CANTATA

A multicentre, phase II randomised controlled trial evaluating cabazitaxel versus docetaxel re-challenge for the treatment of metastatic Castrate Refractory Prostate Cancer, previously treated with docetaxel at inception of primary hormone therapy

PROTOCOL VERSION /DATE

Version 3.0 / 27 June 2014

Amendments/version/date

Version 2.0 dated 16 Nov 2012

Version 3.0 dated 27 Jun 2014

UNIVERSITY OF BIRMINGHAM

NCRN National Cancer Research Network

CANCER RESEARCH UK

Sponsor: University of Birmingham

Sponsor Protocol Number: RG 12-024

CAS Code: PR2103

EudraCT Number: 2012-003835-40

ISRCTN: ISRCTN16465571

Sites: Multicentre Trial

SIGNATURE PAGE

CANTATA Protocol version 3.0, dated 27 June 2014

This protocol has been approved by:

Name:	Prof Nicholas James	**Trial Role:**	Chief Investigator
Signature:		**Date:**	27/JUN/2014.

This protocol describes the CANTATA trial and provides information about procedures for patients taking part in the CANTATA trial. The protocol should not be used as a guide for treatment of patients not taking part in the CANTATA trial.

Principal Investigator signature page

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Version:

I confirm I have received, read and understood the aforementioned version of the trial protocol. I confirm my team and I will adhere to this version of the protocol following receipt of the required local approvals.

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GENERAL INFORMATION

CLINICAL TRIAL PROTOCOL

This clinical trial protocol is intended to provide guidance and information for the conduct of the trial in its participating centres. It is not for use as a guide for the management of other patients outside the trial. Every care has been taken in writing this document, but corrections or amendments may be necessary. These will be circulated to the known investigators in the trial, but centres entering patients for the first time are advised to contact the Trial Office to confirm they have the most recent version of the protocol.

Sponsor: University of Birmingham

Independent scientific peer review

This trial has been reviewed by the NCRI Prostate Cancer Clinical Study Group, and submitted to independent peer review through the Cancer Research UK Clinical Trials Advisory and Awards Committee funding and evaluation process.

Trial Management Group: This trial has been developed by the Trial Management Group

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AMENDMENTS:

The following amendments and/or administrative changes have been made to this protocol since the date of preparation

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	16-Nov-2012	2.0	Update to comply with MHRA request re original submission on 26-Oct-2012	Update inclusion/exclusion criteria: patients with bilirubin equal or larger than ULN must be excluded; ANC notation made consistent throughout protocol.
4	27-Jun-2014	3.0	Substantial Amendment	Inclusion of text regarding optional tissue collection sub-study; change to haemoglobin notation

STUDY SYNOPSIS

Title: A multicentre, phase II randomised controlled trial evaluating cabazitaxel versus docetaxel re-challenge for the treatment of metastatic Castrate Refractory Prostate Cancer, previously treated with docetaxel at inception of primary hormone therapy.

Trial Design: Phase II multicentre, randomised controlled trial.

Objectives: To assess the safety and levels of activity of cabazitaxel versus docetaxel re-challenge in patients previously exposed to combined docetaxel and androgen deprivation as first line treatment for advanced prostate cancer.

Outcomes measures:

Primary outcome measures	Secondary outcome measures
Clinical Progression-free survival (CPFS). Clinical progression is defined as the earliest of the: • Date of pain progression (date patient is seen in clinic and pain progression identified) • Date of occurrence of a cancer-related skeletal-related event • Date of death from any cause	• Toxicity • Skeletal-related event free survival • Pain progression-free survival • PSA progression-free survival • Overall survival • Quality of life

Patient Population: Patients with radiological, biochemical or clinically confirmed metastatic castrate resistant prostate cancer.

Sample Size: There are currently over 3000 patients recruited within the STAMPEDE trial, more than 800 of whom will have been randomised to receive up to 6 cycles of docetaxel (up to and including March 2012). Trial patients will be recruited primarily from this pool of patients. Target recruitment is 69 patients per arm, 138 patients in total.

Main inclusion criteria

- Diagnosis of histologically proven prostate adenocarcinoma, that is castrate refractory
- Previously treated with up to 6 cycles of docetaxel as part of the STAMPEDE trial (or treated with the same drug outside of the trial at primary diagnosis)
- Confirmed biochemical, radiological or clinical progression
- Metastatic disease
- Aged 18 or over
- WHO performance status grade 0 to 2
- Adequate organ function as evidenced by:
  - ANC >1.5 x10^9/L
  - WBC >3.0 x10^9/L
  - Haemoglobin >100g/L
  - Platelet count > 100 x10^9 L
  - Total bilirubin <1.0 xULN
  - AST or ALT <1.5 xULN

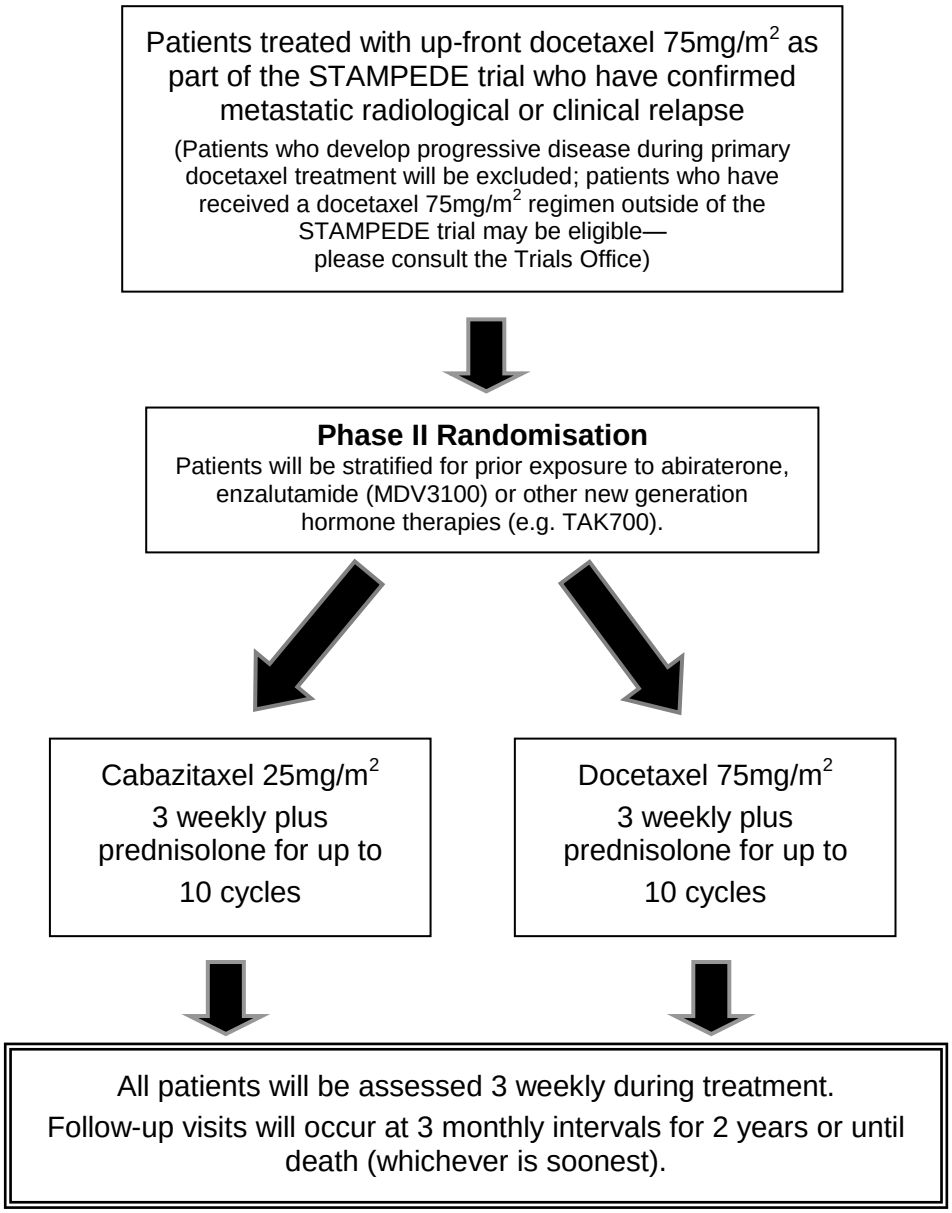
  - GFR >30mL/min (calculated by EDTA clearance, 24h urine collection, or Cockcroft-Gault)
- Available for long-term follow-up
- Patient's written informed consent

