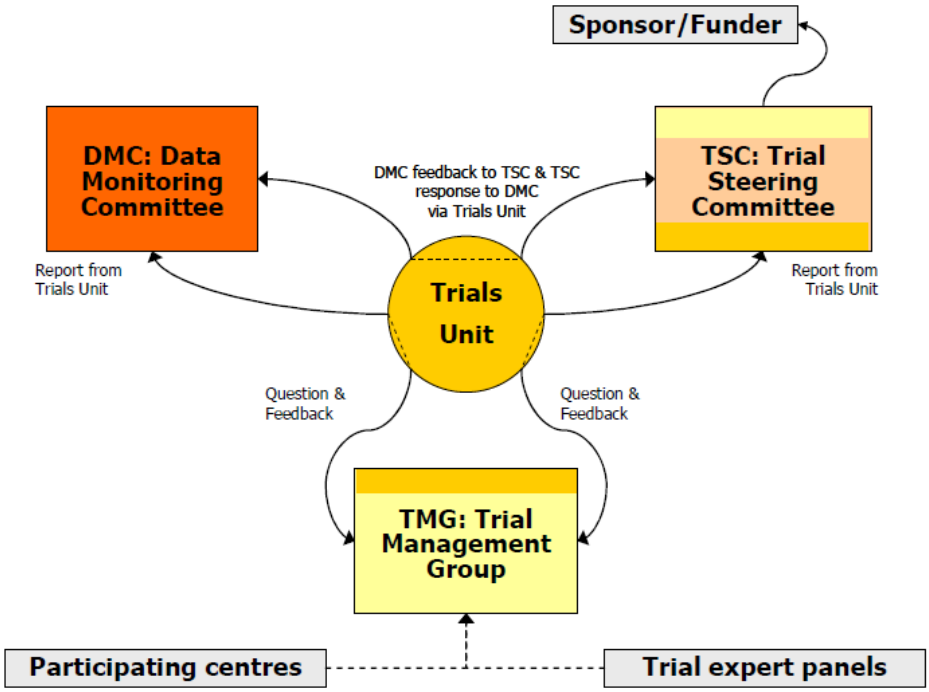
16.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

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**) 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 is discontinued.

From protocol 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 will 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. Initial participation in this study was limited to the first 700 patients recruited (this was reached in Sep-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) (38) 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 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 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 that continue to recruit into their final Efficacy Stage IV.

17.3 TRANSLATIONAL SUB-STUDIES

17.3.1 DNA ANALYSIS

Blood samples from as many patients as possible have been collected for future translational research. With patient consent, an additional droplet of blood sample has been collected using FTA

Elute cards and stored for DNA and protein analysis in order to try to identify molecular features of clinical significance.

FTA Elute cards supplies have not been available since Dec-2013 and the STAMPEDE TMG has pursued an alternative method for genomic DNA collection using the Oragene® DNA kits for saliva sampling.

Oragene kits are widely used for collection of DNA from patients participating in clinical trials and they have been demonstrated to be a suitable alternative to DNA collection from whole blood providing a non-invasive, painless method of high quality sample collection.

A subset of patients may be asked if they would like to donate a blood sample for additional genetic research analysis.

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 histopathology lab. 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. Additional analyses e.g. DNA extraction may also be performed on the tissue arrays.

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:

- To be as inclusive as possible where this is practicable
- To ensure that there is justification for anyone to be named as an author
- 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 led 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.

A detailed Publication Plan is documented elsewhere.

19 PROTOCOL AMENDMENTS

19.1 PROTOCOL

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

Administrative changes such as typos, word change etc.

Name additions/changes to:

TMG members

TSC members

IDMC members

'General Information' Section – additional information re. Abridged version of protocol

Section 1.2 – Figure 1, Celecoxib duration amended

Section 1.3 – Figure 2, addition of cardiovascular assessment form, name and timings amended

Section 2.3 – Docetaxel information updated

Section 2.4 – Additional text re dose and duration justification for Celecoxib use.

Section 3 – Title change and content updated

Section 4.2 – New exclusion criteria added

Section 4.3.1 – New investigations added and additional text re testosterone measurements and additional text re. prior celecoxib treatment

Section 6.1.4 – Celecoxib duration amended

Section 6.1.5 – Additional text re. Co-administration of docetaxel and bisphosphonates

Section 6.1.6 – Celecoxib duration amended

Section 6.2.2 – additional docetaxel information

Section 6.2.3 – addition of CV event history

Section 11 – Safety reporting updated

Section 12.1 – Additional text re. the collection of blood for genetic and serum marker studies

Section 15 – Additional information re. Central Subvention for docetaxel arms

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

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)

General Information section – SAE reporting fax number and timeframe added.