Main exclusion criteria

- Prior systemic therapy with chemotherapy drugs other than docetaxel
- Progressive disease whilst on primary docetaxel therapy
- Metastatic brain disease or leptomeningeal disease
- Patients with bilirubin ≥ 1.0 xULN
- Previous extensive palliative radiotherapy to bone marrow, e.g. hemibody radiotherapy
- Active grade ≥2 peripheral neuropathy (NCI CTC)
- Active infection requiring systemic antibiotic or anti-fungal medication
- Patients with reproductive potential not implementing accepted and effective method of contraception
- Malignant disease within the previous 5 years, other than adequately treated basal cell carcinoma

Trial Duration: Follow up for all patients for a minimum of 2 years or until death (whichever is soonest) post last chemotherapy treatment.

STUDY SCHEMA



SCHEDULE OF ASSESSMENTS

Tests & Procedures	Before Start of Chemotherapy		Chemotherapy Treatment	End of Treatment	Follow up
	Screening	Baseline	Treatment every 3 weeks for 10 cycles	30 Days post treatment	Every 3 months for 2 years
Confirmation of disease progression after prior treatment with docetaxel	✓ (Patient must have received up to 6 cycles of docetaxel)				
Patient Information Sheet	✓				
Informed consent signed	✓				
Scanning Procedures (CT scan/MRI scan, Chest X-ray, Bone scan)	✓ Must be within 6 weeks of randomistion		(Done only if clinically indicated)		✓ (as clinically indicated)
Pre-existing toxicity information collected		✓			
Medical history		✓			
Concomitant medication		✓	✓	✓ (30 days after last infusion)	✓
Height		✓			
Physical examination and Weight		✓	✓	✓	✓
Vital signs		✓	✓		
Toxicity Assessment			✓	✓	✓
Blood tests including PSA Test	✓ Must be within 7 days of randomisation	✓ *	✓	✓	✓
Quality of Life assessments	✓			✓	✓

* Within 7 days of first treatment—can use screening bloods if within the window.

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALP	Alkaline phosphatase
AST/ALT	Aspartate aminotransferase / Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
CPFS	Clinical Progression Free Survival
CR	Complete Response
CRF	Case Report Form
CRCTU	Cancer Research UK Clinical Trials Unit
CRPC	Castrate Refractory Prostate Cancer
CT	Computed Tomography
DCF	Data Clarification Form
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
FBC	Full Blood Count
GFR	Glomerular Filtration Rate
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LFT	Liver Function Tests
LREC	Local Research Ethics Committee
mCRPC	Metastatic Castrate Refractory Prostate Cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
OS	Overall survival
PFS	Progression Free Survival
PIS	Patient Information Sheet
QoL	Quality of Life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SRE	Skeletal Related Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TTP	Time To Progression
U & E	Urea and Electrolytes

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1. BACKGROUND AND RATIONALE

1.1 Background

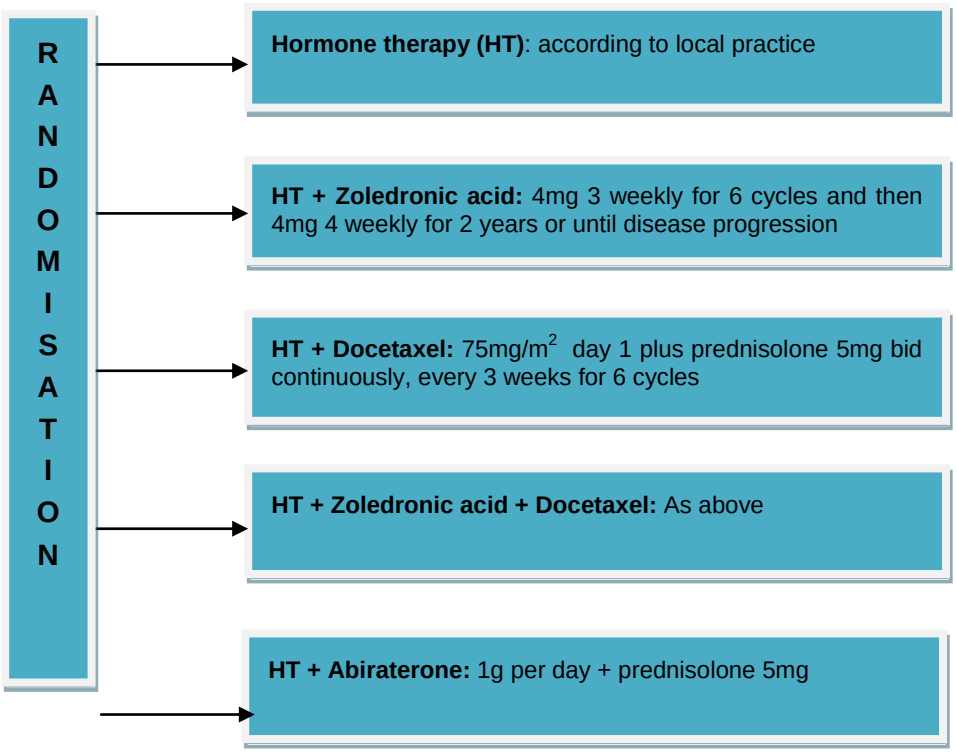
Prostate cancer is a major worldwide health problem and represents 12% of all diagnosed cancers in the UK. In 2008 in the UK, 37,051 men were diagnosed with prostate cancer, of whom 10,168 died from the disease[1]. The first line treatment for locally advanced or metastatic prostate cancer is androgen deprivation, either surgically via bilateral orchidectomy, or medically with LHRH analogues or an anti-androgen[2]. Hormone therapy is not curative and all patients will become refractory to standard hormone therapies, with a median time to progression of 18-24 months on first line treatment, at which point the prognosis becomes poor (historically median survival was 7-15 months[3]). Over the last decade a range of treatments have been licenced for what used to be called hormone refractory prostate cancer (HRPC) but which is increasingly referred to as castrate refractory prostate cancer (CRPC). This reflects the fact that there are new hormone therapies such as abiraterone and MDV3100 (enzalutamide) which clearly act by hormonal mechanisms in the presence of castrate levels of testosterone.

Second line treatment options for patients with CRPC include further hormonal manipulation, bisphosphonates, cytotoxic chemotherapy[10, 12], or abiraterone[8] with a range of further new agents pending (radium-223, MDV3100 [enzalutamide] and others). The landscape is thus becoming very complex, with no current relative efficacy data for the exciting range of new agents, nor any data on optimal sequencing of therapy.

The STAMPEDE (www.stampedetrial.org; figure 1) and GETUG-12[21] trials are both investigating the role of docetaxel in the first line setting in high risk prostate cancer patients. The GETUG-12 trial is a phase III trial of upfront docetaxel–estramustine (DE) in high-risk localised prostate cancer, and has recently reported its one year data for PSA response, toxicity and quality of life (QoL)[21]. The trial has demonstrated a PSA level of ≤0.2 ng/mL (after 3 months of treatment) in 34% in the androgen deprivation therapy (ADT) + DE arm and 15% in the ADT arm, ($p < 0.0001$), which is a promising result. A longer follow-up is required to assess whether this yields a benefit in progression free survival (PFS) and overall survival (OS).

The STAMPEDE trial has not directly published data on PFS with docetaxel but benefit can be inferred from the published statistics plan (see www.stamepdetrial.org), which states that arms must show a hazard ratio for PFS of at least 0.92 to pass the second interim efficacy analysis. The docetaxel arms completed this analysis in 2011. Thus two large trials have demonstrated positive effects of upfront docetaxel on PFS, with OS data expected in the next few years. If GETUG-12 and STAMPEDE confirm positive effects on survival (or indeed large effects on PFS) it is likely that the use of docetaxel may move from the relapse to the upfront setting.