Section 1.2 – Addition of anti-androgen use for M0 patients as a method of HT

Section 1.2 – Increase in amount of blood needed & addition tissue sample request.

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

Section 2.1 – Addition of anti-androgen use for M0 patients as a method of HT

Section 4.1.3 – Inclusion criteria Vii "Normal testosterone prior to hormone treatment" removed.

Section 4.1.3 - φnote has been omitted and moved to section 4.2 (see number 8)

Section 4.2 – Exclusion criteria added to exclude patients with active peptic ulceration, gastrointestinal bleeding and inflammatory bowel disease.

Section 4.2 – Exclusion Criteria added to exclude patients with planned major dental work

Section 4.3.1 - All blood test timelines changed from 14 days to 28 days.

Section 4.3.1 – Hormone Therapy pre-randomisation deadline extended from 4 weeks to 12 weeks.

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

Section 4.3.2 – Updated to ask for all vitamins and minerals the patient is taking to be recorded.

Section 4.3.3 – Updated to include the extra blood required and the request for consent of patients' tissue samples.

Section 6.1.1 – Addition of anti-androgen use for M0 patients as a method of HT

Section 6.1.6 – Addition of the calcium & vitamin name "calcichew".

Section 6.6.2 – asking also to collect vitamins and minerals under concomitant medication.

Section 6.6.3 – New section to inform investigators that patient's, who they wish to give radiotherapy to, are also eligible for STAMPEDE

Section 6.6.4 – New section to detail what data is being collected on the radiotherapy given to patients.

Section 7.1; figure 4 – Addition of radiotherapy form and in note, addition of AA alone

Section 7.1.2 – omission of repeated scans and x-rays at 24 weeks, also omitted in note under figure 4.

Chapter 11 – Safety reporting section updated

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 - Clarification that protocol developed with NCRI rather than on behalf of

Front Cover - Clarification that 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 4th 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

General Information Section - Coordinating Centre – address change

General Information Section – change of Sponsor address

Section 1.1 – ratio of patients randomised to the investigational arms updated

Section 1.2 – figure 1b added to clarify trial design from Apr-2011 onwards

Section 1.2 – paragraph added to explain trial changes after the second activity analysis

Section 1.2 – wording added to clarify that QL data only collected for first 700 patients randomised

Section 1.3 – SSA Favourable Opinion removed from list of trial documentation required ahead of site accreditation

Section 2.1 – Amount of men diagnosed with prostate cancer annually updated

Section 2.4 –note added to explain completion of recruitment to celecoxib- containing arms

Section 2.5.2 - note added to explain completion of recruitment to celecoxib- containing arms

Section 3 – SSA Favourable Opinion removed

Section 4.2 – Exclusion criterion xiii greyed out

Section 4.3.1 – paragraph removed regarding potential randomisation to celecoxib-containing arms

Section 5 – Randomisation instructions expanded to exclude public holidays or dates when notice has been given by the CTU

Section 6.1.4 – formatting changed to grey font to reflect recruitment completion for arm D

Section 6.1.6 - formatting changed to grey font to reflect recruitment completion for arm F

Section 6.2.3 – recruitment note added

Section 6.6.3 – radiotherapy statement changed to reflect data from recent trials

Section 7.1.2 – removal of reference to SRE- specific CRF

Section 7.3 – Figure 3 - Addition of Bone Density Risk Factor Form and BMD sub-study assessment forms to summary of timing table

Section 7.3 – Figure 4 – Weeks added to timings of assessments post 2 years

Section 7.3- Figure 4 – note added to explain recruitment completion for arms D and F

Section 12.1 – Wording changed to reflect change to randomisation allocation ratio

Section 12.1 – Addition of statement regarding new information emerging during the trial

Section 12.2 – Reference to SSA removed

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 Apr-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

19.1.10 Amendments Made To Protocol Version 8.0 (Sep 2011)

Throughout protocol – numbering, sections headings, tables, figures and bibliographical references have been updated in some sections to accommodate new information that has been added

Throughout protocol – Androgen Deprivation Therapy has replaced Hormone Therapy as deemed more representative of the type of hormone therapy used in the study

General Information Section – New staff members of the MRC CTU and Co-Investigators added and contact details updated

General Information Section – Abbreviations list updated

Section 1.1 – Information regarding the new research radiotherapy treatment inserted

Section 1.1 – Information regarding docetaxel updated

Section 1.2 – Wording updated to reflect the addition of the new research comparison arm

Section 1.3 – Additional criteria for the re-accreditation of participating centres (for protocol version 9.0 only)

Section 2.1.1 – Wording updated to clarify the use of anti-androgen in trial patients

Section 2.1.2 – Information added to describe the rationale for the RT comparison arm

Section 2.8 – Information added to describe research RT treatment to prostate for patients with newly diagnosed metastatic disease

Section 3.1 – Information added to describe RT Quality Assurance procedures and centre accreditation

Section 4.1.1 to 4.1.3 – Wording updated to clarify inclusion criteria for all patients groups (newly diagnosed non-metastatic, metastatic and relapsing patients)

Section 4.2 – Clarification added on cardiovascular exclusion criteria

Section 4.2 – New exclusion criterion added concerning patients with prior exposure to hormone therapy

Section 4.2 – New exclusion criterion added to reflect the addition of the new RT comparison arm

Section 4.4.1 – Clarification added regarding pre-randomisation checks

Section 4.4.2 – Clarification added regarding permissible hormone therapy duration prior to randomisation

Section 4.4.5 – Information added regarding starting research radiotherapy treatment

Section 4.4.6 – Information updated on concomitant medications

Section 5 – Clarification regarding randomisation allocation added to reflect the addition of the new RT research arm

Section 6.1.8 – Information added to describe the administration of research radiotherapy

Section 6.2.1 – Clarification added regarding the measurement of serum creatinine levels prior to the administration of zoledronic acid

Section 6.2.3 – Clarification regarding the completion of recruitment to the celecoxib containing arms

Section 6.25 – Information added regarding the administration of research radiotherapy treatment

Section 6.6 – Clarification incorporated to describe the administration of standard-of-care radiotherapy

Section 7.1.4 – Information added regarding data collection and non-administration of standard radiotherapy

Section 7.2 – Section updated to include new treatment specific CRFs and timing of CRFs

Section 8.1 – Clarification added for the criteria to stop treatment for patients randomised to arm G

Section 8.2 – Section expanded to include additional details on study patient transfer to different centres

Section 8.3 – Additional sentence inserted to reinforce the importance of compliance with follow up assessments

Section 9.1 – Additional paragraph inserted to clarify the method of randomisation and allocation distribution in the light of the introduction of the new RT arm

Section 9.4 – Wording updated to clarify the assessment of safety data

Section 9.5.4 – Wording updated concerning the end of randomisations to arm G

Section 9.6 to 9.6.4 – Section added describing sample size issues and trial stages for arm H

Section 9.8 – Clarification on intermediate stopping guidelines

Section 9.9 – Clarification on the outline analysis plan

Section 11 – Information on safety reporting updated to reflect the addition of the research RT comparison arm

Section 11 – Clarification added regarding arm A safety reporting timelines

Section 12.1 – Clarification added regarding the Principal Investigator's responsibilities

Section 14 – Indemnity section updated to reflect current MRC policy

Section 16 – Clarification regarding TMG membership

Section 17.3 – Section on Bone Mineral Density sub-study removed

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

Section 20 – References updated

19.1.11 Amendments Made To Protocol Version 9.0 (Oct-2012)

Throughout protocol – numbering, sections headings, tables, figures and bibliographical references have been updated in some sections to accommodate the completion of recruitment to original research arms B, C and E.

Throughout protocol – Tenses have been changed to reflect activities that were in the future and which have now been passed.

Section 1 – Figure added and clarifications added to each figure

Section 2 – Previous reference 8 removed

Section 4 – Clarification of acceptable alternatives to bone scans

Section 6.2.5 – Correction of an error defining the PTV: the wording has been reordered

Table 4 – Dose-volume objectives corrected: order swapped

Table 5- Correction CRFs names

Section 17.3.2 – Clarification that DNA may be extracted

19.1.12 Amendments Made To Protocol Version 10.0 (Apr-2013)

Throughout protocol – numbering, sections headings, tables, figures and bibliographical references have been updated in some sections

Throughout protocol – typos have been corrected

Section 4 –Clarification of exclusion criteria V (now V and VI)

Section 6 – Timing of orchidectomy prior to randomisation extended to 12 weeks

Section 6 – Clarification of hypokalaemia, blood pressure and fluid retention management

Section 9 – Statistical considerations amended in light of the recruitment extension for the abiraterone comparison