Figure 1: Current arms of the STAMPEDE trial*



*Set up as a six arm trial with additional arms of celecoxib and celecoxib and zoledronic acid, however interim analyses demonstrated no benefit in the celecoxib arms and therefore the two arms containing celecoxib were discontinued. An additional arm containing abiraterone was added November 2011.

Most of the patients enrolled in STAMPEDE will ultimately relapse with metastatic CRPC (mCRPC), the majority of whom would likely be fit for further chemotherapy. Currently the standard of care in first line mCRPC is docetaxel[5]. Therefore, in patients who have mCRPC and have received docetaxel within trials such as STAMPEDE or GETUG-12, it is debatable whether further chemotherapy should be regarded as first line mCRPC chemotherapy or second line. Surveys of the STAMPEDE investigators suggest that trial patients relapsing in the docetaxel arm are offered re-challenge with docetaxel at relapse, unless there is clear evidence of docetaxel resistance (i.e., disease progression whilst on chemotherapy).

If the position of docetaxel in the treatment pathway is moved to the upfront setting in high-risk disease, the question arises as to which chemotherapy drug should be used in the metastatic castrate resistant setting in patients who received primary docetaxel. The TROPIC trial, which compared cabazitaxel with mitoxantrone in patients previously treated with docetaxel, has shown a statistically significant survival advantage with cabazitaxel[10]. On the basis of this trial cabazitaxel is now licensed for use after failure of docetaxel in mCRPC. The mean number of prior docetaxel chemotherapy cycles in TROPIC was around 9, and the median gap between first and second line treatment was approximately 3 months. In contrast, the median time to relapse in the STAMPEDE trial control arm is around 2 years[4] and the maximum chemotherapy exposure is 6 cycles. Therefore, although still second line chemotherapy, the patient exposure to prior chemotherapy, the recovery interval and hence the likely risks of toxicity are much more favourable.

In light of the positive results from the TROPIC trial, there is a unique opportunity to investigate the role of cabazitaxel in relapsing metastatic CRPC patients treated with primary docetaxel. The data gained from the proposed randomised phase II trial will provide an ideal platform for a larger phase III trial if the STAMPEDE and GETUG-12 docetaxel studies support a change to the use of docetaxel within high risk and metastatic prostate cancer at diagnosis. This opportunity exists uniquely in the UK as the GETUG-12 trial completed recruitment some years ago and is significantly smaller than STAMPEDE.

1.2 Trial Rationale

1.2.1 Justification for treatment choice

Over recent years there has been increasing evidence of the clinical efficacy of chemotherapy in prostate cancer. Docetaxel in combination with prednisolone was NICE approved in 2006 for the treatment of mCRPC, and is currently considered the standard of care for such patients. This is primarily based on two large randomized controlled trials comparing this combination to the previously established standard of mitoxantrone and prednisone[11,12]. Tannock and colleagues[12] reported a 2.4 month survival benefit with 3 weekly docetaxel compared to mitoxantrone plus prednisone[1], prolonging survival from 16.5 months to 18.9 months. Petrylak and colleagues[11] also reported longer survival times with docetaxel-estramustine combination chemotherapy compared with mitoxantrone (median survival, 17.5 vs. 15.6 months).

With the adoption of docetaxel as standard first line treatment for mCRPC, the standard of care in relapsing mCRPC is evolving. Palliative effects have been observed in mCRPC patients with either corticosteroid alone[13], or with mitoxantrone and either prednisone or hydrocortisone [14,15,16,17]. Mitoxantrone with corticosteroid therapy has been used as a reference post-docetaxel treatment mainly based on the results of two phase III clinical trials carried out in the pre-docetaxel era [16,17]. Although superior palliative symptoms, such as pain control and time to treatment failure, were observed in these trials with mitoxantrone and prednisone vs prednisone alone, no OS benefit was observed[16,17].

Until recently there was a need for new treatments in advanced prostate cancer, but in 2010 de Bono and colleagues published the results of the TROPIC trial[10]. TROPIC was a randomised phase III trial in men with mCRPC who had previously been treated with hormone therapy, but whose disease had progressed during or after treatment with docetaxel. Patients were treated with prednisolone 10mg daily and randomly assigned either 3 weekly mitoxantrone or cabazitaxel. Cabazitaxel demonstrated a statistically and clinically significant OS improvement compared with mitoxantrone (15.1 months vs 12.7 months). The secondary endpoints of PFS, RR and TTP were also significantly improved. Cabazitaxel is, however, associated with a range of typical chemotherapy side effects. Of these, myelosuppression was prominent, and included neutropenia (94%), severe neutropenia (82%), anaemia (97%), thrombocytopenia (46%) and diarrhoea (47%)[10].

[1] Within the UK prednisone is not available and prednisolone is usually substituted in its place. It is proposed to use prednisolone in this study. In general, where we refer to one or other agent, it can be assumed that we are referring to both interchangeably.

It is important to note, however, that within the TROPIC trial[10] all grades of myelosuppression were comparable between the cabazitaxel and mitoxantrone arms (anaemia 97.3% vs 81.4%, leukopenia 95.7% vs 92.5%, neutropenia 93.5% vs 87.6%, thrombocytopenia 47.4% vs 43.1%). This is likely to reflect previous exposure to docetaxel, particularly as ~70% of patients (cabazitaxel 72.2% and mitoxantrone 75.6%) were treated within 3 months of receiving docetaxel[10]. Thus the myelosuppression seen with cabazitaxel may be partly due to the clinical context of the TROPIC trial.

The TROPIC trial[10] also demonstrated that patients who received a total cumulative dose of docetaxel ≥900mg/m^2 had better responses (HR 0.51; 95% CI 0.33-0.79) than those who received less than 900mg (≥675-900mg/m^2 [HR 0.73; 95% CI 0.48-1.10], ≥450-675mg/m^2 [HR 0.83; 95% CI 0.6-1.15], ≥225-450mg/m^2 [HR 0.60; CI 0.43-0.84], <225mg/m^2 [HR 0.96; CI 0.49-1.86]). However, whether this is a causal relationship or an incidental finding due to other factors (overall fitness, innate chemosensitivity of the tumour being treated, etc.) cannot be resolved.

Within our phase II trial, toxicity is a secondary outcome measure. There is no published data in the clinical setting chosen for the trial, however, we anticipate lower toxicity than in the TROPIC trial due to the lower pre-treatment chemotherapy exposure (maximum 6 cycles docetaxel vs mean of 9 in TROPIC) and longer treatment free interval (median >2years in this trial versus 3 months in TROPIC). Growth factor support with G-CSF, in an attempt to reduce the risk/incidence of neutropenia, will be recommended in patients experiencing neutropenia in cycle 1.

Based on the results of the TROPIC trial, cabazitaxel, in combination with prednisone or prednisolone, was approved by the US Food and Drug Administration (June 2010) and the European Medicines Agency (March 2011), for the treatment of patients with mCRPC who have previously been treated with docetaxel. There are also four clinical trials currently recruiting which are assessing cabazitaxel safety and efficacy in this group of patients (NCT00417079, NCT01308580, NCT01308567, NCT01324583).

In conclusion, treatment with cabazitaxel is a potential therapeutic option for patients with mCRPC whose disease has progressed during or after docetaxel-based therapy. Caution, however, must be employed due to its significant haematological toxicities.

1.2.2 Treatment drugs

Cabazitaxel

Cabazitaxel is a third generation, semisynthetic taxane antineoplastic agent selected to have high activity in both docetaxel sensitive and docetaxel resistant cell lines. It works by disrupting the microtubular network that is essential for mitotic and interphase cellular functions and causes inhibition of cell division and cell death. Cabazitaxel in combination with prednisolone is intended to provide a further treatment option for patients with progressive disease following or during docetaxel-based treatment.

Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions and causes inhibition of cell division and cell death. It is licenced for use in patients with relapsing mCRPC as first line therapy.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

2.1.1 Aims

This study is a randomised controlled phase II clinical trial which aims to compare the safety and levels of activity of cabazitaxel versus docetaxel re-challenge in patients previously exposed to combined docetaxel and androgen deprivation as first line treatment for advanced prostate cancer. If this study demonstrates improved CPFS, then we would intend to proceed to a phase III trial.

2.1.2 Primary Objectives

The primary objectives of this phase II study are to determine the tolerability and activity of cabazitaxel compared with docetaxel re-challenge as second-line chemotherapy treatment in metastatic patients who received primary therapy with docetaxel.

2.2 Outcome Measures

2.2.1 Primary outcome measures:

The primary outcome measure is clinical progression-free survival (CPFS). CPFS time is defined as the time between the date of randomisation and the date of clinical progression. Clinical progression is defined as the earliest of the:

- date of occurrence of pain progression (date patient is seen in clinic and pain progression identified);
- date of occurrence of a cancer-related skeletal-related event;
- date of death from any cause.

2.2.2 Secondary outcome measures:

To determine:

- Toxicity (National Cancer Institute Common Toxicity Criteria version 4)
- Skeletal-related-event-free survival
- Pain progression-free survival
- PSA-progression free survival
- Overall survival
- Quality of life

3 TRIAL DESIGN

This is a phase II randomised controlled trial investigating cabazitaxel versus docetaxel re-challenge for the treatment of metastatic castrate refractory prostate cancer. Patients will be randomised to treatment with either up to ten 3-weekly cycles of cabazitaxel or up to ten 3-weekly cycles of docetaxel (plus 10mg prednisolone daily in either regimen). The trial design is based on a Jung design [22]. The difference between treatment arms in terms of the number of patients who have a clinical event (clinical progression or death) will provide the evidence whether the levels of activity of cabazitaxel warrant further investigation in the phase III setting.

3.1 Trial Duration

Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles of cabazitaxel or docetaxel (a total of 30 weeks). Each patient will have long-term follow up until death or for a maximum of up to 2 years (104 weeks). Maximum study duration including long-term follow up for each patient will be about 134 weeks.

3.2 Quality of Life sub-study

An optional quality of life (QoL) sub-study is being performed to assess the impact of treatment on the quality of patients' lives. All patients should be asked if they are willing to participate. The EORTC QLQ-C30 with the prostate-specific module QLQ PR25 will be used as described in Appendix 6. Key items for assessment are pain reduction for patients with metastatic disease and urinary symptoms for patients with locally advanced disease.

The Patient Information Sheet, which the patient receives prior to entering the trial, provides information about the QoL study. The first questionnaires should be administered on the day of obtaining informed consent. The subsequent questionnaires will be administered at the end of the treatment and during the follow up period. 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 QoL questionnaire 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.

3.3 Optional Tissue Collection sub-study

In addition to the Quality of Life sub-study, we would like to collect tissue from any existing biopsy (or surgical) samples or biopsies collected during the course of the trial and to use any surplus from these tissue samples for future research. These tissue samples will be collected retrospectively, and would be sent to the University of Birmingham Biorepository for use in future ethically approved biomarker studies.

4. ELIGIBILITY

This study will primarily enrol patients with mCRPC who were previously treated with, and have relapsed following treatment with, docetaxel as part of the STAMPEDE trial. Patients who progress during primary treatment with docetaxel will be excluded. Those who have received treatment similar to the STAMPEDE treatment, although outside the trial, would also be eligible. However, such patients must be discussed with the Chief Investigator or deputy CI prior to inclusion.

4.1 Inclusion Criteria

- Diagnosis of histologically proven prostate adenocarcinoma, that is castrate refractory
- Previously treated with up to 6 cycles of docetaxel as part of the STAMPEDE trial or treated with docetaxel outside of the trial at primary diagnosis (defined as commencing within 3 months of instigation of primary hormone therapy).
- Confirmed biochemical, radiological or clinical progression.
- Metastatic disease
- Aged 18 or over
- WHO performance status grade 0 to 2
- Adequate organ function as evidenced by:

- ANC >1.5 x10^9/L
- WBC >3.0 x10^9/L
- Haemoglobin >100g/L
- Platelet count > 100 x10^9 L
- Total bilirubin <1.0 xULN
- AST or ALT <1.5 xULN
- GFR >30ml/min (calculated by EDTA clearance, 24h urine collection, or Cockcroft-Gault)

- Available for long-term follow up
- Patient's written informed consent

4.2 Exclusion Criteria

- Prior systemic therapy with chemotherapy drugs other than docetaxel
- Progressive disease whilst on primary docetaxel therapy
- Metastatic brain disease or leptomeningeal disease
- Patients with bilirubin ≥ 1.0 xULN
- Previous extensive palliative radiotherapy to bone marrow, e.g. hemibody radiotherapy
- Active grade ≥2 peripheral neuropathy (NCI CTC v 4)
- Active infection requiring systemic antibiotic or anti-fungal medication
- Patients with reproductive potential not implementing accepted and effective method of contraception
- Malignant disease within the previous 5 years, other than adequately treated basal cell carcinoma.

5. SCREENING AND CONSENT

5.1 Screening

Potential patients will be identified by clinicians or trial staff during their treatment or follow up as part of the STAMPEDE trial. Investigators will be expected to maintain a screening log of all potential study candidates. This log will include limited information about the potential candidate (e.g., date of birth), and the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

If the patient meets the inclusion criteria, the Investigator can provide the patient with the Patient Information Sheet to allow the patient to make an informed decision regarding their participation. If informed consent is given, the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data.

5.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part in, or stop treatment on, the trial at any time. The patient should be given ample time (usually at least 24 hours) to read the Patient Information Sheet and to discuss their participation in the trial with others outside of the site research team. The patient must be given an opportunity

to ask questions, which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they must sign and date the latest version of the Informed Consent Form. The Investigator must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy filed in the hospital notes, and the original placed in the Investigator Site File (ISF). In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trials Office for review. Once the patient has been entered into the study, the patient's trial number must be entered on the Informed Consent Form maintained in the ISF.

Details of the informed consent discussions should be recorded in the patient's medical notes: these must include date of, and information regarding, the initial discussion; and the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial, the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation in the trial should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process described above must be followed, and the patient's right to stop treatment on the trial respected.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and, with the patient's prior consent, their General Practitioner (GP) must also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

Treatment should be commenced as soon as possible after consent is obtained.

6. TRIAL ENTRY

Prior to recruitment of patients into the study, the Principal Investigator for each site, or their designee, should have returned all required documentation to the Trial Office, and the site personnel involved with the trial must have received appropriate training from the Trial Coordinator.

Patient eligibility will be established before treatment randomisation and randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation, with eligible patients being randomised in a 1:1 ratio (cabazitaxel : docetaxel). Randomisation will be stratified for prior exposure to abiraterone, enzalutamide (MDV3100) or other new generation hormone therapy (e.g., TAK700). The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Web Recognition System (IWRS) database which is accessed by CRCTU on behalf of randomising centres.

Once a potential patient has been consented to the study, the randomisation form must be completed and the patient randomised onto the study by calling the Cancer Research UK Clinical Trials Unit Birmingham on the number below, between 9.00 am and 5.00 pm Monday to Friday.

☎ 0800 371 969

The following information will be required at randomisation:

- Name of Hospital, Consultant and person randomising the patient
- Confirmation that the patient is eligible for the trial by completing the checklist

- Confirmation that the patient has given written informed consent
- Patient's full name, hospital number, date of birth and NHS number.

The CRCTU will assign each patient a unique Trial number which will be used for all trial forms. The patient's Trial number must be recorded on the randomisation form and this must be signed and sent to the Trial Office along with a copy of the patient's Informed Consent Form (if the patient has initialled the consent form to have it collected by the Trial Office). A copy of the randomisation form must also be filed in the Investigator's Site File and the patient's details (Trial number, Initials, DOB) entered onto the enrolment log.

A fax confirming the patient's treatment arm will be sent to the randomising investigator and pharmacist at the end of the randomisation.

7. TREATMENT DETAILS

7.1 Treatment drugs – Supply, labelling and accountability.

7.1.1 Cabazitaxel (Jevtana®)

Cabazitaxel will be supplied by Sanofi free of charge for all trial patients. Orders for cabazitaxel will be arranged with the distributor by the trial office. This will include both the initial order and any re-supplies.

DO NOT REFRIGERATE unopened vials of the drug and solvent. The concentrate and solvent vials must be used immediately upon opening. Please refer to Pharmacy file for storage conditions for the diluted medicinal product.

7.1.2 Docetaxel

Docetaxel will be not be provided for the study as it is considered standard care at present: any generic version may be used, supplied from each centre's own pharmacy stock.

Please see the Pharmacy manual for use and handling instructions.

7.1.3 Labelling

All drugs dispensed for use in this trial must be labelled in accordance with the EU directive (Directive 2001/20/EC, and Medicines for Human Use (clinical trials) Regulations 2004 which implement the directive). Guidance for this can be found at www.ct-toolkit.ac.uk under annex 13. The CANTATA Trial Office will supply the appropriate labels for both cabazitaxel and docetaxel in the Pharmacy Folder provided to sites.

Both cabazitaxel and docetaxel will be classed as IMPs for this study. Prednisolone, which is given daily during treatment cycles, will be classed as a NIMP for this study.

7.1.4 Drug accountability

The investigator must maintain adequate records documenting the use, loss, or other disposition, of the IMP once made-up for trial use. The Trial Office will supply a drug accountability form which must be used for the IMPs, or you may request to use your standard dispensing forms by contacting the Trial Office. In either case, the forms must identify the IMP, including batch or code numbers and expiry dates, and account for its allocation on a patient-by-patient basis, including specific dates and quantities. The Trial Office will also supply an accountability log to be used when dispensing prednisolone, which is classed as a NIMP. The forms must be signed by the individual who dispenses the drug, and copies must be provided to the Trial Office on request. The prescribed dose must also be recorded in the patient's medical records.

7.2 Treatment Schedule

7.2.1 Experimental Arm

Cabazitaxel will be administered in an out-patient setting and according to the schedule stated below.

Cabazitaxel will be administered at a dose of 25 mg/m^2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) is ≥ 1.5 x10^9 L, the platelet count is ≥ 100 x10^9 L, and non-haematological toxicities (except alopecia) have recovered to baseline. Patients will be monitored closely for toxicity. In addition to optimising supportive care, chemotherapy doses may be adjusted after the first cycle of therapy and/or recovery to grade ≤1. Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles.

Premedication Regimen: Administer intravenously 30 minutes before each dose of cabazitaxel:

- Antihistamine (chlorpheniramine 5 mg or equivalent antihistamine)
- Dexamethasone 8 mg or equivalent steroid
- H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist)
- Antiemetic prophylaxis (oral or intravenous) is recommended as needed, and should follow local policy.
- Variations based on local practice can be considered after discussion with the Trial Office

G-CSF: Patients experiencing severe neutropenia or neutropenic sepsis should be considered for G-CSF prophylaxis with subsequent cycles.

7.2.2 Control Arm

Docetaxel will be administered in an out-patient setting and according to the schedule stated below.

Docetaxel will be administered at a dose of 75 mg/m^2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) is ≥ 1.5 x10^9 L, the platelet count is ≥ 100 x10^9 L, and non-haematological toxicities (except alopecia) have recovered to baseline. Patients will be monitored closely for toxicity. In addition to optimising supportive care, chemotherapy doses may be adjusted after the first cycle of therapy and/or recovery to grade ≤1. Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles.

The recommended pre-medication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion, however other schedules are also acceptable if SPC regimen is different to local practice.

The recommended anti-emetic regimen is:

30 minutes prior to docetaxel administration:

- Ondansetron 8mg IV stat or equivalent
- Dexamethasone 8mg IV stat or equivalent steroid

Followed by:

- Ondansetron 8mg BD/PRN for 3 days
- Domperidone 20mg PO QDS/PRN

7.3 Treatment Assessments

All patients require the following examinations to have been performed within 6 weeks prior to commencement of chemotherapy (the latest available scans should be used):

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

The following blood tests to be completed within 7 days prior to commencement of chemotherapy:

- Urea and Electrolytes (U&E)
- Liver Function Tests (LFTs)
- PSA Test
- Serum creatinine
- Serum corrected calcium
- Magnesium
- Albumin

7.4 Dose Modifications

7.4.1 General Rules

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

7.4.2 Dose reduction

The dose of chemotherapy can be reduced by 20 percent when necessary, as described below. This corresponds to a dose of 20mg/m^2 for cabazitaxel and 60mg/m^2 for docetaxel. The dose which has been reduced for toxicity must not be re-escalated. Only one dose reduction will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should go off study.

7.4.3 Chemotherapy Delay

A treatment delay ≥4 days should be justified (i.e., to be reported in the CRF). Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should go off study.

7.5 Dose reductions and delays

7.5.1 Dose modifications and treatment alterations for cabazitaxel

Myelosuppression

Table 2 - Chemotherapy dose modifications for haematologic toxicity

Haematologic Toxicity	Grade 3	Grade 4
Neutropenia If duration ≥7 days, or if complicated by T ≥38.5°C, or T ≥38.1°C x 3 during a 24-hour period, or infection.	Delay* next infusion until ANC ≥1.5 x 10^9/L, then reduce cabazitaxel to 20 mg/m^2. The treatment should be discontinued if a patient continues to experience neutropenia at a reduced dose.	
Thrombocytopenia	Delay* infusion until platelets ≥100 x 10^9/L. No dose reduction is required.	Delay* infusion until platelets ≥100 x 10^9/L and reduce cabazitaxel to 20 mg/m^2. Withdraw from study treatment in case of recurrence.

*Maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment
T=temperature

Allergy (Anaphylactic and Hypersensitivity reactions)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of chemotherapy. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well-being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (ie, antihistamine, corticosteroids, aminophylline, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed in Table 3:

Table 3:

Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside • Complete cabazitaxel infusion at the initial planned rate. • At subsequent cycles consider whether additional premedication is required
Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. >80 mmHg	• Stop cabazitaxel infusion • Give IV chlorpheniramine 10mg and/or IV dexamethasone 10mg • Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 7.2 when cabazitaxel is re-infused more than 3 hours after the interruption • Administer cabazitaxel over 2 hours for all subsequent infusions with additional IV antihistamine and steroid premedication.
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	• Stop cabazitaxel infusion • Give IV chlorpheniramine 10mg and/or IV dexamethasone 10mg • Add epinephrine or bronchodilators and/or IV plasma expanders if indicated. • Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 7.2 when cabazitaxel is re-infused more than 3 hours after the interruption • Administer cabazitaxel over 2 hours for all subsequent infusions. • If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	NO FURTHER PROTOCOL TREATMENT

Nausea/Vomiting

A prophylactic antiemetic treatment should be given to the patients in all cycles as listed above. More aggressive antiemetic prophylaxis (e.g.,aprepitant or equivalent) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of chemotherapy. If despite dose reduction, nausea/vomiting still occur at grade ≥3, the patient will go off study.

Diarrhoea

No prophylactic treatment for diarrhoea is recommended in Cycle 1. However, following the first episode of diarrhoea, the patient should receive symptomatic treatment with loperamide 4 mg orally and then 2 mg orally following each new episode until recovery of diarrhoea (no more than 16 mg daily). If despite the use of loperamide, grade ≥3 diarrhoea still occurs, reduce the dose of cabazitaxel to 20mg/m^2. If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient will go off study.

Stomatitis

If grade 3 or worse stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of cabazitaxel should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will go off study.