Section 14 - Section updated to reflect the changes in the structure of the MRC CTU (now MRC CTU at UCL) and indemnity arrangements

19.1.13 Amendments Made To Protocol Version 11.0 (Sep-2013)

Throughout protocol – numbering, sections headings, tables, figures and bibliographical references have been updated in some sections

Throughout protocol – typos have been corrected

Co-investigators list updated to reflect the addition of the “enzalutamide + abiraterone comparison” lead

Section 1.2 – Enzalutamide added as trial treatment

Section 1.2 – Protocol version 12.0 added to the list of amendments

Section 2.10 – Rationale for the combination of enzalutamide and abiraterone

Section 4.2 – Eligibility criteria amended to reflect the addition of enzalutamide + abiraterone arm

Section 4.4.2 – Wording clarified

Section 6.8 – Clarification regarding end of trial treatment after starting trial therapy

Section 6.10 – Section added to describe enzalutamide and abiraterone treatment for the new research arm (Arm J)

Section 6.11.4.A – Section added to describe the management of toxicities from trial abiraterone

Section 6.11.4.B - Section added to describe the management of toxicities from trial enzalutamide

Section 9.1.4 – Section added to describe the statistical considerations concerning the introduction of Arm J

Section 9.3 – Principles and assumption for the introduction of Arm J added

Section 9.7 and sub-sections – Sample size issues and trial stages for Arm J

Section 9.9 – Details on interim monitoring and analyses for Arm J added

Section 11.2.1.D – Wording clarified regarding safety reporting requirements for control arm

Section 12.1 – Wording clarified

Section 15 – Details on funding for the “enzalutamide + abiraterone comparison” added

Section 19 - Amendments made to protocol updated

Reference list updated

19.1.14 Amendments Made To Protocol Version 12.0 (Jan-2014)

Throughout protocol – typos have been corrected

Section 4.4.2. Wording clarified

Section 4.3. Wording clarified for eligibility to M1|RT comparison

Section 6.10. Addition of use of dexamethasone post-biochemical progression for Arm J patients

Section 6.11.4.A. Correction of CTCAE version

Section 6.11.4.C. Clarification on enzalutamide dose modification to be in line with current SmPC

Section 9.6. Sample size increase for M1|RT comparison

Section 11. Correction of safety reporting timelines for Arm A patients

Section 17. Addition of saliva samples collection for DNA analysis

Table 4, 5 and 6. Clarification on Case Report Forms and Follow-up schedule

19.1.15 Amendments Made To Protocol Version 13.0 (FEB-2014)

Throughout protocol – typos have been corrected

Throughout protocol – clarification on the new definition of standard-of-care

Table of contents updated to reflect any changes to the protocol

Section 1.1. Wording added throughout section to include reference to survival results from “original comparisons”

Section 2.1.1. Section improved to include reference to survival results from “original research comparisons”

Section 2.1.2. Section improved to include reference to survival results from “original research comparisons”.

Section 2.1.3. Additional section added to describe the role of docetaxel for men with M0 or M1 disease

Section 2.9. Clarification on treatment completion and primary results for “original research comparisons”

Section 4.2. Clarification of Exclusion criteria XIII and XVI

Section 4.4.2. Clarification on HT prior to randomisation

Section4.4.3. New section to clarify standard-of-care docetaxel treatment prior to randomisation

Section 4.4.7. Clarification on concomitant medication and contra-indicated concomitant medications

Section 4.5. Clarification provided on tissue block collection

Section 6. Inclusion of docetaxel into the standard-of-care

Section 6.2.3 New section to describe standard-of-care docetaxel administration

Section 6.11. Improvement throughout sections and sub-sections for abiraterone and enzalutamide-related toxicity management

Section 6.12. Section improved throughout to incorporate clearer details on concomitant medications and drug-to-drug interactions

Section 7.1.4. New section to describe data collection for standard-of-care docetaxel

Section 9.7.4. Clarification provided about implications for “enzalutamide+ abiraterone comparison” following change of standard-of-care treatment

Section 11.2.1.D Clarification on SAE notification timelines to reflect change in standard-of-care treatments (addition of docetaxel)

Figure 1. Figure updated to reflect change in standard-of-care

Figure 2. Figure updated to reflect trial history and recruitment over time

Figure 3. Figure updated to reflect changes in standard-of-care and recruiting arms

Table 1. Table updated to remove repetition

Table 13. Table updated to include new CRF to report standard-of-care docetaxel treatment

Table 15. Table updated to include only active trial treatments

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