Peripheral neuropathy

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

- Grade ≤1: No change
- Grade 2: Retreat with reduced dose of 20mg/m^2
- Grade 3: Patient will go off protocol therapy

Liver toxicity

In case of increase of ALT and/or AST to >1.5 x ULN or bilirubin to >ULN, delay study cabazitaxel treatment for up to 2 weeks until ALT and/or AST returned to ≤1.5 x ULN and bilirubin to ≤ULN. Then retreat patient at reduced dose for rest of the treatment.

Other Toxic Effects

For any other toxicity grade 2, manage symptomatically, and retreat without dose reduction. If toxicity is grade 3 or worse (except for alopecia), trial drug administration should be stopped until there is resolution to grade 2. Once there is resolution to grade 2, then trial drug can be re-instituted, if medically appropriate, with a reduced dose (20mg/m^2).

7.5.2. Dose modifications and treatment alterations for Docetaxel

Myelosuppression

Table 4 - Chemotherapy dose modifications for haematologic toxicity

Haematologic Toxicity	Grade 3	Grade 4
Neutropenia If duration ≥7 days, or if complicated by T ≥38.5°C, or T ≥38.1°C x 3 during a 24-hour period, or infection.	Delay* next infusion until ANC ≥1.5 x 10^9/L, then reduce docetaxel to 60 mg/m^2. The treatment should be discontinued if a patient continues to experience neutropenia at a reduced dose.	
Thrombocytopenia	Delay* infusion until platelets ≥100 x 10^9/L. No dose reduction is required.	Delay* infusion until platelets ≥100 x 10^9/L and reduce docetaxel to 60 mg/m^2. Withdraw from study treatment in case of recurrence.

Allergy (Anaphylactic and Hypersensitivity reactions)

Docetaxel in combination with prednisolone: Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of the general sense of well-being and of blood pressure and heart rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention can occur in

response to symptoms of an untoward reaction. Facilities and equipment for resuscitation must be immediately available. If a reaction occurs, the specific treatment that is medically indicated can be given (e.g. adrenaline in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.). In addition, it is recommended to take the measures listed below:

Table 5:

Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside • Complete docetaxel infusion at the initial planned rate. • At subsequent cycles consider whether additional premedication is required
Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. >80 mmHg	• Stop docetaxel infusion • Give IV chlorpheniramine 10mg and/or IV dexamethasone 10mg • Once all signs and/or symptoms of hypersensitivity reaction disappear, docetaxel may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 7.2 when docetaxel is re-infused more than 3 hours after the interruption • Administer docetaxel over 2 hours for all subsequent infusions with additional IV antihistamine and steroid premedication.
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	• Stop docetaxel infusion • Give IV chlorpheniramine 10mg and/or IV dexamethasone 10mg • Add epinephrine or bronchodilators and/or IV plasma expanders if indicated. • Once all signs and/or symptoms of hypersensitivity reaction disappear, docetaxel may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. • Re-administer premedication regimen as described in Section 7.2 when docetaxel is re-infused more than 3 hours after the interruption • Administer docetaxel over 2 hours for all subsequent infusions with additional IV antihistamine and steroid pre-medication • If a severe reaction recurs, patient will be withdrawn from protocol therapy

Nausea/Vomiting

A prophylactic antiemetic treatment should be given to patients from the first cycle. If despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of docetaxel to 60mg/m^2. If despite dose reduction, nausea/vomiting still occur at grade ≥3, the patient should be withdrawn from trial treatment.

Diarrhoea

No prophylactic treatment for diarrhoea is recommended from cycle one. However, following the first episode of diarrhoea, the patient should receive symptomatic treatment with loperamide 4mg following the first episode, and then 2mg following each new episode until recovery from diarrhoea (no more than 16mg daily). If despite the use of loperamide, grade ≥3 diarrhoea still occurs, reduce the dose of docetaxel to 60mg/m^2. If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient should be withdrawn from trial treatment.

Stomatitis

Grade ≤2: No change, docetaxel should be withheld until resolution to grade ≤1.

Grade 3: If grade 3 stomatitis occurs, docetaxel should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of docetaxel should be reduced 60mg/m^2 for all subsequent doses.

Grade 4: In case of grade 4 stomatitis, the patient should be withdrawn from trial treatment.

Peripheral Neuropathy

If symptoms or signs are experienced by the patient, dose modification should be performed as follows:

Grade ≤1: No change

Grade 2: Dose reduction to 60mg/m^2

Grade 3: Patient should be withdrawn from trial treatment.

Skin Toxicity

Grade ≤2: No change

Grade 3: Delay until resolved to grade ≤1 (maximum two weeks) then reduce dose of trial drug by one dose level; if no recovery to ≤ grade 1 within two weeks' delay, patient should be withdrawn from trial treatment.

Liver Toxicity

In case of increase of ALT and/or AST>1.5xULN or bilirubin>ULN, delay docetaxel treatment for up to 2 weeks until ALT and/or AST returned to ≤1.5xULN and bilirubin ≤ULN. Then treat at 60mg/m^2. Liver function should be checked immediately prior to the first cycle of docetaxel if an anti-androgen has been administered. Treatment should be delayed if LFTs are abnormal.

Docetaxel-induced fluid retention

In case of fluid retention (peripheral oedema and/or effusions) during the treatment with docetaxel, the patient's body weight should be recorded and followed as frequently as possible to document any weight gain, which could be related to oedema. Treatment should not commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline ≥1 grade not otherwise explained. Based on the hypothesis of capillary damage due to docetaxel, the following treatment is recommended in case fluid retention occurs: furosemide 20mg po once daily.

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

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

Docetaxel-induced hyperlacrimation

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

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

- No dose reduction planned
- Frequent instillation of artificial tears
- Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate): 2 drops each eye bid for 3 days starting the day before docetaxel administration, in patients without history of herpetic eye disease.

7.6 Non-trial treatment

7.6.1 Medications permitted

Any additional treatment that the responsible physician feels is appropriate is permitted. However, vaccination with a live attenuated vaccine should be avoided in patients receiving cabazitaxel.

7.6.2 Data on concomitant medication

All concomitant medication will be recorded on the baseline form prior to starting treatment and on any subsequent Serious Adverse Event forms.

7.6.3 Radiotherapy

Investigators may plan to give radiotherapy (RT) for suitable patients; these patients remain eligible for drug treatment. Note that giving RT after treatment has commenced is likely to be evidence of tumour progression and hence treatment termination.

7.7 Treatment compliance

Treatment compliance will be measured at each clinic visit and recorded in the treatment CRF. All dose modifications, delays and omissions must be recorded on the appropriate CRF. If treatment is permanently discontinued due to toxicity, the Deviation form must be completed.

7.8 PSA Measurements/biochemical progression

All patients should have PSA measured pre-treatment (within two weeks of starting treatment) and at the beginning of each cycle (every 3 weeks), and thereafter every 12 weeks, up to 2 years post initiation of cabazitaxel treatment. 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.

Patients who have a rising PSA and fulfil the criteria in Appendix 7 will be defined as having biochemical progression.

7.9 Pain Progression

Pain progression is defined as clinical evidence of an increase in pain which, in the opinion of the treating clinician, is sufficient to warrant discontinuation of trial treatments and to trigger a change in therapy.

7.10 Radiological Progression

Disease progression confirmed as per RECIST 1.1 guidelines (Appendix 8).

7.11 Quality of Life

A Quality of Life (QoL) study is being performed to assess the impact of treatment on the quality of patients' lives, and all patients should be asked if they are willing to participate. The EORTC QLQ-C30 with the prostate-specific module QLQ PR25 will be used (see Appendix 6).

7.12 Toxicity

Toxicity will be monitored by clinical examination and laboratory tests (haematology and blood chemistry). All toxicities will be categorised according to the National Cancer Institute Common Toxicity Criteria version 4 (Appendix 4).

7.13 Follow-up

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

7.14 Stopping of treatment or follow-up

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

7.15 Stopping trial interventions

This is an early phase, single stage trial with no planned stopping rules since the primary outcome measure requires follow-up of patients to 6-months. The follow-up timelines preclude a 2-stage design.

A patient may stop trial treatment for the following reasons:

1. Progression whilst on therapy; note however, clinicians may continue therapy if progression is PSA only—see table below
2. Unacceptable toxicity
3. Intercurrent illness which prevents further treatment
4. Withdrawal of consent for treatment. If this occurs, the Investigator will need to verify whether consent for follow-up remains.
5. Any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion.

Patient's pathway post-progression

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

The reason should be recorded on the treatment and/or follow-up forms as well as the End of Treatment form. Unless a patient states otherwise, it should be assumed that consent is given to continue to record trial data.

7.16 Patient transfers

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

7.17 Withdrawal from the trial completely

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

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

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 5. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the (compendium of) Summary of Product Characteristics.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this includes abnormal laboratory findings.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition).

8.1.3 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
    - Pre-planned elective procedures unless the condition worsens
    - Treatment for progression of the patient's cancer.

8.1.4 Monitoring pregnancies for potential Serious Adverse Events

In the event that a patient's partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. The patient should be given a Pregnancy Release of Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy, they should sign the Pregnancy Release of Information Form. Once consent has been obtained, please provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form and if necessary, also complete an SAE Form.

8.1.5 Reporting Period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. In addition, any SAEs occurring after the last IMP treatment is given, and

which are considered to be related to the treatment by the Investigator, must be reported as an SAE, regardless of when they occur.

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the Trials Office.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Serious Adverse Events

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0800 414 2230 or 0121 414 3700

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Refer to the SAE Form Completion Guidelines included in the Investigator Site File for further information.

8.2.2 Trials Office

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious

Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e., is not defined in the (compendium of) Summary of Product Characteristics), it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.2.3 Reporting to the Competent Authority and main Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

8.2.3.2 Serious Adverse Reactions

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

8.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.2.3.4 Other safety issues identified during the course of the trial

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

8.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.2.5 Data and Safety Monitoring Committee

The independent Data Monitoring Committee (DSMC) will review all SAEs.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection

The CRF must be completed, signed/dated and returned to the Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the specified timeframe (see CRF completion guidelines). The exception is the SAE Form which must be co-signed by the Investigator. If, however, the Principal Investigator is unreachable (e.g., on annual leave), the SAE must be faxed to the Trial Office without his/her signature but signed by the person reporting the SAE. In this case, assessment of relatedness will not be included. Notification of an SAE to the Trial Office should not be delayed in the case where the Investigator's signature cannot be obtained immediately. See Adverse Event reporting section 8.2 for further details.

Table 4: Table of standard forms and summary of data to be collected.

Form type	Summary of data collected
Eligibility Form	Confirmation of eligibility
Randomisation Form	Confirmation of patient details, optional consents
Baseline Form	Pre-trial blood results with physical examination, disease details, pre-trial investigations and concomitant medications.
Cabazitaxel Treatment Form	Details of chemotherapy doses, date given, toxicities and any reduction or omission details.
Docetaxel Treatment Form	Details of chemotherapy doses, date given, toxicities and any reduction or omission details.
Follow up Form	Every 6 weeks for 30 weeks, then every 12 weeks until 2 years.
Follow up form, post progression	At the first occurrence of each type of progression (biochemical, radiological, clinical and SRE).
Progression and additional treatment form	Details of disease progression and treatment for progression.
Additional treatment update form	Details of any further additional treatment.
End of treatment form	Details of end of treatment for any reason.
Death Form	Details of death including date, cause and post-mortem report.
Quality of life form	At baseline, end of treatment, then every 12 weeks until 2 years.
Serious Adverse Event form	Details of the SAE including the date, symptoms, concomitant medications, treatment.
Pathology Form	Details for research sample
Palliative radiotherapy form	Details of ratiotherapy treatment
Withdrawal Form	Details regarding withdrawal of patient from trial.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections of a CRF must be completed before returning the CRF to the Trials Office.

Source data is all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial. In the following case only, the CRF will be considered the source document: Quality of Life booklets.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate. The completed originals must be sent to the Trial Office and a copy filed in the Investigator Site File.

Trial CRFs may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs, etc.) at their site are securely retained for at least 5 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. QUALITY MANAGEMENT

10.1 Site Set up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition, all participating investigators will be asked to sign the necessary agreements, trial registration forms and supply a current CV to the Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy Manual containing essential documentation, instructions, and other supporting materials required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms

for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC and the Medicines for Healthcare products Regulatory Agency (MHRA).

10.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trials Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11 END OF TRIAL DEFINITION

For the purpose of complying with UK Clinical Regulations introduced on May 2004, the trial will be considered ‘closed’ when the last patient has completed protocol treatment plus 30 days. This will allow sufficient time for the completion of protocol procedures, data collection and data input. For the purposes of main REC approval, the trial end date is deemed to be the date the last recruited patient attends for their 2 year follow up clinic visit.

After closure of the trial with the MHRA, the Sponsor is no longer required to notify the MHRA and main REC of changes of Principal Investigator. However, sites should continue to notify the Trials Office of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV.

The Trials Office will notify the MHRA and main REC that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

12. STATISTICAL CONSIDERATIONS

12.1 Definition of Primary Outcome

Disease progression is defined as any of the following events:

- PSA progression
- Pain progression (as defined in 7.9)
- Cancer-related skeletal related event.

Clinical progression-free survival (CPFS) is defined as the interval in whole days between the date of randomisation into the trial and the earliest date of detection of clinical progression or date of death without recorded progression. Those patients who are still alive and progression free will be censored at date of last follow-up time to progression (TTP), defined as the interval in whole days between the date of randomisation into the trial and the earliest date of detection of clinical progression. Patients who have died will be censored at date of death, and those alive and progression free will be censored at the date of last follow-up.

12.2 Definition of Secondary Outcome

Acute toxicity: Treatment safety is defined as the proportion of patients developing adverse events (AEs) during treatment and graded according the NCI-CTC version 4. Adverse events will be classified by causality, grade, type, duration and system involved.

Late toxicity: Toxicity reported after trial therapy has been completed, defined as 30 days after the last injection of cabazitaxel or docetaxel and resolution of associated acute toxicity.

Tolerability: Defined as the proportion of patients with no grade 3 or 4 haematological toxic events during treatment.

PSA response (applies only to patients with baseline PSA ≥20 ng/ml): Response requires a PSA decline of ≥50% confirmed by a second PSA value at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied. 'Best' PSA response during treatment and prior to progression will contribute to the primary outcome.

Overall survival (OS): Is defined as the number of whole days from date of randomisation into the trial until death by any cause. Patients who do not die will be censored at the date of last follow-up.

Drug dose administered: Will be defined by dose intensity, incidences of dose reductions, interruptions, escalations and discontinuations.

12.3 Statistical Analysis

All analyses will be conducted on an intention-to-treat basis in that once a patient is randomised they will remain in the statistical analysis in their randomised treatment group. If the percentage of patients who do not start treatment is above 5% then the DMC may recommend recruiting additional patients. As a phase ii trial, the statistical analysis will be based on descriptive statistics. All statistical analyses will be carried out on all randomised patients including patients who were protocol violators and ineligible patients. Ineligible patients are defined as those patients who are subsequently found to not meet the eligibility criteria of the trial. The number of ineligible patients and reasons for their ineligibility will be reported. Protocol violators will be reported as part of treatment compliance. A sensitivity analysis will be carried out on the subgroup of patients who start treatment to ascertain robustness of the trial and conclusion.

Time to event outcomes: estimates of time to progression and time to death will be calculated using the Kaplan-Meier method. Median and 6-month 'survival' estimates will be presented with confidence intervals. A hazard ratio of the treatment effect will be estimated and presented with 95% confidence intervals.

Treatment safety will be analysed descriptively in terms of AEs incidence, grade, causality, duration, type and body system affected. The proportion of patients experiencing grade 3 and grade 4 toxicities on each arm will be reported as a proportion of i) all patients registered in the trial and ii) all patients receiving at least one dose of treatment in the trial.

Drug dose administered will be analysed in terms of incidence of dose reductions, interruptions and discontinuations which will be classified with respect to frequency, causality, level and duration.

Changes in pain score and QoL will be assessed using longitudinal methods of analysis and will account for informative dropout including dropout for death.

12.4 SAMPLE SIZE

The sample size calculation is based on Jung's single stage design (Jung 2008) and the primary outcome measure of clinical progression free survival at 6-months. Previous evidence in this group of patients receiving docetaxel suggests a response rate of 20% after 6-months. This design is based on ensuring that the type i and type ii error rates are less than or equal to 0.10 and 0.15 respectively and assumes a response rate on the control arm (docetaxel) of 20% and a 15% expected absolute improvement in the treatment arm (cabazitaxel) to 35%.

The statistical design stated above requires 65 patients to be randomised to each treatment arm with the target recruitment therefore being 69 patients per arm (138 in total) to allow for a 5% drop out rate to provide evidence that the cabazitaxel treatment warrants further investigation in the phase III setting.

12.5 TIMINGS OF INTERIM AND FINAL ANALYSIS

The interim data will be presented annually to the DMC who may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. Stopping guidelines will serve as guidelines at DMC consultation and are not absolute rules that would result in automatic closure of study recruitment.

Analysis of the primary outcome is planned for when all patients have a minimum of 6 months follow-up following randomisation and analysis of the long term outcome when all patients have a minimum of 24 months follow-up. The final study analysis will take place when all patients have completed 24 months follow up. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

University of Birmingham

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

A Trial Management Group (TMG) will be established and will include the Chief Investigator (Prof Nicholas James), Co-Investigator (Dr Robert Stevenson), clinical collaborators and other identified collaborators, the trial statistician and the trial coordinator. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in person as required.

13.4 Data and Safety Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The trial statistician and members of the DSMC will be the only individuals who see the confidential, accumulating data from the trial; however the Chief Investigator and Trial Coordinator will receive subsets of the report, as seen fit by the DSMC (e.g. accrual, compliance, data completeness). During the recruitment phase of the trial, the DMC is scheduled to meet one month prior to the due date of the Annual Safety Report and annually thereafter. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Management Group (TMG) who will convey the findings of the DMC to MHRA, funders, and sponsors. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable, or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

13.5 Finance

This trial is a clinician-initiated and clinician-led trial. The trial administration is funded by Sanofi. Sanofi will also supply cabazitaxel at no cost for trial patients. Academic support is funded through the University of Birmingham.

No individual per patient payment will be made to NHS Trusts, Investigators or patients.

13.6 NCRN Adoption

This study has been adopted by the NCRN and will therefore use the CSP system for gaining local R&D approvals.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will

be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

The personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the patient's consent, their full name, date of birth and National Health Service (NHS) number will be collected at trial entry, to allow flagging with the Data Linkage Service (which collates data for the NHS). Patients will be identified using only their unique trial number, initials, hospital number and date of birth on the Case Report Form and correspondence between the Trials Office and the participating site.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of the patient's cancer. Representatives of the CANTATA trial team may be required to have access to patient notes for quality assurance purposes, but patients should be reassured that their confidentiality will be respected at all times.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1 – TUMOUR STAGING - TNM CLASSIFICATION

	TNM staging
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging T1a Tumour incidental histological finding in ≤5% tissue resected T1b Tumour incidental histological finding in ≥5% tissue resected T1c Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour confined within the prostate T2a Tumour involves one half of one lobe or less T2b Tumour involves more than one half on one lobe, but not both lobes T2c Tumour involves both lobes
T3	Tumour extends through the prostatic capsule T3a Extracapsular extension (unilateral or bilateral) T3b Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles; bladder neck, external sphincter, rectum, levator muscles, or pelvic wall
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other site(s)
	Histopathological grading
GX	Grade cannot be assessed
G1	Well differentiated (Gleason 2-4)
G2	Moderately differentiated (Gleason 5-6)
G3-4	Poorly differentiated/undifferentiated (Gleason 7-10)

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2,3,4
	T1b,c	N0	M0	Any G
	T1, T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

APPENDIX 2 – WMA DECLARATION OF HELSINKI

http://www.wma.net/en/30publications/10policies/b3/index.html

APPENDIX 3 – DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

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

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

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

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatient's hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

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

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

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms), or for social reasons (e.g. respite care), are not regarded as an SAE.

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

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

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

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

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

APPENDIX 4 – COMMON TOXICITY CRITERIA (CTC) GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 5 – STAMPEDE TRIAL PROTOCOL

See www.stampedetrial.org for details

APPENDIX 6 – QUALITY OF LIFE QUESTIONNAIRE

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, is the product of more than a decade of collaborative research. Following its general release in 1993, the QLQ-C30 has been used in a wide range of cancer clinical trials, by a large number of research groups; it has additionally been used in various other, non-trial studies.

The prostate cancer module is meant for use among patients with prostate cancer varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.).

These two modules will be combined together in a single booklet and patients who consent to the QoL sub-studies will be asked to complete the booklet prior to seeing the clinician. A nurse can support the patient in completing the booklet, but all assessments should be the patient's own.

APPENDIX 7 – DEFINITION OF BIOCHEMICAL FAILURE

The initial response to hormonal therapy for prostate cancer can be variable. A few patients exhibit only a small fall in PSA, with little evidence of clinical response. At the other extreme a rapid fall to the normal range or even undetectable levels of PSA occurs. In a group of patients the response lies between these two extremes. The rate of fall of PSA and the level of the PSA nadir are recognised to have prognostic significance. However, in defining PSA relapse, the extent of the primary response has to be taken into account.

Three groups of patients will be defined:-

- **A.** If the PSA nadir is more than 50% of the last pre-treatment PSA, the patient should be defined as a treatment failure (at time zero).
- **B.** For patients whose PSA falls by more than 50% of the last pre-treatment PSA, but remains above 4ng/ml, PSA relapse will be deemed to have occurred when PSA is confirmed as increasing by 50% above the nadir level.
- **C.** For patients whose PSA falls below 4ng/ml, PSA relapse will be defined by either 50% increase from their nadir or the PSA increasing above 4ng/ml, whichever is the greater. For example, a nadir PSA of 3.6 would require a PSA of 5.4 to define relapse, while PSA nadir of 2.5 will be considered to have relapsed at a PSA of 4.

Timing of PSA tests: Once on trial, PSA tests will be performed at every three weeks from the start of cabazitaxel or docetaxel treatment and at each follow-up visit (3 monthly until 2 years).

Nadir PSA: The PSA nadir will be the lowest reported PSA level between the start of treatment and the 30 week PSA assessment. The critical value that would constitute subsequent biochemical progression will be calculated from this nadir value. Once the 6 month PSA level has been recorded and sent promptly to the CRCTU, a letter will be sent to the responsible clinician confirming the PSA level which would be taken as progression.

Confirming Failure-Free Survival (including biochemical failure): In applying the definitions of Failure-Free Survival (including biochemical failure) above, the increase in PSA must be confirmed (i.e. at least two readings are required). The following approach will be applied:

1. Patient reaches nadir PSA and continues with 3-monthly PSA assessments. [Any PSA measurement taking place within 6 weeks of a change in hormone therapy or a manipulation (e.g. cystoscopy) that could produce a spurious increase in PSA is to be ignored].
2. At a subsequent assessment (say, assessment X), the PSA value is noted to have risen above the critical value, but patient is symptom free.
3. Patient should be recalled for a confirmatory PSA test between one week and 3 months later. If this value is at the same level or higher, the patient will be considered to have reached the biochemical failure endpoint.

Confirmatory step 3 will not be required if the patient has demonstrable local progression, new metastases or death from prostate cancer during the intervening period.

Time to Failure-Free Survival (including biochemical failure): Patients in Group A (treatment failure) will be recorded as events at time zero. The time to FFS for patients in Groups B and C will be from randomisation to either cabazitaxel or docetaxel to the first PSA above the critical value (i.e. assessment X).

Non-protocol treatment: No new non-protocol treatment for prostate cancer should be administered until trial progression has been confirmed.

APPENDIX 8 – DEFINITION OF RADIOLOGICAL PROGRESSION

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf