STAMPEDE

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

A multi-arm multi-stage randomised controlled trial

Version: **21.0**
Date: **20 October 2020**

MRC CTU AT UCL ID:	**PR08**
ISRCTN #:	**ISRCTN78818544**
NCT #:	**NCT00268476**
EUDRACT #:	**2004-000193-31**
CTA #:	**20363/0404/001**
MREC #:	**04/MRE07/35**

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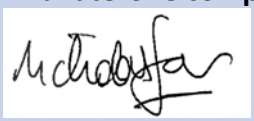

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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 4.0. It describes the STAMPEDE trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Cancer And Other Non-Infectious Diseases Group, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z6364106), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

*Until the Clinical Trials Regulation EU No 536/2014 becomes applicable, the trial will be conducted in accordance with the Clinical Trials Directive as implemented in the UK statutory instrument. When the directive is repealed on the day of entry into application of the Clinical Trial Regulation the trial will work towards implementation of the Regulation (536/2014) following any transition period.

International sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC [where applicable]) and applicable national regulations.

SPONSOR

UCL is the sponsor of STAMPEDE and MRC CTU has been delegated responsibility for the overall management of STAMPEDE. Queries relating to UCL sponsorship should be addressed to the Director, Professor Max Parmar, Institute of Clinical Trials & Methodology, MRC CTU at UCL, 2nd Floor, 90 High Holborn, London, WC1V 6LJ UK, or via the STAMPEDE Trial Team.

FUNDING

Cancer Research UK's Clinical Research Committee (formerly the Clinical Trials Advisory Awards Committee), Medical Research Council, and educational grants from Novartis, Sanofi-Aventis, Pfizer, Janssen Pharma NV, Astellas, Clovis Oncology.

AUTHORISATIONS AND APPROVALS

The following persons are authorised to sign the final protocol and protocol amendments for the sponsor: Chief Investigator and Trial Statistician and the Co-Chief-investigators for each comparison subsequently added.

TRIAL REGISTRATION

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

RANDOMISATION
Call MRC CTU at UCL, Monday to Friday 0900-1700
Excluding public holidays or dates when notice has been given by the Unit.
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SAE REPORTING
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Clinical Safety Committee	Prof Noel Clarke
Comparison Management Groups	Each led by Comparison Chief Investigator(s)
Metabolic Translational Group	Prof Silke Gillessen
Outcome Review Group	Prof Robert Jones
Site Advisory Team	Mr William Cross
Quality of Life Group	Prof Nicholas James

CONTENTS

SUMMARY OF TRIAL

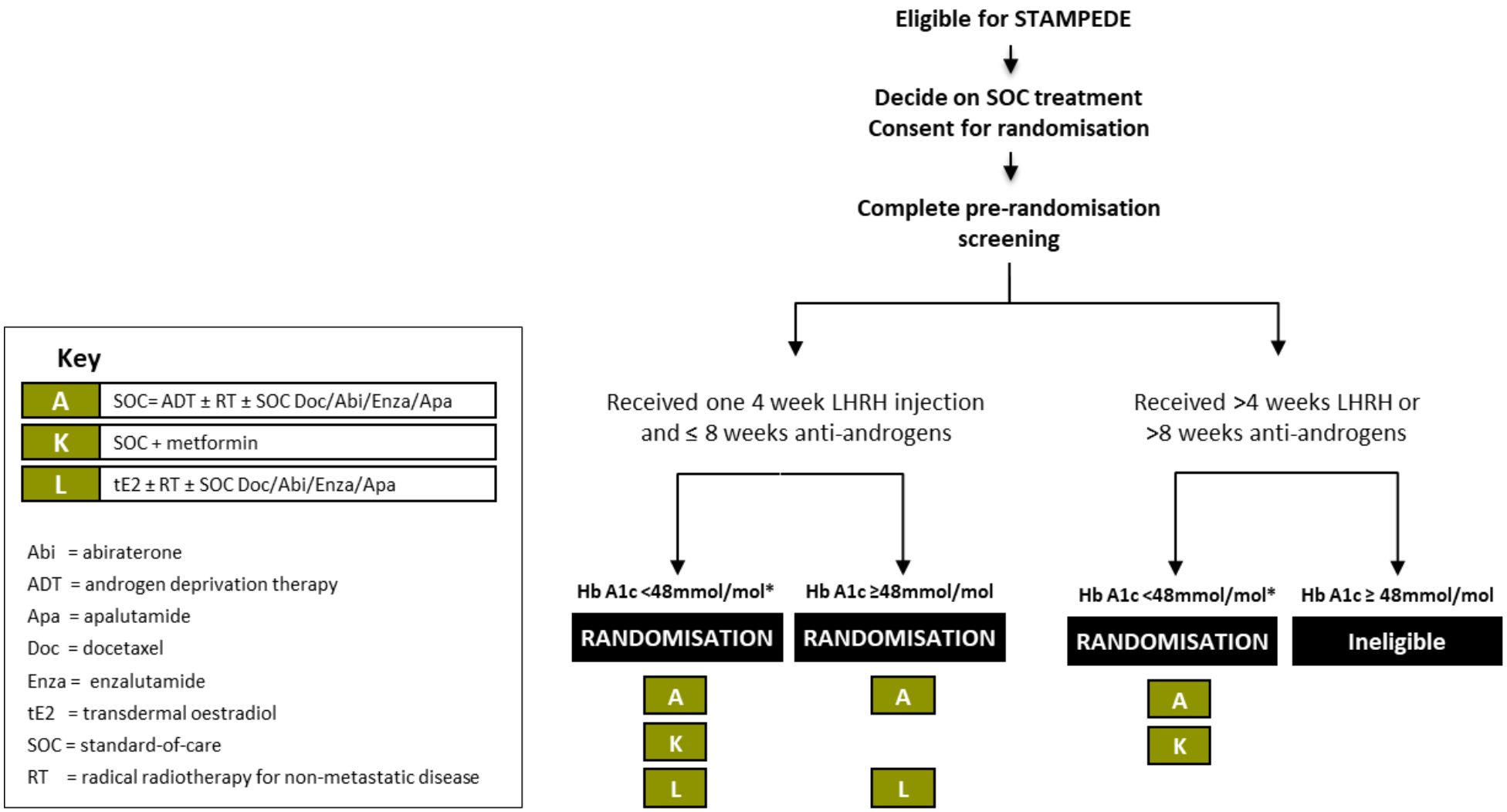
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	STAMPEDE
Long Title of Trial	Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A multi-arm multi-stage randomised controlled trial
Version	21.0
Date	20-October-2020
MRC CTU at UCL ID	PR08
NCT #	NCT00268476
EudraCT #	2004-000193-31
Study Design	Multi-arm multi-stage platform randomised controlled trial
Type of Participants to be Studied	People starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer
Setting	Tertiary care
Interventions to be Compared	Various - see comparison-specific tables
Study Hypothesis	Various - see comparison-specific tables
Definitive Primary Outcome Measure	Overall survival (unless stated)
Intermediate Primary Outcome Measure	Failure-free survival (unless stated)
Secondary Outcome Measure(s)	Toxicity Symptomatic skeletal events Quality-of-life Cost-effectiveness
Randomisation	Minimisation using a random element across a number of stratification factors
Number of Participants	See comparison-specific tables
Duration	See comparison-specific tables
Sponsor	University College London
Funders	Cancer Research UK Medical Research Council Astellas Clovis Oncology Janssen Novartis Pfizer Sanofi-Aventis

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
"Original comparisons"	
Type of Participants to be Studied	People starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer
Control Arm	• Arm A: Standard-of-care (SOC)
Interventions to be Compared	• Arm B: SOC + zoledronic acid • Arm C: SOC + docetaxel • Arm D: SOC + celecoxib • Arm E: SOC + zoledronic acid + docetaxel • Arm F: SOC + zoledronic acid + celecoxib
Allocation ratio	• 2 control arm : 1 research arm [2A:1B:1C:1D:1E:1F]
Study Hypothesis	Research interventions will improve survival over SOC
Definitive Primary Outcome Measure	Overall survival
Intermediate Primary Outcome Measure	Failure-free survival
Status	Primary results published and **active follow-up discontinued** Summer 2018 (1, 2)
"Abiraterone comparison"	
Type of Participants to be Studied	People starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer
Control arm	• Arm A: Standard-of-care (SOC)
Intervention to be Compared	• Arm G: SOC + abiraterone
Allocation ratio	• 1 control arm : 1 research arm [1A:1G]
Study Hypothesis	Addition of abiraterone to SOC will improve survival over SOC alone
Definitive Primary Outcome Measure	Overall survival
Intermediate Primary Outcome Measure	Failure-free survival
Number of Participants	Around 1,800 patients for 267 control arm definitive primary outcome measure events
Duration	6 to 8 years
Status	Primary results published (3), remains on active follow-up to permit a further longer-term analysis
"M1|RT comparison"	
Type of Participants to be Studied	People starting long-term hormone therapy for newly-diagnosed metastatic prostate cancer with no contraindication to prostate radiotherapy
Control arm	• Arm A: Standard-of-care (SOC)
Intervention to be Compared	• Arm H: SOC + radiotherapy to the prostate (RT)
Allocation ratio	• 1 control arm : 1 research arm [1A:1H]
Study Hypothesis	Addition of RT to SOC will improve survival over SOC alone

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Definitive Primary Outcome Measure	Overall survival
Intermediate Primary Outcome Measure	Failure-free survival
Number of Participants	Around 1,800 patients for 267 control arm definitive primary outcome measure events
Duration	6 to 8 years
Status	Primary results published (4) remains on active follow-up to permit a further longer-term analysis
"Enzalutamide + abiraterone comparison"	
Type of Participants	People starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer
Control Arm	• Arm A: Standard-of-care (SOC)
Interventions to be Compared	• Arm J: SOC + enzalutamide + abiraterone
Allocation ratio	• 1 control arm : 1 research arm [1A:1J]
Study Hypothesis	Addition of enzalutamide, in combination with abiraterone, to SOC will improve survival over SOC alone
Definitive Primary Outcome Measure	Overall survival
Intermediate Primary Outcome Measure	Failure-free survival
Number of Participants	Around 1,800 patients for 267 control arm definitive primary outcome measure events
Duration	6 to 8 years
Status	In follow-up
"Metformin comparison"	
Type of Participants to be Studied	Non-diabetic people, with no contraindication to metformin, starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer
Control arm	• Arm A: Standard-of-care (SOC)
Intervention to be Compared	• Arm K: SOC + metformin
Allocation ratio	• 1 control arm : 1 research arm [1A:1K]
Study Hypothesis	Addition of metformin to SOC will improve survival over SOC alone
Definitive Primary Outcome Measure	Overall survival
Intermediate Primary Outcome Measure	Overall survival
Number of Participants	Around 2800 patients, including around 1,700 M1 (metastatic) patients, for 473 control arm definitive primary outcome measure events among M1 patients
Duration	7 years

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Status	Recruiting
"Transdermal oestradiol comparison"	
Type of Participants to be Studied	People starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer, having had no more than one 4-week (or one-month) LHRH (Luteinizing hormone releasing hormone) injection & 8 weeks of anti-androgens
Control arm	• Arm A: Standard-of-care (SOC)
Intervention to be Compared	• Arm L: Transdermal oestradiol ± RT ± docetaxel/abiraterone/enzalutamide/apalutamide
Allocation ratio	• 1 control arm : 1 research arm [1A:1L]
Study Hypothesis	Transdermal oestradiol will be non-inferior to standard hormone therapy, while having fewer side-effects and improved quality-of-life
Definitive Primary Outcome Measures	Co-primary endpoints of progression-free survival and overall survival
Intermediate Primary Outcome Measure	Progression-free survival
Number of Participants	Around 700 to include within a meta-analysis with the PATCH trial (EudraCT 2005-001030-33), which will include around 2,500 patients overall
Duration	4 to 6 years
Status	Recruiting

Figure 1: Randomisation schema from protocol v21.0 onwards



*Participants must not have received any treatment with any anti-diabetes medication but diet controlled diabetes is allowed if HbA1c now in limits.

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

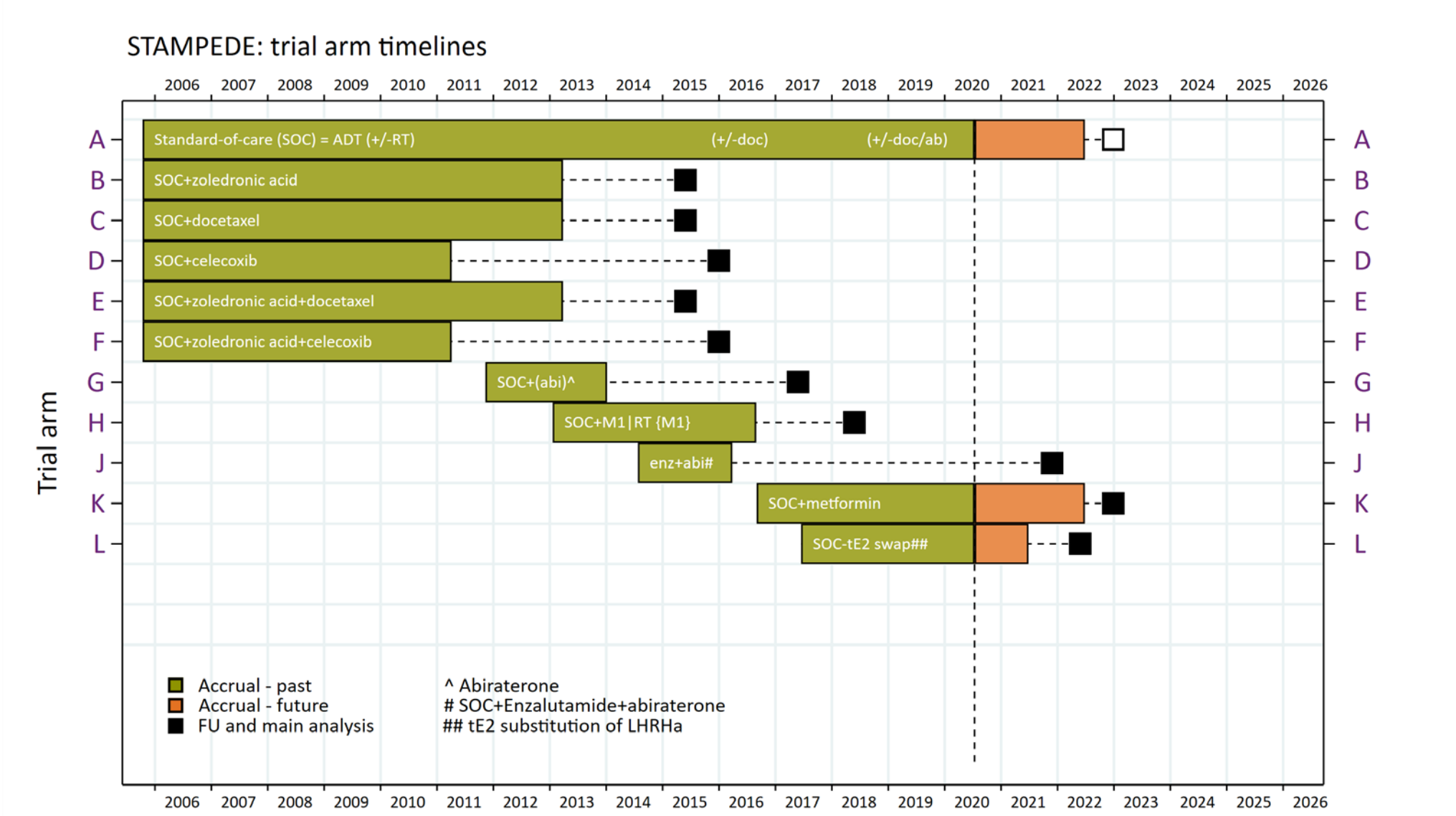


Table 1: Schedule of Assessments for Participants Randomised before 05-Sep-2016

	ASSESSMENT WEEK											ALL FURTHER VISITS [1]	AT EACH DISEASE EVENT [2]	END OF TRT	PRIOR TO 2ND LINE TRT
	4-6	12	18	24	36	48	60	72	84	96	104				
Arm A/G/J															
Blood collection cell-free DNA Streck™ tubes [3]						X [4]		X [4]	X [4]				X	X	X
Saliva sample [3]	Any time point														
FFPE block [3]	Once, at the point of request														
PSA	X	X	X	X	X	X	X	X	X	X	X	X			
Waist circumference + Weight	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X			
QL + HE [5,3]	X	X	X	X	X	X	X	X	X	X	X	X			
Arm G&J only															
Blood pressure[6]	X	X	X	X	X	X	X	X	X	X	X	X			
Safety bloods (LFTs and potassium) [6]	X	X	X	X	X	X	X	X	X	X	X	X			

[1] Follow-up visits after year 2 need to be carried out every 6 months for the first 5 years. At year 6 and onwards visits should be every 12 months whilst active follow-up continues.
[2] Disease events are defined as each type of disease progression: PSA (biochemical), clinical (symptomatic) and radiological (objective).
[3] Only if participating in relevant sub-study, for information regarding samples see the **Sample Collection & Handling Manual** available via the STAMPEDE website for details
[4] Sample only required for participants with metastatic disease at trial entry (M1)
[5] Review **Table 38** for a breakdown of participants that are still required to complete Quality-of-life (QL) + health economic (HE) questionnaires
[6] For participants receiving research abiraterone, BP, liver function tests (LFTs) and serum potassium monitoring is required 2-weekly in the first 12 weeks, then monthly until 12 months on treatment. For participants who have not experienced Toxicity following 12 months of treatment, this may be reduced to every 2 months whilst research abiraterone continues. Arm J participants continuing on enzalutamide alone may reduce to 3 monthly BP monitoring, no requirement for ongoing safety blood tests. Increased monitoring is required in participants experiencing toxicity; see **Table 13**, **Table 14** and **Table 15** for details.

Table 2: Schedule of Assessments for Participants Randomised on or after 05-Sep-2016

	Pre-Rand[n]	ASSESSMENT WEEK											ALL FURTHER VISITS [1]	AT EACH DISEASE EVENT [2]	END OF TRT	PRIOR TO 2ND LINE TRT
		4-6	12	18	24	36	48	60	72	84	96	104				
Arms A/K/L																
Cardiac (BP)	X															
Screening bloods[3]	X															
Full radiological screening[4]	X															
WHO PS	X															
Blood collection cell-free DNA Streck™ tubes[5]	X						X[3]		X[3]	X[3]				X	X	X
Saliva sample[5]	Any time point															
FFPE block[5]	At the point of request															
Waist circumference + Weight	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X															
QL & HE[5, 6]	X	X	X	X	X	X	X	X	X	X	X	X	X			
HbA1c & Lipid profile[7]	X				X[8]		X[8]					X[8]	X[8]			
Glucose & Triglycerides	X				X[8]		X[8]					X[8]	X[8]			
PSA	X[9]	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X			
Arm K only																
Safety bloods (eGFR) [10]					X		X		X		X		X			
Arm L only																
Testosterone & Oestradiol [11]		X[12]	X		X		X		X		X		X			

[1] Follow-up visits after year 2 need to be carried out every 6 months for the first 5 years. At year 6 and onwards visits should be every 12 months whilst active follow-up continues.
[2] Disease events are defined as each type of disease progression: PSA (biochemical), clinical (symptomatic) and radiological (objective).
[3] U&Es, LFTs, Serum creatinine and FBCs to be completed before randomisation. Cholesterol, albumin, serum corrected calcium, phosphate, magnesium within 4 weeks before or after randomisation.
[4] Pre-randomisation imaging must be representative of current disease status, see **section 4.2.1**
[5] Only if participating in relevant sub-study, for information regarding samples see the **Sample Collection & Handling Manual** available via the STAMPEDE website for details
[6] Review **Table 38** for a breakdown of participants that are still required to complete Quality-of-life (QL) + health economic (HE) questionnaires
[7] HBA1c required prior to randomisation for participants being considered for "metformin comparison".
[8] If missed, samples can be obtained +/-12 weeks of the scheduled FU visit, maintaining 10-12 weeks in between the tests due at week 24 and 48 weeks.
[9] Pre-ADT PSA must have been obtained within 6 months prior to randomisation and another PSA analysis should be completed within 2 weeks of randomisation.
[10] Increased monitoring of renal function required if renal function declines see **Table 23**. To continue until metformin permanently stopped.
[11] Hormone tests are required whilst the participant is receiving research transdermal oestradiol. Note that additional tests may be necessary as detailed in **Section 6.2.5.B**.
[12] First hormone tests for patients receiving research transdermal oestradiol should be at 4 weeks.

ABBREVIATIONS & GLOSSARY

ABBREVIATION	EXPANSION
AA	Anti-androgen
ACE	Angiotensin-Converting Enzyme
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse Event
AR	Androgen receptor
AS	Activity Stage
AUC	Area under the plasma concentration–time curve
BID	Twice a day (bis in die)
BP	Blood pressure
BRCA2	BReast CAncer gene 2
BRG	Biological Research Group
BSA	Body surface area
CCI	Comparison Chief Investigator
CF	Consent Form
CI	Confidence interval
Co-CCI	Comparison Co-Chief Investigator
Cox-2	Cyclooxygenase 2
CRF	Case Report Form
CRN	Clinical Research Network
CRUK	Cancer Research UK
CRPC	Castrate-Resistant Prostate Cancer
CT	Computerised tomography
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Advisory and Awards Committee
ctDNA	Circulating tumour DNA
CTC	Common Toxicity Criteria
CTU	Clinical Trials Unit
CTV	Clinical Tumour Volume
CVS	Cardiovascular
CXR	Chest X-ray
DAB	Dual Androgen Blockade

ABBREVIATION	EXPANSION
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic Acid
DPA	Data Protection Act
ES	Efficacy Stage
IB	Investigator Brochure
ICH	International Conference on Harmonization
ECG	Electrocardiogram
FBC	Full Blood Count
FFS	Failure-Free Survival
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
HbA1c	Glycosylated haemoglobin
Hb	Haemoglobin
HE	Health Economics
HES	Hospital Episode Statistics
Hr	Hour
HR	Hazard Ratio
HRA	Health Research Authority
HSCIC	Health & Social Care Information Centre
HSPC	Hormone Sensitive Prostate Cancer
HT	Hormone Therapy
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IMRT	Intensity Modulated Radiation Therapy
INR	International Normalized Ratio
IR	Immediate-Release
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Units
IV	Intravenous
LFTs	Liver Function Tests
LHRH	Luteinising Hormone Releasing Hormone
LHRHa	Luteinising Hormone Releasing Hormone antagonist/agonist

ABBREVIATION	EXPANSION
LREC	Local Research Ethics Committee
m	Month
mcg	Microgram
MHRA	Medicine and Healthcare Products Regulatory Agency
min	Minutes
MRC	Medical Research Council
MREC	Main Research Ethics Committee
MRI	Magnetic resonance imaging
mTOR	Mammalian Target of Rapamycin
M0	Non-metastatic
M1	Metastatic
NCI	National Cancer Institute (USA)
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
N0	Node-negative
N+	Node-positive
NSAID	Non-Steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
OD	Once per day (omne in die)
ONS	Office for National Statistics
OS	Overall Survival
PATCH	Prostate Adenocarcinoma: TransCutaneous Hormones
PFS	Progression-free survival
PHE	Public Health England
PI	Principal Investigator
PIS	Patient Information Sheet
po	Orally (per orum)
PSA	Prostate Specific Antigen
pts	Patients
PTV	Planned Tumour Volume
QALY	Quality-adjusted Life Years
qds	Four times each day (quater die sumendus)
QL	Quality-of-life
RSI	Reference Safety Information
RTDS	National Radiotherapy Dataset

ABBREVIATION	EXPANSION
R&D	Research and Development
SACT	Systemic Anti-Cancer Therapy Dataset
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
sc	Under skin (sub-cutaneous)
SmPC	Summary of Product Characteristics
SOC	Standard-of-Care
SR	Sustained-Release
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWOG	South West Oncology Group
tE2	Transdermal Oestradiol
TMG	Trial Management Group
TMT	Trial Management Team
TEAE	Treatment-emergent adverse event
TURP	Trans-Urethral Resection of Prostate
TSC	Trial Steering Committee
T2DM	Type 2 Diabetes Mellitus
UCL	University College London
ULN	Upper Limit of Normal
U+E	Urea and Electrolytes
WHO	World Health Organisation

TERM	DEFINITION
ADT	Androgen deprivation therapy given in the form of LHRH agonists/antagonists (abbreviated to LHRH) or alternatively, transdermal oestradiol.
Anti-androgens	Refers to 1st generation oral androgen receptor blockers including bicalutamide, flutamide and cyproterone. Please note that the use of cyproterone will impact on comparison-specific eligibility.
Comparison	In STAMPEDE many research treatments are evaluated and compared with participants receiving the current protocol standard-of-care. The term comparison describes the participants who have been randomised to receive research treatment and their comparable controls, each comparison is named by the research treatment e.g. the "metformin comparison" refers to all participants in arm K and the comparable non-diabetic patients contemporaneously randomised to arm A.
Hormone Therapy	Refers to all forms of hormone therapy given in the first line setting and includes LHRH, anti-androgens, transdermal oestradiol, GnRH agonists and antagonists. This term does not include novel AR-targeted agents such as abiraterone or enzalutamide.
PSA nadir	For trial purposes, this refers to the lowest PSA value detected between randomisation and week 24 on trial. This is used to derive the PSA progression value.
Protocol research treatment	Investigational Medicinal Products (IMPs) that are additional treatments participants allocated to research arms receive as part of the STAMPEDE protocol e.g. metformin for participants allocated to arm K, or alternative in the case of transdermal oestradiol for participants allocated to arm L.
Protocol standard-of-care (SOC) treatment	Standard forms of background treatment which are IMPs, permitted as part of the STAMPEDE protocol which include licenced ADT (e.g. LHRH analogues) given in the setting of hormone-naïve prostate cancer and first-line use of docetaxel, abiraterone, enzalutamide or apalutamide.
Non-protocol treatments	All prostate cancer treatments given following disease progression in the management of CRPC.
Prednisolone	In Swiss sites this may be referred to as prednisone.

1 LAY SUMMARY

STAMPEDE is a large clinical trial that aims to assess new treatment approaches for people affected by high-risk prostate cancer. The trial has been open since 2005 and has tested many different ways of treating prostate cancer and some results are now already known. Each new or alternative treatment is compared with the current standard approach, referred to as a "comparison". More than 11,000 people have joined STAMPEDE so far with answers becoming available throughout the trial as information on life expectancy and disease control rates are gathered and compared.

New participants joining the trial from protocol v21.0 onwards may be eligible to join one of two treatment comparisons:

- The "metformin comparison" made between the control arm (arm A) who receive standard treatment only and the metformin treatment group (arm K) who receive standard treatment and metformin. **Note: randomisation is open to only a select number of sites participating in the metabolic substudy.**
- The "transdermal oestradiol comparison" made between the control arm (arm A) and the transdermal oestradiol treatment group (arm L) who receive transdermal oestradiol as an alternative form of standard hormone treatment.

Eligibility for each treatment group is dependent on several factors including the stage of prostate cancer, whether it has spread to involve other parts of the body (metastatic), and how long a patient has received hormone therapy prior to joining STAMPEDE. A computer program will be used to randomly allocate participants between all treatment groups for which they are eligible. **Table 3** summarises which treatment arms are currently open to recruitment.

Trial participants are asked whether they would like to join certain sub-studies being run alongside the trial. These aim to address several additional research questions such as what effect each treatment has on quality-of-life (QL), and which provides the greater value for money for the health service. Some sub-studies are focused on improving our understanding of the biology of prostate cancer. For example, can genetic changes be identified in prostate cancer cells that could predict which treatments might work best and may explain why some treatments stop working?

Table 3: Summary of treatment groups currently open to recruitment (Protocol version 21.0)

TREATMENT BEING TESTED	TREATMENT GROUP	SUMMARY	FROM PROTOCOL VERSION
Metformin	Arm K	This anti-diabetic medication is proposed to have anti-cancer effects and may help prevent the side-effects of long-term ADT. STAMPEDE will investigate whether adding metformin to the current standard-of-care for non-diabetic people can improve life expectancy. Please note from protocol v21 onwards only sites participating in the metabolic sub-study can recruit to Arm K.	15.0
Transdermal oestradiol	Arm L	This is a form of hormone treatment which can suppress testosterone as effectively as standard forms of androgen-deprivation therapy (ADT) and has been shown to avoid some of the side-effects. For example, treatment with transdermal oestradiol does not appear to cause the bone to thin, a common problem with standard forms of ADT which might lead to the bones becoming fragile (osteoporosis) and more likely to break. It may also help to avoid some of the side-effects and therefore improve overall quality of life compared with standard forms of ADT. STAMPEDE will investigate whether transdermal oestradiol can treat prostate cancer as well as current standard forms of ADT. Transdermal oestradiol is currently being tested in another large clinical trial called PATCH which already has over 1,400 men participating.	16.0

Further results are expected in the next few years from other treatments tested in STAMPEDE, which have completed recruitment, summarised in **Table 4.**

Table 4: Summary of treatment groups closed to recruitment; results awaited but follow-up ongoing

TREATMENT BEING TESTED	TREATMENT GROUP	SUMMARY	FROM PROTOCOL VERSION
Abiraterone and Enzalutamide combination	Arm J	Enzalutamide is another novel hormone treatment, similar to abiraterone, which is also used in advanced prostate cancer, when standard hormone therapy has stopped working. Enzalutamide works by blocking androgen receptors and this may complement abiraterone. STAMPEDE is testing whether this treatment combination is a more effective way of controlling prostate cancer growth for longer and improving life expectancy.	12.0

Abiraterone was tested alone in arm G and the primary results of this comparison have been presented. Follow-up is ongoing as a further longer term analysis is planned.

Table 5: Summary of treatment group for which primary results reported but follow-up ongoing

TREATMENT TESTED	TREATMENT GROUP	SUMMARY OF RATIONALE AND RESULTS	PROTOCOL VERSION ADDED
Abiraterone	Arm G	This is a novel hormone treatment which works by inhibiting steroid hormone synthesis so blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following anti-hormonal therapies. The results of STAMPEDE have shown that the addition of abiraterone with prednisone improves life expectancy and disease control or relapse rates when used earlier, for people with locally-advanced or metastatic disease.	8.0
Prostate radiotherapy	Arm H	This is treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory within STAMPEDE for participants with cancer that is confined to the prostate gland as large trials have shown it improves life expectancy. The results from the primary analysis of the Arm H comparison demonstrate RT to the prostate prolonged overall survival in patients with oligometastatic (low burden) prostate cancer. Prostate RT did not provide any survival benefit to patients with high burden metastatic disease.	9.0

In the past STAMPEDE also tested whether adding docetaxel chemotherapy, zoledronic acid, or celecoxib, alone or in combination, and radiotherapy to prostate in M1 patients was beneficial in controlling prostate cancer growth and improving life expectancy. Recruitment has been completed to all of these original treatment groups, the results have been presented and it is no longer necessary to provide follow-up information relating to participants allocated to these comparisons, see **Table 6**.

Table 6: Summary of treatment groups reported and no longer on active follow-up

TREATMENT TESTED	TREATMENT GROUP	SUMMARY OF RATIONALE AND RESULTS	PROTOCOL VERSION ADDED
Zoledronic acid	Arm B	Prostate cancer cells can spread to bones and weaken them. Zoledronic acid is a drug that reduces bone destruction and hardens bones. The results of STAMPEDE show that the addition of zoledronic acid alone does not prolong life expectancy. These results were comparable with data from other similar trials.	1.0
Docetaxel	Arm C	Docetaxel is a type of chemotherapy which can stop cells replicating. It has been used to treat advanced prostate cancer for some time, and is also used in e.g. the treatment of lung, breast and ovarian cancer. The results of STAMPEDE show that the addition of docetaxel to hormone treatment does improve life expectancy, most markedly in people with metastatic disease, and delays time to progression or relapse for people with locally-advanced and metastatic disease. The results of STAMPEDE were combined with other similar trials testing docetaxel and together, the results support this effect. Docetaxel may now be given as part of standard treatment to all suitable people entering STAMPEDE (from protocol v14.0).	1.0
Celecoxib	Arm D	Celecoxib is an aspirin-like drug that is used to treat arthritis. It slows down the growth of cancer cells in the laboratory. STAMPEDE tested whether the addition of celecoxib could delay the growth of prostate cancer cells. Recruitment stopped early as an earlier analysis failed to demonstrate sufficient benefit. The final results were presented at GU ASCO 2016, a major international congress, and show that alone, celecoxib does not improve life expectancy.	1.0
Docetaxel and zoledronic acid combination	Arm E	The combination of these two medications did not offer any benefit to overall survival compared to the docetaxel alone. Currently we do not recommend this combination as treatment for HSPC in STAMPEDE	1.0
Zoledronic and celecoxib	Arm F	The combination of these two medications did not improve overall survival in all patients randomised to this comparison. However, there was a small effect seen in patients with metastatic disease. Currently we do not recommend this combination as treatment for HSPC in STAMPEDE	1.0

For further information relevant to these treatment groups, refer to the STAMPEDE website where you can see earlier versions of the protocol and find summaries of the results and links to the scientific publications, www.stampedetrial.org.

2 BACKGROUND

2.1 INTRODUCTION AND SETTING

Prostate cancer is a major health problem world-wide and accounts for nearly one fifth of all newly-diagnosed male cancers. In the UK, approximately 47,150 people were diagnosed with prostate cancer in 2015 and over 11,000 people died from the disease (5).

2.1.1 Long-term Androgen Deprivation Therapy

The initial (first-line) treatment for locally-advanced or metastatic prostate cancer is based on androgen deprivation therapy (ADT) achieved either surgically with bilateral orchidectomy, or medically with LHRH agonists or antagonists (6). Long-term use of oral anti-androgens is permitted only when given with LHRH agonists, to achieve dual androgen blockade (previously termed maximum androgen blockade - MAB).

When used alone ADT produces initial responses in up to 95% of patients but is rarely curative. STAMPEDE aims to improve outcomes for people affected by high-risk prostate cancer by testing if additional treatments added to ADT can improve disease control and life-expectancy. Data from the control arm in STAMPEDE has shown that for people with newly-diagnosed metastatic disease treated with ADT alone, the time to progression is just 11 months (6). Such progressive disease is referred to as castrate-resistant prostate cancer (CRPC).

Another important issue with ADT is the numerous associated side-effects, particularly with prolonged use. Since patients continue on LHRH after disease progression (with additional agents added), many people remain on treatment for a decade or longer. STAMPEDE is evaluating alternative forms of ADT and additional treatment with metformin aiming to mitigate some of the adverse effects of ADT which include osteoporosis (leading to an increased risk of fracture), adverse metabolic disturbance, cognitive decline, sexual dysfunction, hot flushes, physical deterioration and fatigue.

2.1.2 Role Of SOC Radiotherapy

Two randomised trials, SPCG7 (7) and NCIC PR.3 / MRC PR07 (8-10) have tested the question of whether ADT alone combined with radiotherapy is the best treatment for patients with high-risk localised prostate cancer (N0M0). Both trials demonstrated an improvement in overall and disease specific survival from the addition of radiotherapy to ADT. The size of this overall survival benefit is substantial (hazard ratio 0.68 in SPCG7 and 0.77 in PR07). As these two mature, large, well-conducted randomised trials have demonstrated benefit, we now mandate that radiotherapy be standard for patients with N0M0 disease (i.e. no nodal or metastatic spread). Patients with node-negative M0 prostate cancer will only be allowed to enter the trial if standard radiotherapy is planned. For patients with node-positive, M0 disease there are no randomised data on whether radiotherapy is indicated or not. However the NCIC PR.3 / MRC PR07 trial included patients with unknown nodal status who received whole pelvic radiotherapy (11) and demonstrated a large overall benefit. Additionally, non-randomised data from the STAMPEDE control arm suggests that the benefit observed in patients with N0M0 disease can be extended to those with pelvic nodal involvement. Therefore the STAMPEDE TMG recommends that pelvic nodal radiotherapy be considered for patients with node-positive, M0 disease at the discretion of the treating clinician (12).

More recently, data from the “M1:RT” arm showed that in patients with oligo-metastatic disease, RT to the prostate improved overall survival (4). Therefore, the STAMPEDE TMG recommends that

prostate RT is considered for patients with oligometastatic (low burden) disease at the discretion of the treating physician.

2.1.3 Role Of SOC systemic therapy: docetaxel, abiraterone, enzalutamide or apalutamide in addition to ADT

A variety of trials have demonstrated that addition of systemic therapy at the start of long term ADT prolongs survival, particularly in participants with metastatic disease. On the basis of the studies described below, the STAMPEDE TMG stongly recommends the clinician to consider either docetaxel, abiraterone, enzalutamide or apalutamide in all participants with metastatic disease at presentation who are commencing ADT for the first time and are fit enough to additional treatment. Choice of which systemic therapy to use is at the discretion of the clinician, but will need to be guided by availability of each treatment at site. We also suggest site investigators keep abreast of the latest published literature to inform choices between these treatments when options are available.

The primary analysis of the "original comparisons" has shown docetaxel significantly prolongs survival (HR 0.78; 95% CI 0.66-0.93)(1). This is in support of the results of the CHAARTED trial which showed docetaxel improved survival in people with metastatic disease (13, 14). There was no evidence of heterogeneity in STAMPEDE in the treatment effect across any patient subgroups and median survival was improved by 10 months, from 71 to 81 months. In a well powered and pre-planned sub-group analysis of people with metastatic disease at randomisation the treatment effect was most apparent with a median survival benefit of 15 months.

Data from the long term follow up of the docetaxel arm, specifically in men with non-metastatic disease, demonstrate that men who had RT to the prostate without chemotherapy had a superior FFS, PFS and a trend towards better OS, compared to men treated with both (15) . Therefore, although docetaxel is now permitted as part of the standard-of-care for all people entering STAMPEDE, we recommend patients with non-metastatic disease should be considered primarily for prostate RT, and chemotherapy considered only for those in whom RT is contra-indicated. Ultimately the decision is at the discretion of the treating clinician and patient.

The primary analysis of the “abiraterone comparison” has shown abiraterone improves survival in the HSPC setting (HR 0.63; 0.52 to 0.76; p<0.001)(3). The results are consistent with the co-published LATITUDE trial which recruited an overlapping subset (newly-diagnosed high-risk metastatic patients (16)) of the population eligible for STAMPEDE. A post-hoc subgroup analysis of the metastatic HSPC participants recruited to the STAMPEDE abiraterone comparison, suggest that benefit from abiraterone was irrespective of risk stratification via “risk” or “volume” measures (17).

The ENZAMET trial (18) demonstrated that enzalutamide used alongside ADT in the metastatic HSPC setting improved overall survival (HR 0.67; 0.52 to 0.86; P=0.002). Where available it is acceptable to use the addition of enzalutamide to ADT on the basis of evidence of benefit. Of note, there was no additional survival benefit seen in those patients treated with both docetaxel and enzalutamide in the upfront setting, whilst this combination resulted in higher rates of peripheral sensory neuropathy.

The TITAN trial (19) demonstrated that apalutamide used alongside ADT in the metastatic HSPC improved overall survival (HR 0.67; 0.51 to 0.89; p=0.005).

In the absence of data supporting a combination of treatment in the upfront setting, investigators are required to specify which upfront treatment will be used. It is **not** appropriate to use a **combination** of these treatments. Therefore, from protocol v21.0 onwards, SOC use of docetaxel**, or**

abiraterone, **or** enzalutamide, **or** apalutamide is permitted at the discretion of the treating clinician and patient. The choice of SOC treatment must be selected **prior** to randomisation.

Transdermal oestradiol has not previously been used alongside abiraterone, enzalutamide or apalutamide. Therefore the first cohort of participants recruited to STAMPEDE and started on this combination will have enhanced safety monitoring, with close monitoring of hormone levels. Any concerns that an interaction between these treatments is impacting efficacy will result in a pause to recruitment whilst this is investigated. A pre-planned review of early efficacy to achieve castration will be carried out once sufficient participants have been treated with these combinations. See **Section 9.7.4** for further details.

2.2 DESIGN

STAMPEDE (also known as MRC PR08) is an innovative, multi-arm multi-stage (MAMS) randomised controlled trial open in multiple sites in the UK and Switzerland. The multi-arm design allows many treatment approaches to be tested simultaneously, and multi-stage refers to the pre-specified interim analyses that can be used to stop recruitment early to arms showing insufficient evidence of activity. The trial recruits people with high-risk locally advanced or metastatic prostate cancer, commencing long-term ADT for the first time.

The trial opened to recruitment in 2005 and initially assessed the effects of a bisphosphonate (zoledronic acid), a cytotoxic chemotherapeutic agent (docetaxel) and a cyclooxygenase (Cox-2) inhibitor (celecoxib), as single agents or combinations (arms B-F), referred to as the "original comparisons".

Since the start of the trial, a number of new research arms have been added to STAMPEDE to evaluate:

- Abiraterone, a steroid synthesis inhibitor (arm G)
- Prostate radiotherapy for patients with newly-diagnosed metastatic disease (arm H)
- Enzalutamide, an inhibitor of androgen receptor signalling, given with abiraterone (arm J)
- Metformin, a repurposed anti-diabetic medication (arm K)
- Transdermal oestradiol, a repurposed alternative form of ADT (arm L)

2.3 PREVIOUSLY-REPORTED RESEARCH TREATMENTS

Data have been reported on the "original comparisons" evaluating zoledronic acid, docetaxel, celecoxib and the combination of zoledronic acid with docetaxel or with celecoxib (1, 2, 20). As such, the rationale for these treatments, along with their design and details of treatment administration, are no longer covered within this version of the protocol.

The primary survival analysis of the "abiraterone comparison" has also now been reported although these participants remain on active follow-up as subsequent analyses of long-term follow-up are planned (3). The rationale can be found in previous protocol versions, however treatment information remains as it is relevant to participants who remain on abiraterone given alone (arm G) and in combination with enzalutamide (arm J).

The primary survival analysis of the "M1:RT" comparison testing RT to the primary tumour for men with newly diagnosed metastatic prostate cancer (Arm H) has now also been reported. These patients remain on active follow-up as subsequent analyses of long term follow-up planned. The treatment information is no longer covered within this version of the protocol as all treatment has now completed, however this can be accessed via previous versions of the protocol as below.

All previous versions of the protocol are available via www.stampedetrial.org, please refer to:

- Protocol version 11.0 and before for information relevant to "original comparisons" (Zoledronic acid, docetaxel, celecoxib)
- Protocol version 8.0 to 13.0 for information relevant to the "abiraterone comparison"
- Protocol version version 9.0 to 15.0 for information relevant to the "M1:RT comparison"

2.4 COMPARISONS IN FOLLOW-UP

The rationale for comparisons that have completed recruitment and remain in follow-up can be found in previous versions of the protocol. Recruitment was completed to the "enzalutamide and abiraterone comparison" in March 2016, as the recruitment target was reached. Participants remain on treatment therefore this information remains in this protocol version.

All previous versions of the protocol are available via www.stampedetrial.org, please refer to:

- Protocol version 16.0 or older for details relevant to "enzalutamide & abiraterone comparison"

2.5 RATIONALE FOR RECRUITING COMPARISONS

2.5.1 Metformin

All people joining STAMPEDE are planned for long-term ADT, a treatment associated with an increased risk of insulin resistance, hyperglycaemia, dyslipidaemia and obesity. Over 50% of people receiving long-term ADT will develop metabolic syndrome resulting in increased cardiovascular morbidity and mortality (21). Obesity and high bind insulin C-peptide levels, indicating insulin resistance are independent predictors of increased prostate cancer-specific mortality and the presence of metabolic syndrome and diabetes in people treated with ADT is associated with shorter survival.

Metformin, which in non-diabetic individuals has been shown to lower the incidence of diabetes, counteracts some of these side-effects of ADT, including insulin insensitivity, hyperinsulinaemia and diabetes. It also reduces the levels of cholesterol, LDLs and triglycerides by inhibiting the fatty acid synthesis via activation of Adenosine Monophosphate Activated Kinase (AMPK) and decreases the platelet aggregation factor 1, platelet aggregation, vascular adhesion molecules, CRP and leptin (22-25). Through mitigation of the cardiovascular and metabolic consequences of ADT, metformin is proposed to reduce treatment-associated morbidity and improve all-cause mortality.

In addition, recent data has emerged consolidating the knowledge that cancer progression is linked integrally with metabolic modulators and that modification of this process by metformin has an important effect on cancer progression and survival. Pre-clinical data has shown that metformin is an important stimulator of AMPK which acts as the cellular "master switch" for energy regulation. AMPK acts to inhibit the effects of elevated insulin levels which promote metastasis, tumour growth and treatment resistance. Insulin increases mRNA and protein expression of steroidogenic enzymes leading to the up-regulation of intracellular testosterone levels, secreted androgens, thereby activating the AR (26). Metformin also influences the PI3K-AKT pathway and has an anti-proliferative effect via inhibitor of mTOR as well as targeting cancer stem cells. In vitro, metformin has been shown to inhibit androgen-induced IGF-IR up-regulation through disruption of androgen signalling (27).

Evidence in support of this includes a systematic review and meta-analysis of 13,008 people with type 2 diabetes mellitus (T2DM) and concurrent cancer which has shown improved survival in people treated with metformin compared with other anti-diabetic agents. In a systematic review of

observational data from over 1 million people, there was a significant association seen between metformin and decreased risk of death from any cancer. Another systematic review found that the use of metformin in diabetic patients was associated with a significantly lower risk of cancer incidence and cancer mortality (28). In a large retrospective cohort study of 3837 diabetic people with prostate cancer, metformin was associated with a decreased risk of prostate cancer specific mortality (HR=0.76 [0.64-0.89]) and death (HR=0.76 [0.70-0.82]). In a prospective non-randomised phase II study in non-diabetic CRPC patients, 36% of patients receiving metformin were progression-free at 3 months and >50% had a prolongation of their PSA doubling time (29).

In summary, meformin is proposed to mitigate many of the adverse side-effects of long-term ADT as well as having multiple potential anti-cancer effects and therefore STAMPEDE will evaluate re-purposing this treatment as a novel therapeutic approach in the management of high risk locally-advanced or metastatic prostate cancer.

2.5.2 Transdermal Oestradiol

2.5.2.A Background & Rationale

ADT with LHRH analogue injections suppresses testosterone to castrate levels, but also depletes oestradiol, since around 80% of oestradiol in men is derived by aromatisation from testosterone. Thus men who are treated with LHRHa will have toxicities caused by low levels of both testosterone and oestrogen. The LHRH-associated toxicities which are due to low testosterone include loss of libido, erectile dysfunction and decrease in muscle mass. Other toxicities associated with LHRHa such as osteoporosis, increased fracture risk, hot flushes, memory loss, dyslipidemia and increased body fat deposition are thought to be due to oestradiol deficiency. In particular, the adverse effect of LHRHa on bone health has been well documented. Oestradiol deficiency prolongs the life-span of bone-resorptive osteoclasts, with the resulting imbalance between osteoclasts and bone-forming osteoblasts increasing the rate of bone thinning. This may lead to osteoporosis and increased risk of fracture, with the rate of fracture increasing with duration of LHRHa (30).

Transdermal oestradiol is a potential alternative to LHRHa that may avoid some treatment-related side-effects, therefore improving quality-of-life, which would be advantageous if shown to be equally effective at prolonging survival. Exogenous administration of oestradiol suppresses androgen production through a negative feedback loop involving the hypothalamic-pituitary axis, whilst avoiding the fall in oestradiol associated with castrate levels of testosterone (31). This, in turn, mitigates the toxicities of LHRH associated with oestradiol deficiency. Oral oestrogen was previously used for ADT before the development of LHRHa, but discontinued as first-line treatment due to increased thromboembolic toxicity, attributable to first-pass hepatic metabolism (32).

Parenteral administration (e.g. intravenous, intramuscular or transdermal oestradiol) avoids first-pass hepatic metabolism, mitigating the cardiovascular risk, as supported by results so far from the ongoing PATCH (Prostate Adenocarcinoma TransCutaneous Hormones [MRC PR09; ISRCTN70406718]) trial and previous studies evaluating parenteral oestradiol in the form of intramuscular polyestradiol phosphate (31, 33).

To date, there are a number of encouraging results from the PATCH trial demonstrating the safety and early activity of transdermal oestradiol compared to LHRH agonists in people with advanced hormone-naïve prostate cancer (see **Appendix I** for further details). In particular, similar rates of cardiovascular events have been observed in the transdermal oestradiol and LHRHa arms, as well as equivalent rates of testosterone suppression (based on around 900 patients enrolled up to Oct-2015) (31). Transdermal oestradiol has been shown to avoid the loss in bone mineral density associated with LHRHa, and results in improved metabolic profiles and quality-of-life compared to LHRHa (34). Furthermore, a pre-planned, confidential, interim analysis of the PATCH trial in Jun-2013 based on progression-free survival (PFS) led to the trial being extended to phase III; that analysis

included n=638 participants with 206 PFS events, reviewed against a pre-specified non-inferiority margin hazard ratio of 1.25 and 1-sided alpha 0.25. The phase III evaluation of clinical efficacy for transdermal oestradiol will be based on progression-free and overall survival as co-primary outcome measures.

Demonstrating that transdermal oestradiol is an equally effective approach to ADT would provide a globally important alternative (to LHRHa), with the potential to reduce treatment-associated morbidity and improve quality-of-life. In addition, there is a possibility that transdermal oestradiol may improve overall survival compared to standard hormone therapy. First, transdermal oestradiol may reduce treatment-associated morbidity and could potentially benefit overall survival. Second, up to 30% of people with castrate-resistant prostate cancer respond to oral oestrogen as post-relapse therapy, suggesting oestradiol may potentially have additional direct anti-tumour effects (35).

2.5.2.B Meta-Analysis With PATCH Trial

To further assess the clinical efficacy of transdermal oestradiol, the relevant data from the "transdermal oestradiol comparison" within STAMPEDE will be combined with data from patients recruited into PATCH, i.e. the "transdermal oestradiol comparison" within STAMPEDE is not sufficiently powered to form a stand-alone analysis. The evaluation of transdermal oestradiol will be based on a non-inferiority approach (in contrast to the other comparisons within STAMPEDE which are superiority questions), to test the hypothesis that transdermal oestradiol is at least as effective as standard hormone therapy, but with fewer side-effects.

Recruitment of patients to the "transdermal oestradiol comparison" through STAMPEDE enables the transdermal oestradiol research question to be answered more quickly than via PATCH alone. It also reduces the number of participants allocated standard treatment alone in both trials, thereby increasing the proportion of participants receiving a novel treatment approach and improving trial efficiency.

As of Feb-2017, nearly 1,200 participants had been recruited directly to the PATCH trial (also coordinated by MRC CTU at UCL) for the phase III evaluation of clinical efficacy of transdermal oestradiol. The overall recruitment target for the transdermal oestradiol evaluation is approximately 2,500 participants (including around 700 to be recruited through STAMPEDE).

3 SELECTION OF INSTITUTIONS AND INVESTIGATORS

Sites who wish to participate in STAMPEDE should be registered with the MRC CTU at UCL for this purpose. Before any participants are randomised, the CTU must receive a completed and signed Investigator Statement. The STAMPEDE Investigator Statement is signed by the Principal Investigator for that institution (download from http://www.stampedetrial.org/). The return of the Investigator Statement will be taken as confirmation of agreement to adhere to the trial protocol. In addition, a fully-signed model agreement is also required before recruitment can begin.

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

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

Following substantial amendments and new comparisons opening, sites will be notified of relevant documents and training required and if and when they are able to participate. Further accreditation packs may be circulated as a result to update trial documentation.

3.1 SITE/INVESTIGATOR CRITERIA

3.1.1 Principle Investigator's Qualifications & Agreements

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, the IRB, and/or the regulatory authorities.

2. The investigator must hold a long term contract with their site. Locum members of staff cannot fill the role of Principle Investigator (PI).

3. The investigator should be thoroughly familiar with the appropriate use of the investigational products, as described in the protocol, current Investigator Brochure or Summary of Product Characteristics and in other information sources provided by the Sponsor.

4. The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

5. The investigator/site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authorities.

6. The investigator should maintain a delegation log of appropriately-qualified persons to whom the investigator has delegated significant trial-related duties.

7. The investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

3.1.2 Adequate Resources

1. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (that is, the investigator regularly treats the target population).

2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely. In addition, the investigator should arrange for suitably qualified investigator cover for safety reporting in the event of their absence.

4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational products, and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data return to the CTU.

3.2 COMPARISON-SPECIFIC SITE ACCREDITATION

3.2.1 Transdermal Oestradiol Comparison: arms A & L

Only UK sites participating in STAMPEDE will be accredited for the “transdermal oestradiol comparison”.

3.3 REQUIRED TRIAL DOCUMENTATION

Table 7 presents a summary of the required trial documentation for participating sites. Templates are provided on the STAMPEDE website, www.stampedetrial.org.

Table 7: Trial documentation required for participating sites

TRIAL DOCUMENTATION	TIMING
Confirmation of capacity and capability (including IRMER approval)	Before site participation
Signed Investigator Statement	Before site participation
Signature list & delegation of responsibilities	Before site participation
Trial personnel contact details	Before site participation
Participant information sheets (PIS), GP Letter & Informed consent form (ICF) on local paper	Before site participation
Signed Clinical Trial Agreement between Trust and Sponsor (or Variation if applicable)	Before site participation
Site initiation training	Before site participation
Signed Pharmacy Pack acknowledgment	Before site participation

4 SELECTION OF PARTICIPANTS

4.1 IDENTIFYING POTENTIAL TRIAL PARTICIPANTS

STAMPEDE recruits participants with high-risk prostate cancer who are commencing long-term androgen-deprivation therapy (defined as at least 2 years) for the first time. All participants must fulfil one of the following **broad disease categories:**

- High-risk newly-diagnosed non-metastatic, node-negative disease
- Newly-diagnosed metastatic or node-positive disease
- Previously radically treated, now relapsing with high risk features

See **Section 4.4** for detailed category inclusion criteria

4.2 APPROACH TO INFORMED CONSENT

Potential participants should be provided with information about STAMPEDE at the earliest opportunity to allow sufficient time to consider their participation and complete the required screening procedures to determine comparison-specific eligibility.

Informed consent is an ongoing process and participants must be made aware that refusal to take part in all or any aspect of the trial at any time for any reason is permitted, without incurring any consequence or impact on their standard treatment. All aspects of the trial e.g. sub-studies should be presented and optional participation discussed, and investigators are encouraged to adopt a staged approach where possible to avoid information overload.

Original signed consent forms must be stored in the site investigator file, a copy stored in the patient's medical notes (electronic/paper), and a copy provided to the participant. For central monitoring purposes an anonymised copy must also be sent to the CTU, refer to **Section 10.1.1**.

4.2.1 Screening Investigations Prior To Randomisation

All participants must have the following examinations performed to confirm eligibility prior to randomisation. Please note, all screening investigations should be recent such that they reflect the participant's current disease status.

The following imaging is always required within 6 months (184 days) prior to randomisation:

- Cross-sectional imaging (CT, MRI, PSMA-PET-CT or Choline-PET-CT) of pelvis and abdomen, SPECT-CT is not sufficient
- AND Bone Scan (or equivalent e.g. whole body MRI, or SPECT-CT)
- AND Chest X-ray (only if chest was not included in cross sectional imaging i.e. CT, Choline-PET-CT or PSMA-CT-PET which would be preferable; MRI imaging of chest is not sufficient on its own)

Please note, for trial purposes M1 disease will be defined using internationally agreed criteria, therefore M1 staging cannot be based solely on PET avid lesions. To be considered M1, the metastatic lesion must also be visible on standard imaging i.e. CT (can be CT component of PET-CT) or bone scan.

The following blood tests are required within **6 months (184 days)** prior to randomisation:

- Pre-hormone treatment PSA

- Pre-hormone treatment Testosterone (if available)

The following bloods and additional measurements are required within **4 weeks (28 days)** prior to randomisation:

- Haematology: Full blood count*
- Biochemistry: Liver function tests, serum creatinine
- Systolic and diastolic blood pressure
- Waist circumference measurement
- Weight and height

The following bloods and additional measurements are required within **2 weeks (14 days)** prior to randomisation:

- Baseline PSA

* If a participant has started SOC docetaxel please use a full blood count measured shortly prior to chemotherapy. This means in the setting of SOC docetaxel these results provided should be from within the last 16 weeks (112 days) prior to randomisation. This will ensure an appropriate baseline is reviewed to confirm fitness for treatment and eligibility for participants. For all other participants the blood count used should be taken within 4 weeks prior to randomisation.

Participants who initially fail to meet the trial eligibility criteria can be re-screened at a later date if timelines permit.

4.2.2 Baseline Investigations required for participants allocated to arms A, K, L

The following blood tests and additional measurements are required at baseline **within 4 weeks (28 days)** prior to randomisation:

- HbA1c (for participants being considered for metformin comparison)
- Glucose and triglycerides (preferably fasting for metabolic analysis, but if only able to obtain a non-fasting result please record on randomisation CRF)
- Lipid profile (fasting or non-fasting; total cholesterol, LDL and HDL)

See **Table 2** for a detailed schedule of assessments for all participants randomised to arms A, K or L.

We encourage site investigators to carry out any additional investigations they feel are necessary in particular cases to ensure that participants are appropriately fit to be randomised in the STAMPEDE trial.

4.3 PRIOR PERMITTED SOC TREATMENTS

4.3.1 Hormone Treatment Prior To Randomisation

From protocol v16.0, participants can potentially be randomised to the “transdermal oestradiol comparison” and it would be preferable for these participants to have had as little exposure to ADT as possible.

Within the separate PATCH trial, participants are randomised within 8 weeks after starting anti-androgens and cannot have received an LHRHa injection. This approach is also favoured in STAMPEDE, but participants who have received a single 4-week (or 1-month) LHRHa injection remain eligible, as shown in **Table 8.**

Anti-androgen monotherapy is not permitted as a form of long-term hormone therapy but initial use is encouraged to meet the eligibility criteria for the “transdermal oestradiol comparison”. Anti-

androgens may include flutamide or bicalutamide, however use of cyproterone will mean the participant is ineligible for arm L (36).

Table 8: Maximum prior hormone therapy

TIME CONSIDERATIONS	PRIOR ANTI-ANDROGENS	PRIOR LHRH	PRIOR SOC ABIRATERONE, ENZALUTAMIDE OR APALUTAMIDE	ELIGIBLE FOR INCLUSION TO
Maximum duration – all arms except Arm L	14 weeks	12 weeks	12 weeks	A:K
Arm L	≤8 weeks	≤4 weeks	Nil	A:L

Permitted prior hormone therapy for now-relapsing disease: Any patients now presenting with relapsed disease, previously treated with adjuvant or neo-adjuvant hormone therapy alongside their radical surgery or radiotherapy, must have completed that period of hormone therapy **at least 12 months** before joining STAMPEDE and it must have been **no longer than 12 months in duration**.

4.3.2 Standard-Of-Care (SOC) Radiotherapy

In participants with N0M0, N+M0 and oligometastatic disease (as per M1RT definition (4), see **Section 6.1.3**), the treating clinician and participant must have decided, **prior** to randomisation, whether prostate radiotherapy will be given as part of SOC.

4.3.3 Standard-Of-Care (SOC) Systemic Therapy; docetaxel, abiraterone, enzalutamide or apalutamide

The treating clinician and participant must have decided, **prior** to randomisation, whether docetaxel, abiraterone, enzalutamide or apalutamide is to be given as part of SOC.

Please note that only one SOC treatment can be selected at randomisation. See **Section 6.1.4** for treatment details.

Investigators should aim to start SOC docetaxel treatment within 12 weeks after starting ADT, consistent with the timelines achieved for research arm C. Participants may start docetaxel treatment prior to randomisation. See **Section 6.1.3** for treatment details.

If SOC docetaxel treatment was not commenced prior to randomisation and participants are subsequently allocated to receive transdermal oestradiol (Arm L), it is recommended that docetaxel treatment commences **after** participants have been established on transdermal oestradiol for around 4 weeks, when most participants are likely to have completed the induction period (see **Section 6.2.5.A**).

Participants may start abiraterone, enzalutamide or apalutamide prior to randomisation. However the use of these treatments prior to randomisation will impact comparison-specific eligibility. At present participants who have **already started** these treatments will only be eligible for the "metformin comparison". Patients **planned** for these treatments can be considered for both metformin and transdermal oestradiol comparisons.

At present, there are no safety data available on the use of abiraterone, enzalutamide or apalutamide in combination with transdermal oestradiol. The initial cohort of participants randomised to receive transdermal oestradiol and planned for SOC abiraterone, enzalutamide or apalutamide will be subject to additional CTU review to monitor these combinations, and an additional early pre-planned analysis of safety.

When complete, the findings will be reviewed by the relevant committees and sites will be advised as to whether these combinations can continue. If found to be safe in the upfront setting then we will also there-after permit the use of the medications alongside transdermal oestradiol patches in the CRPC setting.

4.4 GENERAL INCLUSION CRITERIA – DISEASE CATEGORIES

Participants must fulfil all the criteria in one of the following three categories:

4.4.1 High-Risk Newly-Diagnosed Non-Metastatic Node-Negative (N0/Nx) Disease

Both:

- At least two of: T category T3/4, PSA≥40ng/ml or Gleason sum score 8-10
- Intention to treat with radical radiotherapy (unless there is a contra-indication)

OR

4.4.2 Newly-Diagnosed Metastatic Or Node-Positive Disease

At least one of:

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

OR

4.4.3 Previously Radically Treated, Now Relapsing (Prior Radical Surgery And/or Radiotherapy)

At least one of:

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

AND

4.5 GENERAL INCLUSION CRITERIA REQUIRED FOR ALL PARTICIPANTS

I. Histologically confirmed prostate adenocarcinoma
II. Intention to treat with long-term androgen deprivation therapy
III. Fit for all protocol treatment[1] and follow-up, WHO performance status 0-2[2]
IV. Have completed the appropriate investigations prior to randomisation
V. Adequate haematological function: neutrophil count ≥1.5x10^9/l and platelets ≥100x10^9/l
VI. Adequate renal function, defined as GFR ≥30ml/min/1.73m^2
VII. Written informed consent
VIII. Willing and expected to comply with follow-up schedule
IX. Using effective contraceptive method if applicable

[1] Medical contraindications to the trial medications are given in **Section 6**
[2] For WHO performance status definitions see **Appendix A**

4.6 GENERAL EXCLUSION CRITERIA

I. Prior systemic therapy for locally-advanced or metastatic prostate cancer (except as listed in **Section 4.3**[1])

II. Prior exposure to hormone therapy for a duration of > 12 months, or prior exposure completing < 12 months before randomisation (see **Section 4.3.1** for permitted prior exposure details)

III. Metastatic brain disease or leptomeningeal disease

IV. Abnormal liver functions consisting of any of the following:

- Serum bilirubin ≥1.5 x ULN (except for participants with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN - site must indicate at randomisation whether one or both tests are performed at site. Where both results are available, both must confirm eligibility.

V. Any other previous or current malignant disease which, in the judgement of the responsible clinician, is likely to interfere with STAMPEDE treatment or assessment

VI. Any surgical wound (e.g. TURP) which in the judgement of the responsible clinician may interfere with or be exacerbated by protocol treatment

VII. Participants with significant cardiovascular disease, including:

- Severe/unstable angina
- Myocardial infarction less than 6 months prior to randomisation
- Arterial thrombotic events less than 6 months prior to randomisation
- Clinically significant cardiac failure requiring treatment, defined as New York Heart Association (NYHA) class II or above[2]
- Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 6 months prior to randomisation
- Any other significant cardiovascular disease that in the investigator's opinion means the participant is unfit for any of the study treatments.

[1] Details timelines for recently initiated SOC docetaxel, abiraterone, enzalutamide, apalutamide
[2] NYHA classifications can be found in Appendix A

4.7 COMPARISON-SPECIFIC ELIGIBILITY CRITERIA

In addition to the general inclusion and exclusion criteria, the following comparison-specific eligibility criteria apply.

4.7.1 Metformin Comparison (randomisation between arm A and arm K)

Please note from protocol v21 only patients willing to participate in the metabolic sub study should be randomised to the metformin comparison. The sub study will be conducted in a limited number of sites, see **section 4.7.4** for further information.

In addition to the general inclusion and general exclusion criteria the following comparison-specific inclusion criteria must be met to be eligible for randomisation to the "metformin comparison":

- Hb A1c <48mmol/mol (equivalent to <6.5%)
- Adequate renal function, defined as GFR ≥45ml/min/1.73m^2 (except for Switzerland[1])
- No history of lactic acidosis or predisposing conditions
- No current or previous treatment with metformin
- No current or previous medication for treatment of diabetes
- No contraindications to metformin
- Willingness to join the metabolic sub study

The method used to determine glomerular filtration rate may vary according to local practice. Equations that either estimate glomerular filtration rate (eGFR) or creatinine clearance (CrCl) may be used and the same threshold value applies. Where possible, HbA1c should be performed prior to commencing SOC docetaxel to reduce the likelihood of corticosteroid-related hyperglycaemia impacting on eligibility. All participants with abnormal baseline HbA1c (i.e. 6.5% or higher) should be informed and referred to their GP for further management.

4.7.2 Transdermal Oestradiol Comparison (randomisation between arm A and arm L)

In addition to the general inclusion and exclusion criteria, participants fulfilling all of the following are eligible for the “transdermal oestradiol comparison”:

- ≤8 weeks of anti-androgen (AR-antagonists) use
- Maximum of 1 dose of monthly or 4-weekly LHRH agonist/antagonist
- No prior LHRH agonist injection with a stated duration of effect greater than 1 month
- ≤12 weeks since first dose of any hormone therapy
- Not had a bilateral orchidectomy
- No use of cyproterone acetate prior to randomisation
- No known porphyria
- No history of radiologically confirmed deep vein thrombosis or pulmonary embolism
- No known thrombophilic disorder (e.g. Protein C, Protein S, antithrombin deficiency)
- Not yet started SOC abiraterone, enzalutamide or apalutamide (see **Section 4.3.4** for information)

[1] Switzerland sites - please refer to SAKK appendix for local guidance

4.8 SUB-STUDY ELIGIBILITY CRITERIA

There are currently four sub-studies that aim to further the understanding of the biology of prostate cancer through additional genetic analyses and correlation with clinical data. For details on each sub-study, see **Section 17.2.**

4.8.1 Eligibility for germline DNA sub-study (Saliva samples)

All newly randomised trial participants who join arms A, K or L are asked to provide a saliva sample from which germline (inherited) DNA can be extracted.

Participants randomised from **15-Nov-2011** onwards who consented to provide a blood spot (Consent Form version 4.0 part K) can also be retrospectively approached to provide a saliva sample providing they have received the REC-approved letter explaining the need for additional saliva sample collection as the DNA extraction using the blood spot method did not work as well as anticipated.

For further information please refer to the **Sample collection and handling manual**.

4.8.2 Eligibility for the circulating tumour DNA sub-study (sequential blood samples)

This substudy is not recruiting currently. For details relating to blood sample collection for patients already participating in the substudy, including eligibility criteria and shipping refer to the **Sample collection and handling manual.**

4.8.3 Eligibility for tumour sample analysis (FFPE blocks)

All newly randomised trial participants should be provided with the STAMPEDE Additional Research Participant Information Sheet in order to consider optional donation of remaining diagnostic prostate cancer tissue stored as formalin fixed paraffin embedded (FFPE) blocks.

The criteria for enrolment into the FFPE block collection:

- Newly randomised STAMPEDE participants
- Informed consent to gift remaining tissue to be used for additional research analyses

Tumour blocks will only need to be sent for a select subset of STAMPEDE patients. For more details, please refer to the **Sample collection and handling manual.**

4.8.4 Eligibility for metformin metabolic sub-study

All newly randomised trial participants who meet the eligibility criteria to join the A/K comparison are eligible to join the metformin metabolic sub-study, if the site where they are being treated is participating in this sub-study. A limited number of sites will be recruiting for this sub-study. Selected sites involved have volunteered and demonstrated they have sufficient resources to undertake the metabolic sub-study.

Participants who are eligible for randomisation to the metformin comparison must be willing to take part in the metabolic sub-study and be able to adhere to the blood sample schedule. Appropriate consent to the additional blood samples must be provided.

5 RANDOMISATION AND ENROLMENT

5.1 RANDOMISATION

Participant eligibility will be confirmed during the randomisation process and participants will be allocated to any of the open research comparisons for which they are eligible (see **Section 4.6**). To randomise a participant please carefully complete the Randomisation CRF and then contact the CTU.

RANDOMISATION
Call MRC CTU at UCL, Monday to Friday 0900-1700
Excluding public holidays or dates when notice has been given by the CTU.
Tel: +44 (0) 20 7670 4777

A trial ID and treatment will be allocated and given over the phone and by email confirmation. In addition, a letter confirming these details will be sent. The trial ID will be the primary way in which the participant will be identified and should be used in all correspondence. Sites should send a letter to the participant's GP to inform them of their trial participation and treatment allocation. The GP letter is supplied as a template and can be downloaded from the trial website www.stampedetrial.org.

The randomisation CRF, eligibility checklist and anonymised consent form* must be submitted to the CTU following randomisation.

**Anonymised consent forms are not required to be submitted for Swiss participants.*

5.2 CO-ENROLMENT GUIDELINES

Interventional clinical trials
STAMPEDE participants should not join any other interventional clinical trials of prostate cancer treatment until the following criteria have been met:

- The participant has experienced at least one failure-free survival (FFS) event
- The participant is no longer on any STAMPEDE research treatment that is permitted to continue post first progression e.g. metformin, abiraterone or enzalutamide

Once both criteria are satisfied the participant may be entered into further treatment studies evaluating treatments for CRPC.

Site investigators should check with the CTU prior to participants commencing any IMP within an **interventional clinical trial** for any other medical condition, such as a new malignancy, to ensure there are no concerns about interactions with STAMPEDE treatments. Note that STAMPEDE treatment can be continued alongside **non-trial treatments** for a new malignancy providing local pharmacy review to ensure there are no interactions.

The primary outcome measure of STAMPEDE is overall survival, therefore follow-up must continue after co-enrolment (unless the participant withdraws consent). Participation in interventional studies must be reported to CTU on the Co-enrolment CRF. Details of any interventional treatments received post-progression in such studies must be reported on the Additional Treatment Log.

Non-interventional clinical trials

Co-enrolment in non-interventional studies for any indication is permitted at any time providing that it does not interfere with treatment or assessment in STAMPEDE. This does **not** require reporting using the Co-enrolment CRF which captures details of interventional prostate cancer clinical trials only.

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

6 TREATMENT OF PARTICIPANTS

6.1 STANDARD-OF-CARE (SOC)

The SOC for this patient group is **androgen deprivation therapy** (ADT) as per local practice (see **Section 6.1.1**). For some participant groups, this should now be supplemented with SOC radiotherapy (see **Section 6.1.2**). From protocol v14.0 onwards, SOC docetaxel is permitted for all suitable participants. From protocol v19.0 onwards, SOC abiraterone is also be permited as an alternative to docetaxel, where this is available. From protocol v21.0 onwards SOC enzalutamide and apalutamide are also permitted as an alternative to docetaxel or abiraterone, where these are available, (see **Section 6.1.4**).

SOC combinations	Metformin comparison	Transdermal oestradiol comparison
ADT alone	Yes	Yes
ADT + prostate RT +/- nodal RT	Yes	Yes
ADT + docetaxel	Yes	Yes
ADT + docetaxel + RT	Yes	Yes
ADT + abiraterone/enzalutamide/apalutamide	Yes	Yes*
ADT + abiraterone/enzalutamide/apalutamide + RT	Yes	Yes*

*See section **7.1.5.C** for guidelines for submitting hormone treatment logs – please send as quickly as possible to facilitate safety monitoring of combination.

6.1.1 Androgen Deprivation Therapy

The planned duration of ADT should be **at least 2 years** and lifelong in those with metastatic disease. With the exception of those allocated to transdermal oestradiol (Arm L), all participants will receive ADT as per local practice to achieve castrate levels of testosterone. The method of planned or current long-term standard-of-care ADT must be specified prior to randomisation. See below for the permitted methods of ADT and see **Section 4.3.1** for more information on ADT timing before randomisation. Participants allocated to Arm L will go on to receive transdermal oestradiol in place of standard ADT methods.

6.1.1.A Bilateral Orchidectomy

Operations should be performed by appropriately trained surgeons. A total or sub-capsular orchidectomy may be performed. Participants having a bilateral orchidectomy are required to adhere to the same timelines for prior LHRH and/or anti-adrogen exposure as specified in **Section 4.3.1.** Note, bilateral orchidectomy is an exclusion criteria for the “transdermal oestradiol” comparison, see **section 4.6.2**.

6.1.1.B LHRH Agonists e.g. goserelin, leuprorelin

LHRH agonists used according to local practice. The prophylactic use of anti-androgens to prevent tumour “flare” is recommended.

6.1.1.C LHRH Antagonists e.g. degarelix

LHRH antagonists used according to local practice. The use of prophylactic use of anti-androgens to prevent tumour “flare” is not necessary.

6.1.1.D Dual Androgen Blockade

Long-term use of anti-androgens alongside LHRH agonists, according to local practice. Note this was previously referred to as maximum androgen blockade. Anti-androgen monotherapy is not deemed an androgen deprivation regimen.

6.1.2 SOC Radiotherapy to prostate

6.1.2.A N0M0 Participants

Investigators should give standard RT to participants with node-negative, non-metastatic disease (N0M0), in accordance with data from the PR07 and SPCG trials (7, 10). If RT is contra-indicated this must be recorded on the Randomisation CRF. See **Section 6.1.3** for further details of RT administration.

6.1.2.B N+M0 Participants

For participants with node-positive, M0 disease there are no randomised data on whether radiotherapy is indicated or not. However the NCIC PR.3 / MRC PR07 trial included participants with unknown nodal status who received whole pelvic RT (11) and demonstrated a large overall benefit. Additionally, non-randomised data from the STAMPEDE control arm (Arm A) suggests that the benefit observed in participants with N0M0 disease can be extended to those with pelvic nodal involvement. Therefore, the STAMPEDE TMG recommends that pelvic nodal RT be considered for participants with node-positive, M0 disease at the discretion of the treating clinician (12).

6.1.2.C Oligometastatic Participants

For participants with oligometastatic disease, data from the M1:RT arm supports the use of RT to the prostate (4). Currently, data strongly supports the use of prostate RT in men with up to 3 bone metastases and/or lymph node only disease, however we are aware that ongoing analyses may redefine which patients benefit from this treatment. Therefore, the STAMPEDE TMG recommends that prostate +/- pelvic nodal RT be considered for participants with oligometastatic disease, with the treating clinician to determine whether the participant has oligometastatic disease that they deem likely to benefit from this treatment.

6.1.2.D Planned Use Of SOC RT

Suitability for RT is assessed by the treating clinicians. Investigators will be asked to state their intention with regards to planned RT in this group at randomisation. Intention to give RT (or not) for **all** participants must be stated at randomisation to ensure that there is no bias towards particular combinations of systemic therapy with RT.

SOC RT administration is not being investigated as part of the trial, therefore only minimal data about SOC RT will be collected. It is accepted that some participants will develop progressive disease before RT can be administered and if this occurs the reasons for non-delivery of treatment must be recorded on the Radiotherapy Detail CRF.

6.1.3 Administration of SOC RT

Standard radiotherapy will be given to appropriate participants in each of the trial arms, following a period of neo-adjuvant ADT therapy, as is generally standard in UK practice. For participants with negative nodes on axial imaging, clinicians may choose between irradiating prostate and seminal vesicles alone or including the pelvic nodes in addition. Additional staging tests such as pelvic node sampling may be considered in making this decision. Conformal or intensity modulated radiotherapy should be used in all participants. Where participants have good clinical evidence that nodes are free of tumour or participants for whom nodal radiotherapy is contra-indicated (e.g. significant bowel disease), treatment may be given to the prostate gland and seminal vesicles only. The recommended dose is 74Gy in 37 fractions to the prostate and seminal vesicles or the equivalent using hypo-

fractionated schedule, 60Gy in 20 fractions. Alternative dosing schedules are permitted but must be agreed with the STAMPEDE Trial Management Group (TMG).

6.1.3.A Standard-Of-Care RT Timing

If receiving docetaxel as part of the standard-of-care (permitted from protocol v14.0), the participant must have sufficiently recovered from any docetaxel toxicity before RT can begin. In all other participants not receiving SOC docetaxel, SOC RT may be started sooner (2-6 months post-randomisation) consistent with the data from the MRC PR07 trial (11).

6.1.4 SOC upfront systemic therapy: docetaxel, abiraterone, enzalutamide or apalutamide

Docetaxel, abiraterone, enzalutamide or apalutamide may be considered for use as SOC treatments, provided the treatment is available locally. Choice of which systemic therapy to use is at the discretion of the clinician. However, we suggest site investigators keep abreast of the emerging literature to inform choices between these treatments, when options are available.

From protocol v14.0 investigators may consider giving docetaxel as part of the SOC for participants with newly-diagnosed metastatic disease, based on the survival benefit demonstrated by both STAMPEDE in the primary analysis of the "original comparisons" and CHAARTED (13) (14, 20). Investigators may also consider giving docetaxel to participants with high-risk locally-advanced disease.

From protocol v19.0 onwards, the treating clinician and participant may consider the use of abiraterone in the newly diagnosed setting, where this is available.

From protocol v21.0 onwards the treating clinician and participant can also consider the alternate options to use enzalutamide or apalutamide in the newly diagnosed setting, if available.

The treating clinician and participant must have decided **prior** to randomisation if SOC docetaxel, abiraterone, enzalutamide or apalutamide is to be given to ensure use is balanced between control and treatment arms. Treatment with SOC systemic therapy may start prior to randomisation, except in Arm L when abiraterone, enzalutamide or apalutamide cannot have started prior to starting trial treatment. In addition, for participants allocated to Arm L who have not already started SOC docetaxel prior to randomisation, it is recommended that docetaxel commences around 4 weeks after starting research treatment (see **Section 6.2.5**).

In the absence of data supporting the routine use of concurrent or sequential use in the absence of disease progression, investigators are required to specify which SOC treatment will be used (i.e.: **one** of docetaxel, abiraterone, enzalutamide or apalutamide) and may **not** plan to use a combination of these. In the case that SOC treatment is changed from one agent to another in order to manage toxicity/intolerance (as per current national guidelines) please update the SOC Systemic Treatment CRF.

We recommend starting SOC systemic therapy within 12 weeks of initiation of ADT. This timing is consistent with the time-scale for starting treatment within the aforementioned clinical trials.

Docetaxel is given according to local protocols as a standard non-trial treatment. The regime used previously within STAMPEDE (Arm C and Arm E) was 75mg/m^2 Day 1 as 1hr IV infusion, plus prednisolone 5mg BID for 21 days repeated every 3 weeks for a maximum of 6 cycles. GCSF use is at the investigator's discretion; prednisolone may be omitted.

Abiraterone, enzalutamide or apalutamide should be given according to local protocols as a standard non-trial treatment. Currently abiraterone, enzalutamide and apalutamide are funded differently by the NHS dependent on burden of disease and which country the participant is being treated in; follow national guidelines for duration and management of therapy once available.

The dosing, safety monitoring and toxicity management contained within the STAMPEDE protocol refers to research abiraterone and enzalutamide given to participants previously allocated to Arms G or J, but may be used as a guide if required. The protocol guidelines for abiraterone were based on the recommendations from the manufacturers, which are included in the summary of product characteristics and can be found online. Similarly, for dosing, safety monitoring and toxicity management of enzalutamide and apalutamide consider referring to the summary of product characteristics produced by the manufacturers, and any local or national guidelines available.

A SOC Systemic Treatment CRF should be completed for all participants randomised to STAMPEDE regardless of whether any SOC systemic therapy was planned. See **Section 7.2.3** for details of data collection for SOC Systemic Treatment.

6.2 RESEARCH TREATMENTS

Research treatment durations are outlined below with a separate section for each individual Investigational Medicinal Product (IMP) detailing the cautions and contraindications, interactions, safety monitoring and toxicity clinical management.

6.2.1 Treatment Duration

Table 9: Intended treatment duration – All arms

RANDOMISED ARM AND TREATMENT	TREATMENT DURATION IS DEPENDENT ON DISEASE STATE		
	M0 WITH PLANNED RADICAL TREATMENT[1]	**M0 WITH NO PLANNED RADICAL TREATMENT[1]**	**M1**
Arm A:SOC androgen deprivation therapy	Minimum 2 years	Continue lifelong	Continue lifelong
Arm G: Abiraterone	2 years - *unless progression occurs before (see* **Table 10***)*	Continue until all categories of disease progression have occurred (see **Table 10**)	Continue until all categories of disease progression have occurred (see **Table 10**)
Arm J: Abiraterone and enzalutamide	2 years - *unless progression occurs before (see* **Table 10***)*	Continue until all categories of disease progression have occurred (see **Table 10**)	Continue until all categories of disease progression have occurred (see **Table 10**)
Arm K: Metformin	Minimum 3 years (continue for 12 months after the last injection of LHRHa to allow for the delay in testosterone levels returning to normal)	Continue lifelong as long as the investigator feels it is in the best interests of the participant.	Continue lifelong as long as the investigator feels it is in the best interests of the participant.
Arm L: Transdermal oestradiol (TE2)	Minimum 2 years – *unless progression occurs before (see* **Table 10***)*	Continue until disease progression at which point it is the site investigators prerogative to choose whether to continue TE2 or change to LHRHa. (see **Table 10** for additional details on treatment post-progression)	Continue until disease progression at which point it is the site investigators prerogative to choose whether to continue TE2 or change to LHRHa. (see **Table 10** for additional details on treatment post-progression)

[1] For trial purposes: Report the planned duration of trial treatment based on the intention at the time of randomisation, i.e.: based on plans for radical RT**. However** if the treatment received is different from that planned, please ensure treatment the participant receives reflects the most appropriate duration:

E.g.: N0M0 patient does not receive planned RT > treat with lifelong ADT as per "M0 with no radical treatment"
N0M0 patient receives RT that was not planned > treat with minimum 2 years ADT as per "M0 with radical treatment"

Table 10: Management of trial treatment post progression

Continues on next page.

RANDOMISED TREATMENT	POST-PROGRESSION: HOW TO MANAGE TRIAL TREATMENT			
	M0 WITH RADICAL TREATMENT - PROGRESSES WHILST STILL ON ADT	**M0 WITH RADICAL TREATMENT - PROGRESSES AFTER COMPLETING 2 YEARS ADT**	**M0 WITH NO RADICAL TREATMENT**	**M1**
Arm A: SOC androgen deprivation therapy	Participants who progress before completing 2 years of ADT should continue with ADT. *ADT after progression is not considered a trial protocol treatment.*	M0 participants who progress after stopping ADT at 2 years, should restart ADT. *ADT after progression is not considered a trial protocol treatment.*	*Continue ADT post-progression but ADT is no longer considered a trial protocol treatment.*	
Arm G: Abiraterone	Continue until all types of progression reported: • PSA progression (as defined in section **7.1.3.A**) • Radiological progression • Clinical progression However, if the participant starts second-line treatment before meeting all progression types, abiraterone must be stopped[1].	If the site clinician wishes to retreat with abiraterone this must be done following national guidelines for use in the CRPC setting. *Re-treating with abiraterone in the CRPC setting is not a trial protocol treatment.*	Continue until all types of progression reported: • PSA progression (as defined in section **7.1.3.A**) • Radiological progression • Clinical progression However, if the participant starts second-line treatment before meeting all progression types, abiraterone must be stopped[1].	
Arm: J Abiraterone and enzalutamide	Continue until all types of progression reported: • PSA progression (as defined in section **7.1.3.A**) • Radiological progression • Clinical progression However, if the participant starts second-line treatment before meeting all progression types, abiraterone and enzalutamide must be stopped[1].	If the site clinician wishes to retreat with abiraterone or enzalutamide this must be done following national guidelines for use in the CRPC setting. Re-treating with abiraterone or enzalutamide in the CRPC setting is not a trial protocol treatment.	Continue until all types of progression reported: • PSA progression (as defined in section **7.1.3.A**) • Radiological progression • Clinical progression However, if the participant starts second-line treatment before meeting all progression types, abiraterone and enzalutamide must be stopped[1].	

[1] Participants may continue on abiraterone or abiraterone and enzalutamide if they receive radiotherapy on a single occasion for a skeletal-related event

	POST-PROGRESSION: HOW TO MANAGE TRIAL TREATMENT			
RANDOMISED TREATMENT	**M0 WITH RADICAL TREATMENT - PROGRESSES WHILST STILL ON ADT**	**M0 WITH RADICAL TREATMENT - PROGRESSES AFTER COMPLETING 2 YEARS ADT**	**M0 WITH NO RADICAL TREATMENT**	**M1**
Arm K: Metformin	Continue metformin post-progression. Post-progression metformin should be continued for as long as the investigator feels it is in the best interests of the participant. Metformin can be given alongside any second-line treatment for prostate cancer. However, if another trial with any IMP is started in the second-line setting, metformin must be stopped.	If progression occurs after stopping ADT but while metformin continues, (i.e. progression within the first 12 months of stopping ADT), continue metformin post-progression. If progression occurs after metformin has stopped (i.e. progression >12 months after the last administration of LHRHa), metformin should not be restarted.	Continue metformin post-progression. Post-progression metformin should be continued for as long as the investigator feels it is in the best interests of the participant. Metformin can be given alongside any second-line treatment for prostate cancer. However, if another trial with any IMP is started in the second-line setting, metformin must be stopped.	
Arm L: Transdermal oestradiol (TE2)	Continuing treatment with TE2 or change to LHRHa is at the discretion of the treating clinician.	Restart treatment with TE2 or LHRHa, the choice is at the discretion of the treating clinician.	Continuing treatment with TE2 or changing to LHRHa is at the discretion of the treating clinician.	
	TE2 can be used in combination with docetaxel, cabazitaxel and radium in the CRPC setting. We are currently evaluating the combination of abiraterone, enzalutamide and apalutamide alongside TE2 in the upfront setting. If this is proven to be safe and effective then sites will be informed and it will thereafter also be allowed in the CRPC setting. In the meantime if you wish to use abiraterone, enzalutamide or apalutamide in the CRPC setting the participant must change to LHRHa. For participants who are on the 3 patch maintenance dose and have castrate levels of testosterone, there is currently no evidence that increasing the number of patches further once the participant has progressed would be beneficial and is therefore not recommended.			

6.2.2 Research Abiraterone + Prednisolone (relevant to Arms G & J)

Note: recruitment has closed to all research comparisons containing abiraterone; that is Arm G (SOC + abiraterone) and Arm J (SOC + enzalutamide + abiraterone).

Participants allocated to Arm G or Arm J will receive abiraterone:

- Arm G: abiraterone alone (taken with prednisolone), in addition to SOC ADT
- Arm J: abiraterone (taken with prednisolone) in combination with enzalutamide, in addition to SOC ADT

6.2.2.A Abiraterone: Clinical particulars – posology and administration

Abiraterone is administered as a single 1000mg daily oral dose (4 tablets to be taken together once a day).

Abiraterone should be taken with prednisolone 5mg (or prednisone 5mg in Switzerland) daily to prevent secondary mineralocorticoid excess. See **Section 6.2.2.H** for further details on prednisolone (and prednisone).

Abiraterone absorption is increased by food therefore should be taken on an empty stomach without food. The tablets should be taken at least 2 hours after food, swallowed whole with water. No food should be eaten for 1 hour afterwards.

6.2.2.B Abiraterone: Clinical particulars - treatment duration

See **Table 9** for details. See **Section 7.1.3** for further information on the trial definition of progression.

6.2.2.C Abiraterone: Safety monitoring

: Hypokalaemia, hepatic impairment and hypertension
Abiraterone may cause:

- Hypokalaemia, due to secondary mineralocorticoid excess; this can be counteracted by co-prescription of prednisolone
- Increased liver enzymes and hepatotoxicity
- Hypertension

Regular monitoring of blood serum potassium, LFTs and blood pressure are therefore required whilst on treatment. Requirements for STAMPEDE are provided in **Table 11**. Safety monitoring requirements are consistent with the approach adopted in the LATITUDE trial in which abiraterone was evaluated in high-risk metastatic hormone-naïve prostate cancer (16) and the abiraterone Investigator Brochure (38).

In summary:

- **Two weekly** monitoring of potassium, LFTs and BP for the **first 12 weeks**
- **Monthly** monitoring of potassium, LFTs and BP from **12 weeks until 1 year**
- **After 1 year** safety monitoring of potassium, LFTs and BP can reduce to **two monthly** if the site investigator thinks it is safe and appropriate to do so.

Table 11: Safety monitoring for participants receiving research abiraterone

Note: In acute toxicity monitoring requirements may increase – see toxicity tables for additional advice.

Adverse event of interest	Monitoring Required	Frequency of monitoring whilst on abiraterone alone or in combination with enzalutamide treatment in the trial setting		
		Weeks 0 – 12	Week 12 – 12 months	12 months – end of treatment
Hypokalaemia	Blood serum potassium*	Every 2 weeks	Monthly	Participants may have the frequency of monitoring reduced to every 2 months*** if judged appropriate by the investigator. Continued monthly monitoring is required for participants if there are concerns related to research abiraterone causing hypokalaemia.
Hepatic impairment	LFTs (ALT or AST, and bilirubin)*	Every 2 weeks	Monthly	Participants may have the frequency of monitoring reduced to every 2 months*** if judged appropriate by the investigator. Continued monthly monitoring is required for participants if there are concerns related to research abiraterone causing hepatic impairment.
Hypertension	Blood pressure**	Every 2 weeks	Monthly	Participants may have the frequency of monitoring reduced to every 2 months*** if judged appropriate by the investigator. Continued monthly monitoring is required for participants if there are concerns related to research abiraterone causing hypertension.

* Blood tests may be taken in the community or by a GP surgery, however the results must be reviewed contemporaneously by the trial team. It is not acceptable to wait until the participant's next oncology appointment before these are reviewed.
**Blood pressure may be monitored using documented self-monitoring or via the GP providing this is reviewed at each follow up.
***Based on advice from Janssen, product IB/SmPC and LATITUDE protocol (16)

:: Hypokalaemia - additional notes
Abiraterone may cause hypokalaemia due to secondary mineralocorticoid excess, this can be counteracted by co-prescription of prednisolone (see management of hypokalaemia Table 14).

After the first 12 months, provided the site investigator feels it is appropriate and safe to do so, it is permissible for patients to be prescribed 3 months of abiraterone. As above, safety monitoring needs to be completed at 2 monthly intervals and these results need to be monitored at the time they are available to ensure it is safe for the patient to continue taking their trial medications.

:: Hepatic impairment – additional notes
Abiraterone treatment can be associated with increased liver enzymes and hepatotoxicity, therefore regular monitoring of LFTs is required whilst on treatment. LFTs should include ALT or AST, and

bilirubin. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular ALT, should be measured immediately (see management of abnormal LFTs **Table 15**).

After the first 12 months, provided the site investigator feels it is appropriate and safe to do so it is permissible for patients to be prescribed 3 months of abiraterone. As above, safety monitoring needs to be completed at 2 monthly intervals and these results need to be monitored at the time they are available to ensure it is safe for the patient to continue taking their trial medications.

:: Blood pressure management – additional notes
Abiraterone may cause hypertension. Investigators are required to ensure blood pressure is performed and reviewed. , it is acceptable for this to be documented self-monitoring or via the GP providing this is reviewed at each follow-up. For the management of abiraterone-induced hypertension see **Table 13**.

6.2.2.D Abiraterone: Cautions and contra-indications

- Unusual or allergic reaction to past abiraterone treatment
- Uncontrolled hypertension
- Uncontrolled heart failure
- Active or chronic liver disease

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

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

:: Renal impairment
No dose adjustments are required in renal impairment; however, caution is advised if participants develop severe renal impairment as there is limited clinical data in this population. Systemic exposure to abiraterone after a single oral 1000mg dose did not increase in participants with end-stage renal disease on dialysis.

6.2.2.E Abiraterone: Special warnings

:: Overdose
Human experience of overdose with abiraterone is limited. There is no specific antidote to abiraterone. In the event of an overdose, administration of abiraterone should be with-held and general supportive measures undertaken, including monitoring for cardiac arrhythmias, liver function and electrolytes.

6.2.2.F Abiraterone: Interactions (medications)

Details on drug interactions are described in **Table 12** provides a summary on the main interactions.

:: Anti-androgens
Abiraterone is steroid synthesis inhibitor and should not be given together with any other anti-androgens given the risk of toxicity. Cyproterone acetate should be discontinued 10 days and finasteride stopped 48 hours before commencing abiraterone. Concomitant use of any anti-androgen including dutasteride, bicalutamide, flutamide and tamoxifen is not recommended.

Participants receiving or planned for dual androgen blockade (DAB) at randomisation should not continue anti-androgens if randomised to receiving abiraterone.

:: Spironalactone
Spironolactone binds to the androgen receptor, may increase PSA levels and is associated with abiraterone resistance therefore concomitant use is **contraindicated.**

:: Statins and medicinal products associated with myopathy/rhabdomyolysis
Myopathy has occurred in patients treated with abiraterone, typically this occurs when first initiating treatment and resolves when abiraterone is stopped. Caution is recommended in participants receiving concomitant treatments with medicinal products known to be associated with myopathy/rhabdomyolysis e.g. statins.

Table 12: Drugs that may interact with abiraterone

DRUGS WHICH MAY REDUCE ABIRATERONE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP3A4 inducers	Anti-epileptics*	Phenytoin Carbamazepine Phenobarbital Primadone (39)	Avoid unless no therapeutic alternative, due to risk of decreased exposure to abiraterone.
	Anti-depressants	St Johns Wart	
	Anti-TB	Rifampicin Rifabutin Rifapentine	
DRUGS WHICH MAY INCREASE ABIRATERONE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP3A4 inhibitors	Anti-retroviral	Atazanavir Saquinavir Ritonavir Indinavir Nelfanavir	Whilst PK studies of other CYP3A4 inhibitors did not indicate a clinically meaningful interaction, there are no specific studies of assessing an abiraterone - anti-retroviral interaction. If it is not possible to avoid the use of anti-retrovirals it would be prudent to have an awareness of a potential for an interaction and monitor for adverse effects from abiraterone.(40)
	Anti-fungal	Ketoconzole	PK studies suggest no clinically meaningful impact of interaction
DRUGS WHICH MAY ACCUMULATE WHEN GIVEN WITH ABIRATERONE			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2D6	Cardiac	Metoprolol Propranolol Propafenone Flecainide	Clinical vigilance required as drug levels may increase with abiraterone use, consider a dose reduction of medicinal products metabolised by CYP2D6.
	Anti-depressants	Desipramine Venlafaxine Citalopram	
	Anti-psychotics	Haloperidol Risperidone	
	Analgesia	Tramadol Codeine Oxycodone	
	Alpha blockers	Tamsulosin (41)	
	Anti-diabetic	Repaglinide (42) Pioglitazone	
	Cough suppressant	Dextromethorpam	

*narrow therapeutic index

6.2.2.G Abiraterone Undesirable Effects

The most common adverse drug reactions observed in the integrated safety data for those participants who received 1000mg abiraterone plus prednisone or prednisolone in clinical studies (n=1,070) were fatigue, arthralgia, peripheral oedema, back pain, bone pain, nausea, constipation, hypokalemia and anaemia.

The adverse events graded as Grade 3 or Grade 4 and which occurred in more than 5% of participants were fatigue, peripheral oedema, anaemia and back pain(38).

In the event of a toxicity not listed below clinicians should use their clinical judgement and take appropriate measures to treat the participant, including interruption of research treatment and/or implementing dose modifications if required. Please update treatment logs with any changes. Contact the MRC CTU for further advice if required.

Table 13: Management of abiraterone-associated hypertension (given alone or with enzalutamide)

TOXICITY EVENT	ACTION
BP repeatedly in range of 120-139/80-89 mmHg	**Continue abiraterone (and enzalutamide).** Management as per investigator.
BP repeatedly in range of 140-159/90-99 mmHg	**Continue abiraterone (and enzalutamide).** Management as per investigator with anti-hypertensive treatment. Follow local guidance for selection of anti-hypertensives but avoid thiazide diuretics to minimise risk of serum potassium derangement. Calcium channel antagonists or beta blockers are often preferred. As with other symptoms of mineralocorticoid excess, consider increasing prednisolone dose to 5mg BID.
BP repeatedly ≥ 160/100 mmHg or life-threatening consequences of hypertension)	**Withhold abiraterone and enzalutamide**. Adjust or add anti-hypertensive medications to mitigate the toxicity. When blood pressure resolves to being predominantly <140/90 or baseline, resume both abiraterone and enzalutamide at full dose with prednisolone 5mg bid.

Record hypertension grade as per CTCAE on the follow-up form if required. If a patient experiences ongoing hypertension that the treating clinician deems clinically concerning then consider referral to cardiologist or hypertension clinic.

Table 14: Management of abiraterone associated hypokalaemia (given alone or with enzalutamide)

TOXICITY EVENT	ACTION
Grade 1 (<LLN – 3.0mmol/L)	**Continue abiraterone (and enzalutamide).** Supplement with oral potassium and monitor closely and increase prednisolone dose to 5mg BID. Exclude and manage other causes of hypokalemia.
Grade 2 (<LLN – 3.0mmol/L and symptomatic)	**Withhold abiraterone (continue enzalutamide).** Supplement with oral potassium and monitor closely and increase prednisolone dose to 5mg BID. Exclude and manage other causes of hypokalemia. Re-start abiraterone with close monitoring, discontinue if recurs.
Grade 3 (<3.0 – 2.5mmol/L) or Grade 4 (<2.5mmol/L and life-threatening)	**Permanent discontinuation of abiraterone** and hospitalisation for intravenous potassium replacement and cardiac monitoring. After the return of serum potassium to normal, prednisolone (prednisone in Switzerland) should also be discontinued. The participant can continue on enzalutamide alone. If hypokalaemia persists, consider a dose reduction of enzalutamide to 120mg once a day.

Table 15: Management of abnormal LFTs associated with abiraterone (given alone or with enzalutamide)

TOXICITY EVENT	ACTION
Grade 1 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT from ULN to 3.0X ULN; increase in total bilirubin from ULN to 1.5X ULN)	**Continue abiraterone (and enzalutamide).** Increase frequency of LFT monitoring to at least weekly, if the investigator judges that the laboratory abnormalities are potentially related to study medication. Providing LFTs are stable for 4 weeks, resume normal LFT monitoring.
Grade 2 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >3.0-5.0X ULN; increase in total bilirubin from >1.5-3.0X ULN)	**Withhold abiraterone, enzalutamide** and all other concomitant medications that are potentially hepatotoxic. Increase frequency of LFT monitoring to at least weekly until the LFTs return to baseline value or Grade 1, when both abiraterone and enzalutamide can be re-started. Enzalutamide can be re-started with no dose reduction. Abiraterone can be re-started with no dose reduction after one episode, providing this resolved within 4 weeks. Dose reduction should be considered if Grade 2 derangements persist or recur; see below.
Grade 3 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >5.0X ULN; increase in total bilirubin to >3.0X ULN),	**Withhold abiraterone and enzalutamide** and all other concomitant medications that are potentially hepatotoxic. Immediately increase the frequency of LFT monitoring to at least weekly until the LFTs return to baseline value or Grade 1. Enzalutamide can be re-started with no dose reduction. Abiraterone can be re-started with dose reduction to 250mg once toxicities resolved to Grade 1 or baseline. This dose can be titrated as per liver function blood tests.
Grade 4 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >20.0X ULN; increase in total bilirubin to >10.0X ULN)	**Immediate discontinuation of abiraterone and enzalutamide.** Increase the frequency of LFT monitoring to at least weekly until the LFTs return to baseline value or Grade 1. Prednisone can then be discontinued and the investigator can consider restarting enzalutamide. Abiraterone should not be re-introduced.
SCENARIO	**ACTION**
Recurrent or persistent Grade 2 AST, ALT, or bilirubin derangement	**Withhold abiraterone and enzalutamide** and all other concomitant medications that are potentially hepatotoxic. Once LFTs return to Grade 1 restart abiraterone at 250mg and titrate upwards, guided by weekly blood tests.
Second episode of Grade 3 AST, ALT or bilirubin derangement	**Withhold abiraterone and enzalutamide** and all other concomitant medications that are potentially hepatotoxic. Immediately increase LFT monitoring at least weekly is required, continue until returned to baseline values or Grade 1. Recommence enzalutamide initially. If abiraterone resumption is then considered, resume study treatment with abiraterone dose starting at 250mg and titrate upwards guided by LFTs
Third episode of Grade 3 AST, ALT or bilirubin derangement	Permanently discontinue abiraterone. Prednisone can then be discontinued and the investigator can consider restarting enzalutamide.

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

Table 16: Management of fluid retention/oedema associated with abiraterone (given alone or with enzalutamide)

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

Table 17: Management of diarrhoea (associated with abiraterone or enzalutamide)

TOXICITY EVENT	ACTION
Grade 1-2	**Continue abiraterone and enzalutamide.** Symptomatic management.
Grade 3-4	**Withhold abiraterone**. Enzalutamide can be continued in the first instance. If no improvement from witholding abiraterone alone, reduce dose of enzalutamide to 120mg per day. If still no improvement reduce dose of enzaluatmide to 80mg. If diarrhoea persists despite this (and it is believed symptoms are caused by abiraterone or enzalutamide) we recommend the patient stops trial treatment Once resolved to Grade 1, recommence abiraterone at 750mg per day.

6.2.2.H Abiraterone: Prednisolone (prednisone in Switzerland)

The co-administration of prednisolone (prednisone in Switzerland) 5mg once daily is required whilst receiving abiraterone to prevent secondary mineralocorticoid excess.

Prednisolone should be taken as a single dose with food in the morning. If mineralocorticoid-related toxicities occur (e.g., hypokalaemia, hypertension, peripheral oedema) the prednisolone dose should be reviewed. See **Table 13**, **Table 14** and **Table 16** for advice on when an increase to 5mg BID is recommended.

If a participant experiences serious symptoms of Cushing's syndrome (e.g., weight gain, muscle loss) investigators may reduce the steroid dose but participants should be closely monitored for symptoms of secondary mineralocorticoid excess. It should be noted that weight gain and muscle loss are also associated with ADT.

If a participant allocated to receive abiraterone develops only biochemical failure, the responsible clinician may switch from abiraterone + prednisolone 5mg OD to abiraterone + dexamethasone 0.5mg OD.

6.2.3 Research Enzalutamide (Arm J)

Note: recruitment has closed to Arm J (SOC + enzalutamide + abiraterone).

Participants allocated to Arm J will receive enzalutamide in combination with abiraterone, in addition to SOC ADT. For information relating to treatment with abiraterone (and prednisolone), refer to Section **6.2.2**.

6.2.3.A Enzalutamide: Clinical particulars – posology and administration

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

6.2.3.B Enzalutamide: Clinical particulars - treatment duration

Enzalutamide will be taken for the same duration as the co-administered abiraterone, unless either abiraterone or enzalutamide is stopped for toxicity, in which case the other drug may continue.

Enzalutamide treatment duration is included in **Table 9**. See **Section 7.1.3** for further information on the definition of progression.

6.2.3.C Enzalutamide: Safety monitoring

Safety monitoring for participants receiving research enzalutamide alone.

Please see **Table 11** for safety monitoring if enzalutamide given alongside abiraterone. In acute toxicity monitoring requirements may increase – see toxicity tables for more advice in this setting.

ADVERSE EVENT OF INTEREST	MONITORING REQUIRED	FREQUENCY OF MONITORING WHILST ON RESEARCH ENZALUTAMIDE **ALONE** (IF ABIRATERONE PREVIOUSLY STOPPED FOR TOXICITY) IN THE TRIAL SETTING		
		WEEKS 0 – 12	WEEK 12 – 12 MONTHS	12 MONTHS – END OF TREATMENT
Hypertension	Blood pressure*	Every 2 weeks	Monthly	Participants may have the frequency of monitoring reduced to every 3 months if judged appropriate by the investigator. Continued monthly monitoring is required for participants if there are concerns related to research enzalutamide causing hypertension.

* Blood pressure may be monitored using documented self-monitoring or via the GP providing this is reviewed at each follow up.

6.2.3.D Enzalutamide: Cautions and contra-indications

:: History of seizures

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

:: Hepatic impairment

A hepatic impairment study showed that the composite AUC of enzalutamide plus N-desmethyl enzalutamide after administration of a single dose of enzalutamide was similar in patients with

baseline mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C respectively) relative to patients with normal hepatic function, and no starting dose adjustment is needed (43).

:: Renal impairment
No dose adjustments are required in renal impairment; however, caution is advised if participants develop severe renal impairment as there is limited clinical data in this population.

6.2.3.E Enzalutamide: Special warnings

:: Overdose
There is no antidote for enzalutamide. In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures taking into consideration the half life of 5.8 days. Participants may be at increased risk of seizures following an overdose.

6.2.3.F Enzalutamide: Interactions (medications)

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

Details on drug interactions are described in **Table 18** provides a summary on the main interactions.

:: Anti-androgens
Enzalutamide is potent androgen receptor antagonist and should **not** be given together with any other anti-androgens given the risk of toxicity. Cyproterone acetate should be discontinued 10 days and finasteride stopped 48 hours before commencing enzalutamide (+ abiraterone). Concomitant use anti-androgens including dutasteride, bicalutamide, flutamide and tamoxifen are **not recommended**.

Participants receiving or planned for dual androgen blockade (DAB) at randomisation should not continue anti-androgens if randomised to receiving enzalutamide (+abiraterone).

Table 18: Drugs which may interact with enzalutamide

DRUGS WHICH MAY INCREASE ENZALUTAMIDE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C8 inhibitors	Lipid-lowering	Gemfibrozil	Avoid, if no alternatives, reduce enzalutamide dose to 80mg
DRUGS WHICH MAY DECREASE ENZALUTAMIDE LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C8 inducers	Anti-tuberculosis	Rifampicin Rifabutin	Avoid if possible. If the therapeutic effect of these medications is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations of these medicinal products, use with caution, due to risk of decreased exposure to enzalutamide.
CYP3A4 inducers	Anti-epileptics	Phenytoin Carbamazepine Phenobarbital	
	Anti-depressant	St John's wort	
	Anti-retrovirals	Atazanavir Saquinavir Ritonavir Indinavir Nelfanavir	Avoid if possible. If the therapeutic effect of these medications is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations of these medicinal products, use with caution. This is due to risk of decreased exposure to enzalutamide and increased risk of toxicity from the anti-retroviral medication.
ENZALUTAMIDE MAY REDUCE DRUG LEVELS			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
CYP2C19	Gastric protection	Omeprazole	Omeprazole AUC reduced by 70% Consider increasing dose of omeprazole for same therapeutic effect
CYP3A4	Analgesia	Fentanyl* Alfentanil* Tramadol	Consider alternatives as clinical effect may be reduced, if no therapeutic alternative monitor closely
	Immunosuppressants	Sirolimus* Tacrolimus* Cyclosporine*	
	Anti-migraine	Ergotamine	
	Cardiac	Nifedipine Ivabradine	
CYP2C9	Anti-epileptics	Phenytoin*	Contra-indicated
	Anti-coagulants	Warfarin*	Warfarin AUC reduced by 56% Consider switching to low molecular heparin, increase INR monitoring if this is not possible
DRUGS WHICH MAY ACCUMULATE WHEN GIVEN WITH ENZALUTAMIDE			
Substrate	**Clinical Use**	**Drug**	**Recommendation**
p-gp		Colchicine* Dabigatran* Digoxin*	Consider alternatives, if no therapeutic alternative monitor closely

*narrow therapeutic index

6.2.3.G Enzalutamide: Undesirable effects

Please refer to section 6.2.2.G for management of hypokalaemia, deranged LFTs, hypertension, fluid retention and diarrhoea that occurs whilst on enzalutamide in combination with abiraterone.

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

Additional toxicity to be aware of relevant to enzalutamide alone include the following:

Table 19: Management of seizure whilst on enzalutamide treatment

TOXICITY EVENT	ACTION
Seizure (any Grade)	If any participant suffers a seizure whilst on treatment, enzalutamide should be permanently discontinued immediately. Abiraterone and prednisolone can be continued providing there are no abiraterone-specific toxicities.

Table 20: Management of arthralgia & muscle pain (associated with enzalutamide)

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

Table 21: Management of fatigue (associated with enzalutamide)

TOXICITY EVENT	ACTION
Grade 1-2	Consider a dose reduction to 120 mg/day
Grade 3	**Pause enzalutamide** for 1 week or until the toxicity grade improves to Grade 2 or lower severity. Re-start at a reduced dose (120mg/day or 80mg/day), dose chosen to restart is at the treating clinicians discretion.

6.2.4 Research Metformin (Arm K)

Note: General recruitment has closed to Arm K. From protocol 21 only participants to be involved in the metabolic sub-study can be randomised to Arm K.

Participants allocated to Arm K will receive metformin, in addition to SOC treatments. All potential SOC systemic treatment options are suitable for combination with metformin.

6.2.4.A Metformin Clinical particulars – posology and administration

For all participants allocated to Arm K, metformin should start as soon as possible after randomisation and ideally within a maximum of 12 weeks.

Metformin will be given as a daily dose in addition to SOC treatment. The target dose is **850mg Std BID.**

The starting dose for metformin is 850mg Std OD. If tolerated, this should be increased to the target dose after 4-6 weeks i.e. at the first follow-up visit.

Metformin should be taken around the same time each day and treatment tolerance is best if taken with or after food. For twice daily dosing, the minimum time between doses should be 8 hours; doses should not be taken closer together if forgotten or missed.

Providing participants have a sufficient supply of STAMPEDE-labelled IMP metformin tablets, a telephone consultation may be sufficient to assess tolerance and give advice regarding dose modification in order to limit hospital visits. This interaction **must be documented** in the medical records.

:: Metformin dose modifications
If metformin target dose of 850mg Std BID is not well tolerated, the dose reductions listed in **Table 22** could be implemented.

Note: Sustained release formulations (SR) can sometimes be better tolerated with less GI side-effects than the standard or immediate release formulations (Std). Both drugs provide similar exposure at a given daily dose.

Table 22: Management of metformin related GI-toxicity

<table>
<tr><td colspan="5">GRADE 1 OR 2 TOXICITY:
ASSUMES STARTING ON 850MG STD BD (1,700MG TOTAL DAILY DOSE) DOSE.
IF TOXICITY OCCURS ON LOWER DOSE – DROP TO THE NEXT DOSE LEVEL DOWN
IF ONGOING TOXICITY</td></tr>
<tr><td>ACTION 1:</td><td>ACTION 1A:
DOSE REDUCTION LEVEL 1
(OPTIONS)</td><td>ACTION 1B:
DOSE ON RESTART AFTER PAUSE
(OPTIONS)</td><td>ACTION 2:
DOSE REDUCTION LEVEL 2
(OPTIONS)</td><td>ACTION 3:
STOP TREATMENT</td></tr>
<tr><td rowspan="2">Ensure metformin is taken with or after food and consider dose reduction
OR
Ensure metformin is taken with or after food and consider 1-2 week treatment pause.</td><td>a) 750mg SR BID (1500mg total daily dose)
OR
b) 500mg SR BID (1000mg total daily dose)
OR
c) 500mg Std BID (1000mg total daily dose)</td><td>a) 850mg Std OD (850mg total daily dose)
OR
b) 500mg SR OD (500mg total daily dose)</td><td>a) 850mg Std OD (850mg total daily dose)
OR
b) 750mg SR OD (750mg total daily dose)
OR
c) 500mg SR OD (500mg total daily dose)
OR
d) 500mg Std OD (500 mg total daily dose)</td><td rowspan="2">If toxicity recurrs after two dose reductions, we recommend stopping treatment</td></tr>
<tr><td colspan="2">Re-attempt a dose escalation after 1-2 month aiming to continue at the maximum tolerated dose</td></tr>
</table>

:: Treatment breaks
It is anticipated that metformin treatment will be paused for approximately 72 hours around the time of contrast-enhanced CT scans (see **Table 24**) and may need to be paused during episodes of inter-current illness.

- If metformin is paused for 6 days or less this information does not need to be recorded and no additional action is needed.
- Treatment pauses of ≥7 days must be recorded by updating the Metformin Treatment Log CRF.
- If metformin treatment is paused for more than 2 weeks, investigators may consider re-starting at 850mg Std once daily for the first 4 weeks before escalating to full dose providing tolerance is acceptable.
- If treatment is paused for >3 months or >50% of doses are missed for any reason, it is at the discretion of site investigators as to whether it is appropriate to restart trial treatment with metformin. Please ensure treatment pauses are recorded and feel free to contact the CTU for any advice if required.

6.2.4.B Metformin: Clinical particulars – treatment duration
Metformin treatment duration is included in **Table 9**.

6.2.4.C Metformin: Safety monitoring
Routine safety monitoring frequency is described in **Table 23**.

Table 23: Renal function monitoring required whilst on treatment with metformin

RENAL FUNCTION:	FREQUENCY OF MONITORING:
• Stable renal function **AND** • eGFR ≥45ml/min/1.73m^2	6 monthly
• Risk of deteriorating renal function **AND/OR** • eGFR falls to >30 and <45 ml/min/1.73m^2	At least 3 monthly (44) *NB: Max dose is 1000mg per 24 hours in this setting*
• eGFR falls to ≤30ml /min/1.73m^2	Metformin should be paused*

*Should the Site Investigator decide the decline in renal function to ≤30ml /min/1.73m^2 is irreversible then metformin must be permanently stopped

6.2.4.D Metformin: Cautions and contraindications
:: Renal impairment
Metformin is not nephrotoxic, but is exclusively excreted by the kidneys. Therefore treatment should only be started in participants with stable renal function. Metformin should be only started when the GFR ≥45ml/min/1.73m^2, as per the metformin comparison-specific eligiblity criteria in section **4.6.1**.

Additional renal monitoring is required in any participant at risk of deteriorating renal function. In line with published prescribing recommendations, if the GFR falls to between 30-45 ml/min/1.73m^2 a **dose reduction** is required to ensure the maximum 24hr dose is 1000mg or less and monitoring of renal function is required at least 3 monthly (44).

Metformin should be **permanently stopped** if the GFR falls to ≤30ml/min/1.73m^2 and is irreversible.

See **Table 24** for situations when metformin treatment should be paused due to the risk of deteriorating renal function.

Table 24: Situations when metformin treatment should be paused due to risk of deteriorating renal function

SITUATIONS	RISK FACTOR
Iodinated contrast agents	Metformin should be paused for 24 hours prior to receiving contrast and re-started 48 hours post-administration(45).
Anaesthesia (peridural; spinal or general)	Pause metformin 48 hours prior to procedure and re-start no earlier than 48 hours following procedure, providing oral intake re-established and renal function is stable and at baseline.
Surgery	Pause metformin 48 hours prior to procedure and re-start no earlier than 48 hours following procedure, providing oral intake re-established and renal function is stable and at baseline.
Dehydration e.g. nausea, vomiting or diarrhoea	Pause metformin and re-start only when oral intake is re-established and renal function is stable and at baseline.
Obstructive uropathy e.g. urinary retention or ureteric obstruction	Pause metformin and re-start only when renal function confirmed to be stable and at baseline.

6.2.4.E Metformin: Special warnings

:: Metformin overdose

Hypoglycaemia has not been reported with even significant metformin overdoses although lactic acidosis has occurred in such circumstances. Participants should be urgently assessed in the event of an overdose and hospital admission considered. The management of metformin overdoses should be as per standard clinical care by the local team. The most effective way to remove lactate and metformin is haemodialysis.

6.2.4.F Metformin: Interactions (medications)

Caution is needed when initiating potential nephrotoxic drugs as metformin is renally excreted and therefore may accumulate if renal function deteriorates. Please refer to **Table 25** for more information on drugs which may require additional monitoring of renal function, at the discretion of the treating clinician.

Metformin does **not** interact with any of the other treatments for prostate cancer and **should be continued** during all further treatments given for disease progression, **provided clinicians feel it remains in the participants best interests**, as per **Table 9**.

As metformin is being given as an IMP in the context of a clinical trial, continued use will not be permitted if participants participate in other interventional clinical trials for prostate cancer (i.e. CRPC setting).

Table 25: Drugs which may require additional monitoring of renal function

Clinical use	Drug	Recommendation
Anti-hypertensives and other cardiac disease	ACE inhibitors/angiotensin II receptor blockers e.g. ramipril, lisinopril, irbesartan	Increased frequency of renal function monitoring until confirmed to be stable
	Diuretics e.g. furosemide, bumetanide	
Antibiotics	Aminoglycoside antibiotics e.g. gentamicin or amikacin	Pause metformin during treatment Re-start once treatment complete
Analgesia	NSAIDs e.g. Ibuprofen, diclofenac, naproxen	Avoid if possible If used increased frequency of renal function monitoring is required until confirmed to be stable

6.2.4.G Metformin: Undesirable effects

:: Gastrointestinal disturbance

Gastrointestinal disturbances are very common with metformin and include nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These are most common when first starting treatment (occur in >1/10 individuals).

If toxicities occur, a dose reduction and/or a switch to a sustained release (SR) preparation, if available, is recommended (see **Table 22**).

Other possible metformin-related toxicites included taste disturbance, skin reactions and B12 deficiency resulting in megaloblastic anaemia. If a participant becomes anaemic whilst taking metformin, investigators should consider measuring haematinics, including vitamin B12, and replace if deficient.

:: Lactic acidosis

Lactic acidosis is a very rare (3/100,000 patient years), but serious metabolic consequence. Reported cases have occurred primarily in diabetic patients with significant renal impairment who are also dehydrated. It is unclear whether this is due to the underlying diabetes or metformin. This is supported by a meta-analysis demonstrating similar rates of lactic acidosis in people with diabetes taking metformin compared with diabetic participants not taking metformin (46). This evidence suggests this side effect may be a complication of diabetes and may not be associated with metformin treatment.

The risk factors for lactic acidosis are: renal impairment, prolonged fasting or malnutrition, excessive alcohol intake, hepatic insufficiency or any condition associated with hypoxia e.g. cardiac or respiratory failure or circulatory shock due to any cause.

The risk of lactic acidosis should be considered in the event of non-specific symptoms such as muscle cramps, abdominal pain and/or severe weakness or lethargy. Any participant with a suspected metabolic acidosis requires **immediate discontinuation of metformin** and evaluation. Lactic acidosis is characterised by metabolic acidosis (decreased blood pH, high lactate above 5mmol/L and an increased anion gap and lactate/pyruvate ratio). The most effective way to remove lactate and metformin is haemodialysis.

6.2.5 Research Transdermal Oestradiol (Arm L)

:: Timeframe for commencing treatment

For all participants allocated to transdermal oestradiol, treatment should start as soon as possible after randomisation (and ideally within 1 week after randomisation). It is not necessary to wait for completion of the 4-week (or 1-month) duration of the LHRHa injection if this was previously given prior to randomisation. For those prescribed bicalutamide or flutamide prior to randomisation, this treatment should be discontinued before treatment with transdermal oestradiol can commence (no washout period is needed).

:: Transdermal oestradiol with SOC treatments

If SOC docetaxel has not been started before randomisation, it is recommended that it is started, for suitable participants, once established on transdermal oestradiol for around 4 weeks, when most participants are likely to have completed the induction period).

From protocol v21.0 onwards, participants randomised to the transdermal oestradiol comparison are also eligible to receive SOC abiraterone, enzalutamide or apalutamide in the upfront setting, as an alternative to docetaxel (see **Section 6.1.4**). However, the use of enzalutamide, abiraterone or apalutamide *prior to starting treatment* with transdermal oestradiol patches is not authorised (see **Section 4.3.3**).

Participants randomised to receive transdermal oestradiol may also receive SOC radiotherapy (see Section **6.1.2**) as clinically appropriate, as has been done in the PATCH trial.

6.2.5.A Transdermal oestradiol: Clinical particulars – posology and administration

Transdermal oestradiol is delivered either as Progynova TS 100 mcg/24 hours or since protocol v21.0 as Femseven 100 mcg/24hours transcutaneous oestradiol patches. Administration should proceed according to the following dose regimen which has been shown within the PATCH trial to be sufficient for achieving castrate levels of testosterone.

The changing of patch brand should be avoided unless absolutely necessary and should only be done following discussion with the CTU trial team.

Other type of patches should only be used in expectional circumstances and after discussion with the CTU team, as we currently do not have sufficient pharmacokinetic and clinical data to recommend the use of other types of patches.

6.2.5.B :: Induction regimen

Four transdermal transdermal oestradiol patches to be changed twice weekly (e.g. Monday and Thursday) for four weeks. A confirmatory testosterone and oestradiol sample should be taken at 4 weeks with the sample drawn the **day before** the patches are changed.

6.2.5.C :: Maintenance regimen

If the participant has achieved a testosterone value of ≤1.7nmol/L and has an oestradiol level >300pmol/L at 4 weeks, then treatment may be changed to a **maintenance regimen** of **three** patches changed twice weekly. However, current observations from the PATCH trial suggest castrate levels of testosterone are typically achieved with a plasma oestradiol level ≥500pmol/L, and sites can opt to wait until oestradiol reaches this level before switching if they prefer.

If a participant's testosterone is >1.7nmol/L or the oestradiol level is <300pmol/L at four weeks then they should remain on the induction regimen for another 4 week period, with monitoring of testosterone and oestradiol samples taken at around the week 8 time point, the day before patches

are changed. Once the participant achieves a castrate level of testosterone ≤1.7nmol/L and an oestradiol level of ≥300pmol/L, they can be switched to the maintenance regimen.

It is expected that participants remain on the prescribed dose, and any potential dose modifications other than those indicated in **Section 6.2.5** should be first discussed with the CTU team.

6.2.5.D :: Administration guidelines

Consecutive patches should be applied to different sites. It is recommended that patches are placed on dry, intact and hairless skin and on areas where little wrinkling occurs, at the following sites only:

- Shoulder girdle
- Upper body
- Hip
- Abdomen
- Back
- Upper arms
- Buttocks

Patches should not be placed on or near the breast area, or on areas of the body where there are large amounts of subcutaneous fat, particularly around the abdomen, as this could affect absorption. Please note that these recommendations are mainly based on studies in women using the patches.

To apply the patch, remove the protective liner and press on to the skin immediately, holding for at least 30 seconds to ensure proper adhesion. If necessary, tape can be used to fix the patch in place. If applied correctly, the participant can bath or shower as normal; however, the patches might come off in very hot water or in a sauna.

Prior treatment start, participants should be provided with the STAMPEDE (Arm L) Study Hormone Patch Application Information for Participants to promote good treatment compliance.

6.2.5.E Transdermal oestradiol: Monitoring Hormone Levels

During enrolment of the first cohort of participants starting treatment with a combination of abiraterone, enzalutamide or apalutamide alongside transdermal oestradiol, the CTU will monitor the changing testosterone, oestradiol and PSA levels in real time. This is to ensure that the combination of treatment does not impact the efficacy of the transdermal oestradiol patches. **Therefore please send the updated hormone results log to the CTU urgently following any blood test in the first 3 months to facilitate this safety analysis.**

Oestradiol and testosterone levels should continue to be monitored throughout follow-up, while the participant remains on transdermal oestradiol treatment, to assess for evidence of compliance and to also ensure the participant is on the appropriate dose. **Table 2** describes when these values are required, noting also that the samples can be taken at the same time as scheduled PSA measurements.

Scenarios when additional oestradiol and testosterone monitoring is required are given below.

:: Oestradiol <300pmol/L or >2000pmol/L or testosterone >1.7nmol/L while on the maintenance regime

A repeat blood test should be carried out within 4 weeks if, at any time, the participant's oestradiol level is found to be <300pmol/L or >2000pmol/L or the testosterone level is >1.7nmol/L while on the maintenance regime, with particular attention paid to the day that the patches are changed

compared to when the blood sample is drawn (should be the day before changing patches). If the participant continues to have out of range oestradiol levels, and/or persistent testosterone >1.7nmol/L, then the CTU team should be contacted for advice.

:: Change of maintenance patch dose

If the maintenance patch dose is changed at any time (for example, reducing from 3 to 2 patches changed twice weekly), then additional oestradiol and testosterone tests are required around 4 weeks after dose modification.

:: Change of patch brand

The changing of patch brand should be avoided unless absolutely necessary (see **Section 6.2.5.A**) but if advised by the CTU trial team, then additional oestradiol, testosterone and PSA tests are required following the change (see **Table 26**). It is important that participants are then monitored in real-time during this initial period, with the CTU team to be contacted if the hormone results are out of range as it may be necessary to modify the dose regimen.

Table 26: Additional assessments required following change of maintenance patch dose or brand

ASSESSMENTS REQUIRED	WEEKS FROM DOSE MODIFICATION OR CHANGE IN PATCH BRAND*			
	WEEK 0 (PRIOR TO CHANGE)	WEEK 4 (POST CHANGE)	WEEK 8 (POST CHANGE)	WEEK 12 (POST CHANGE)
	Change of maintenance dose			
OESTRADIOL TESTOSTERONE PSA	X	X		
	Change of patch brand			
OESTRADIOL, TESTOSTERONE PSA	X	X	X	X**

* These additional tests are timed from the day of dose modification or day of starting new patch brand. However, if the post-change tests coincide within 1 week of scheduled tests (see **Table 2**), it is not necessary to repeat the tests.

** Dependent on prior results, 12 week test may be requested by CTU trial team

6.2.5.F Transdermal oestradiol: Cautions and contraindications

Tamoxifen should not be prescribed for participants receiving transdermal oestradiol.

6.2.5.G Transdermal oestradiol: Special warnings

If a participant has a cardiovascular event (see **Section 7.1.4.A**), discontinuation of treatment with transdermal oestradiol may be considered at the discretion of the treating clinician.

6.2.5.H Transdermal oestradiol: Interactions (medications)

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug metabolising enzymes, specifically CYP450 enzymes. However, with transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers. Oestradiol levels are already monitored as part of trial follow-up while participants are on transdermal oestradiol, therefore no additional monitoring is required when combining enzyme inducers with transdermal oestradiol.

6.2.5.I Transdermal oestradiol: Undesirable effects

Dermatitis can be a common side-effect of using the patches, especially in the induction period, which can usually be controlled by alternating the site of patch application. Participants should be advised that if patches become dislodged they should not put on extra patches, but apply their next set of patches when they are next due to be applied.

Prophylactic irradiation of the breast area, shown to reduce risk of gynaecomastia is permitted: a single fraction of 8Gy is recommended preferably before treatment with transdermal oestradiol (47).

6.3 CONCOMITANT TREATMENTS

All concomitant medications should be continued throughout the trial unless the responsible clinician decides otherwise, or there is a potential interaction with the trial treatment, in which case it is the responsibility of the responsible clinician to take the advised action. Please refer to each individual trial treatment section to see a list of drugs which may potentially interact.

6.3.1.A Data collection on concomitant treatments for participants in arms A, G, H, J, K, L

Long-term (>6 months) use of the following concomitant medications of classes of interest is collected:

- Statins
- Metformin (except as Arm K trial treatment)
- Aspirin
- Bisphosphonates or denosumab

This information is of interest both in terms of baseline use and ongoing use through the trial; as such it should be recorded on the Randomisation CRF and will be collected at each follow-up assessment (see **Table 1** and **Table 2**).

6.4 TRIAL PRODUCTS

Details of the procedures for obtaining the drugs within the trial, dispensing and disposal of unused drug are given in **STAMPEDE Pharmacy Information Sheet**. Arrangements for free or discounted drugs are given in the Finance section (**Section 15**).

6.5 TREATMENT DATA COLLECTION

Data will be recorded on case report forms (CRFs); the original should be sent to CTU for data entry and a copy kept at the local site. Current versions of all CRFs can be found on the trial website (http://www.stampedetrial.org/) and sites will be notified of any changes throughout the course of the trial. The type of data to be recorded is detailed in the Assessments and Procedures section (**Section 7**).

6.6 MEASURES OF COMPLIANCE/ADHERENCE

Date of treatment, dose, delays and reasons for delays or dose modifications of all trial treatments will be recorded. The estimated number of abiraterone tablets, enzalutamide capsules or metformin tablets taken in a given time period will also be recorded as well as any dose reductions. See **Table 28** for a description of the treatment logs.

Oestradiol levels will be collected for participants in the transdermal oestradiol arm and used to assess compliance to treatment (see **Section 6.2.5.C**).

Evidence of compliance with safety monitoring is required for participants on research abiraterone and research enzalutamide e.g. potassium and LFTs, or metformin treatment e.g. renal function, as described in sections **6.2.2.C**, **6.2.3.C**, and **6.2.4.C**. Site investigators should document in the participant's medical records the date of the blood test or review of blood pressure measurements and confirmation that the results were known to be within acceptable limits and if not, the toxicity should be graded according to CTCAE V4.0 and the action described. This should be available at on-site monitoring visits and used to verify the information provided on the follow-up CRF and treatment logs.

Note, safety monitoring for SOC abiraterone, enzalutamide and apalutamide is as per local practice and compliance data is not required by the trial.

7 ASSESSMENTS AND PROCEDURES

7.1 SCHEDULE FOR ASSESSMENTS

7.1.1 Follow-up Schedules

An individualised form with a follow-up schedule will be provided for each randomised participant. Which follow-up schedule applies depends on which comparison the participant was randomised to as summarised in Table 27.

Table 27: Summary of follow-up schedules by participant group

COMPARISON	PARTICIPANT DETAILS	FOLLOW-UP SCHEDULE
"Original"	Arms B, C, D, E, F and Arm A recruited between trial start (2005) and 15-Nov-2011	Active follow-up discontinued in Q3 2018
"Abiraterone"	Arms A and G randomised between 15-Nov-2011 and 17-Jan-2014	See **Table 1**
"Abiraterone and enzalutamide"	Arms A and J randomised between 29-Jul-2014 and 31-March 2016	See **Table 1**
"M1|RT"	Arms A and H randomised between 22-Jan-2013 and 02-Sep-2016	See **Table 1**
"Metformin"	Arms A and K randomised since 05-Sep-2016	See **Table 2**
"Transdermal oestradiol"	Arms A and L randomised since 20-Jun-2017	See **Table 2**

7.1.2 PSA, Testosterone And Oestradiol Measurements

All participants should have PSA measured prior to starting ADT and at every subsequent trial follow-up visit, regardless of allocated treatment arm. For participants who do not have a scheduled hospital visit, it is acceptable for arrangements to be made for blood samples to be drawn at their GP surgery.

For arm L participants, oestradiol and testosterone levels should continue to be monitored while the participant remains on transdermal oestradiol treatment. The first follow-up visit post-randomisation can be scheduled at 4 instead of 6 weeks to coincide with the 4-week hormone tests (see **Section 6.2.5**). These samples could be taken at the same time as the PSA tests, unless additional tests are required as detailed in **Section 6.2.5**. Blood samples should to be taken the day before the oestradiol patches are changed, to allow consistent measurements of testosterone and oestradiol with respect to the pharmacokinetic profile of the patches.

7.1.3 Assessment Of Treatment Failure (Definition Of Progression)

All participants should have baseline radiological examinations as detailed in **Section 4.2.1**. Participants are not routinely assessed for response. However, in order that objective progression can be assessed, it is recommended to have imaging taken at time of best response as judged by the treating clinician. The frequency of imaging is at the discretion of the treating clinician.

The following outcomes should be reported on the Progression log:

- Biochemical failure

- Local progression
- Lymph node progression
- Progression or development of new distant metastases, defined as lymph nodes outside the pelvis, bone or organ involvement
- Skeletal-related events confirmed as progression (see below)

7.1.3.A Biochemical Failure

For the purposes of the STAMPEDE trial, a unique threshold PSA value for biochemical failure is calculated, referred to as the **PSA progression value**.

This value is derived for each participant based on their **PSA nadir,** defined as the lowest PSA value reported between *randomisation* and 24 weeks on trial. Please refer to the PSA progression value calculator on the STAMPEDE website.

The exact method for deriving the progression value for a participant depends on the value of their PSA nadir, and how this compares to their pre-treatment PSA value (i.e. the extent of the fall in PSA from the starting point).

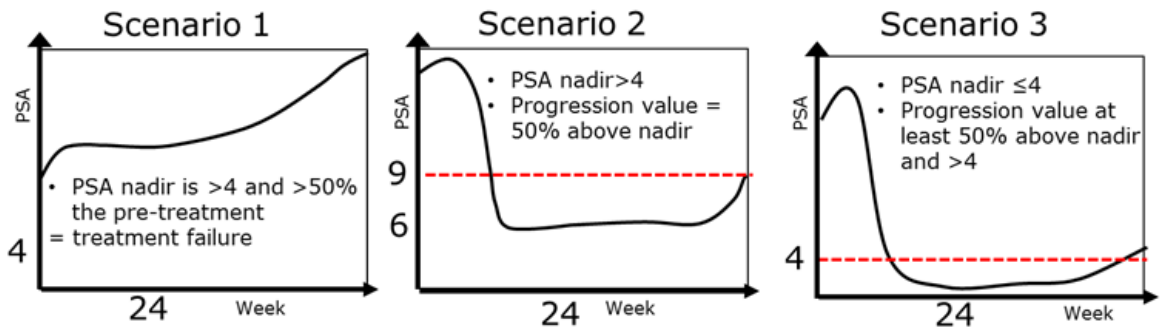
The PSA progression values are shown within **Figure 3**, they are calculated in one of three ways:

A. If the lowest recorded PSA value in the 24 weeks following randomisation is more than 4ng/ml and more than 50% of the pre-treatment PSA level then the participant fulfils the criteria for immediate treatment failure.

B. For participants whose PSA nadir in the 24 weeks following randomisation is less than or equal to 50% of the pre-treatment PSA level but remains above 4ng/ml, biochemical failure will be defined as a rise of 50% above the nadir level.

C. For participants whose PSA nadir is less than or equal to 4ng/ml, biochemical failure is defined as at least a 50% rise above the nadir value that is also above 4ng/ml.

Figure 3 PSA progression example scenarios



Confirming biochemical failure: the timing of assessments needs to be considered because spurious rises in PSA can occur e.g. following procedures involving the urinary tract. For this reason, any isolated rise in PSA should be confirmed before reporting biochemical failure.

In the case that the raised PSA value reaches the progression value, a confirmatory PSA test should be performed between one week and 3 months later. Biochemical failure is confirmed if the second value is around the same level or higher i.e. the trend is confirmed. The date of PSA progression

should be provided on the Progression Log as the date of the **first** raised PSA that fulfilled the trial definition of progression. Only the first instance of biochemical failure needs to be reported.

A confirmatory PSA is not required if there are other signs of progression e.g. progression of cancer related symptoms (clinical progression) or new radiological progression.

Second-line treatment commenced specifically for biochemical failure should not start until the trial definition for biochemical failure has been met. However, if second-line treatment does start before the trial definition is met then report the closest PSA value prior to the treatment start date as the progression value. This is not required if second-line treatment is being started for other signs of progression e.g. clinical or radiological.

Testosterone levels: are only required when reporting biochemical progression whilst receiving hormone treatment to confirm the diagnosis of castrate-resistant prostate cancer. Testosterone levels are not required when reporting biochemical progression in participants not receiving hormone therapy e.g. participants who presented with non-metastatic disease have relapsed following completion of treatment.

7.1.3.B Local, Lymph Node And Metastatic Failure

For each of local, lymph node and distant metastases progression, **both of** the following should be reported:

- Date of first clinical/symptomatic progression
- Date of first objective/radiological progression

7.1.3.C Skeletal-related Events

- Pathological Fracture
- Spinal cord compression
- Requirement for RT to bone (e.g. for pain or impending fracture)
- Requirement for surgery (e.g. for prevention or management of fracture)

SREs are a secondary outcome measure and a disease event of interest. SREs may represent disease progression but can also occur due to treatment-related effects e.g. osteoporotic fracture due to treatment-related bone-mineral density loss. All SREs should be recorded on the Follow-up form.

All SREs should be investigated further to establish whether or not the participant has progressed and, if confirmed as progression, a Progression Log should be completed to record this along with an Additional Treatment Log to give details of any treatment received (e.g. radiotherapy or surgical). The summary of timing of Case Report Forms can be viewed in **Table 28** and **Table 29**.

7.1.3.D Objective/Radiological progression

Investigator determined radiological progression should be reported. For specific comparisons it may be necessary to centrally review baseline and progression scans e.g. CT scans and bone scans. Requests for scans will be made if and when these are required for a proportion of relevant participants and processes put in place for electronic transfer and site reimbursement.

7.1.4 Additional Metabolic And Cardiovascular Outcomes

A number of metabolic and cardiovascular (CVS) outcomes are being assessed in the “metformin comparison” and “transdermal oestradiol comparison” as outlined below. From protocol v17.0 onwards, a metabolic profile (lipids, glucose and HbA1c) will be measured for all participants randomised from 05-Sep-2016 onwards to capture data on metabolic and cardiovascular outcomes for both comparisons. This is collected to improve the understanding of the metabolic impacts of

ADT, and in those participants on metformin, whether any of these effects are mitigated. As this is independent of progression, testing continues post progression. See **Table 2** for a schedule of assessments, please note it is permitted to obtain these measurements within 12 weeks of the scheduled follow-up visit. The summary of timing of Case Report Forms can be viewed in **Table 28** and **Table 29**.

7.1.4.A Cardiovascular Outcomes: Transdermal Oestradiol Comparison

Cardiovascular morbidity and mortality was the primary outcome measure for the first stage in the PATCH trial (completed in 2010), which showed similar rates of CVS events in participants receiving transdermal oestradiol compared to those receiving LHRHa injections (31). These results have been confirmed by longer-term data within the trial (see **Appendix I**). Continued monitoring of CVS outcomes will be undertaken by the PATCH IDMC for both the PATCH trial, as well as for the participants in STAMPEDE allocated to transdermal oestradiol together with their contemporaneous controls.

While Arm L participants are undergoing treatment with transdermal oestradiol, the majority of these CVS events will fall under the definitions of Serious Adverse Events (see **Section 11**). Once a participant has a cardiovascular event, the discontinuation of treatment with transdermal oestradiol may be considered at the discretion of the treating clinician and the participant switched to standard of care hormone therapy.

An increased risk of venous thromboembolism has been observed when docetaxel is used in combination with certain agents for the treatment of prostate cancer. Therefore, the rate of VTE and CVS events will be closely monitored among participants within Arm L who are receiving docetaxel as part of their first-line treatment. For more details see **Appendix I**. However, within the PATCH trial (based on data up to 17-Sep-2017), no cardiovascular endpoint events had been reported among participants on transdermal oestradiol receiving upfront docetaxel.

7.1.5 Additional Safety Assessments

The comparison specific follow-up schedules are summarised in **Table 1** and **Table 2.**
These summarise all the required additional safety assessments that are required whilst participants are receiving research treatments: abiraterone, enzalutamide, metformin and transdermal oestradiol. All safety assessments are required until research treatments have been permanently stopped for more than 30 days.

The summary of the timing of Case Report Forms also can be viewed in **Table 28** and **Table 29**.

7.1.5.A Additional Safety Assessment: Research Abiraterone with or without Enzalutamide

Due to the risk of liver toxicity and secondary hyperaldosteronism with abiraterone, all participants require regular monitoring of **potassium, liver function tests and blood pressure** whilst receiving research abiraterone with or without enzalutamide. Refer to **Section 6.2.2.C** for required frequency of monitoring. Participants from Arm J who remain on enzalutamide alone require regular monitoring of blood pressure. Refer to **Section 6.2.3.C** for required frequency of monitoring.

Confirmation that potassium and liver functions test have been performed regularly and blood pressure control reviewed will be required at each follow-up visit. Any abnormalities should be graded according to CTCAE version 4.03 and recorded on the toxicity section of the follow-up CRF; any abnormalities fulfilling the criteria for a SAE (e.g. requiring hospital admission) should also be reported on a SAE CRF (see **Section 11**).

Please note, the protocol guidance relates to research abiraterone i.e. treatment received by participants allocated to arms G and J. This may be used as a guide when using SOC abiraterone, but investigators should adhere to local practice.

7.1.5.B Additional Safety Assessment: Enzalutamide

Participants in Arm J who stop abiraterone but continue with enzalutamide require ongoing monitoring of **blood pressure every 3 months** whilst receiving research enzalutamide. Safety blood tests are not routinely required for patients who remain on enzalutamide alone but can be completed at the discretion of the treating clinician.

7.1.5.C Additional Safety Assessment: Metformin

Participants with normal and stable renal function receiving metformin require monitoring of **renal function (U&Es) every 6 months** whilst on treatment. More frequent monitoring is required in participants with declining renal function, or when initiating new potentially nephrotoxic medications or at times of intercurrent illness (see **Section 6.2.4.C**). Changes in renal function (eGFR, graded according to CTCAEv.4) are recorded on the Follow-up CRF. It is acceptable for blood sampling to be arranged via the GP at the participant's home or local hospital.

7.1.5.D Additional Safety Assessment: Transdermal Oestradiol

Hormone levels are monitored while participants are on transdermal oestradiol, and if oestradiol levels are found to be >2000pmol/L with confirmed repeat test, please contact CTU for advice (see **Section 6.2.5.B**).

Real-time monitoring of testosterone, oestradiol and PSA levels is required in the first cohort of participants starting treatment with a combination of abiraterone, enzalutamide, or apalutamide alongside transdermal oestradiol (see **Section 6.2.5.C**).

7.2 DATA COLLECTION PROCEDURES

Treatment-related data are collected on Treatment Specific Logs. It is important that **all** treatments given for progressive disease are recorded on the Additional Treatment Log. The summary of timing of Case Report Forms can be viewed in **Table 29.**

7.2.1 Data Collection For SOC Hormone Therapy

Information relating to SOC hormone therapy is recorded on the SOC Hormone Therapy Log, unless it is a treatment change for disease progression. The SOC Hormone Therapy Log should be updated with any changes in long-term hormone therapy e.g. if anti-androgens are being added to LHRHa for dual androgen blockade in the **absence of progression**. If however, anti-androgens are being added as an additional treatment for progressive disease, then this should be recorded on the Additional Treatment Log. Please note SOC hormone therapy refers to LHRHa, anti-androgens or orchidectomy.

If a participant allocated to receive transdermal oestradiol switches to receiving SOC Hormone Therapy i.e. LHRHa, in the **absence of progression**, then this information should be recorded on the SOC Hormone Therapy Log. However, any changes in hormone therapy initiated to treat disease progression should be recorded on the Additional Treatment Log e.g. switching from transdermal oestradiol to LHRH due to progressive disease.

7.2.2 Data Collection For SOC Systemic therapy: docetaxel, abiraterone, enzalutamide, or apalutamide

The decision to use docetaxel, abiraterone, enzalutamide or apalutamide as part of the standard-of-care (SOC) must be made before randomisation and should be recorded on the Randomisation CRF

to ensure the use of SOC agents is balanced between the control and research arms. The date of the starting systemic treatment should be recorded at the time of randomisation; this can be a planned date when randomisation occurs prior to systemic treatment commencing but should be within 12 weeks of starting hormone therapy (see **Section 6.1.3**). For participants allocated to arms A, K or L all further details should be recorded on the SOC Systemic Treatment CRF and this form sent to the CTU by the 24 week follow-up appointment. If a participant does not receive the planned systemic therapy, this must also be recorded on the SOC Systemic Treatment CRF, together with the reason why. For all participants who have started or planned to start SOC abiraterone, enzalutamide, or apalutamide, details relating to starting date of treatment, dose, and permanent stopping of SOC abiraterone, enzalutamide or apalutamide must be recorded on the SOC Systemic Treatment Log. If a participant does not receive the planned SOC treatment, this must also be recorded on the SOC Systemic Treatment CRF together with the reason why.

7.2.3 Data Collection And Non-Administration Of Standard Radiotherapy

The Radiotherapy Detail CRF should be completed for **all STAMPEDE participants** regardless of being planned for, or subsequently receiving, primary radiotherapy. Where radiotherapy is not reported as planned at randomisation, this form should still be received for confirmation it was not given. For participants where radiotherapy was reported as planned at randomisation but not given, a reason should be provided on the Radiotherapy Detail CRF for example, due to early metastatic progression or participant refusal, whether this is standard-of-care radiotherapy for participants (on any research arm) or research RT to the prostate for Arm H participants.

All radiotherapy and details should be recorded on the Radiotherapy Detail CRF upon completion of the RT schedule. We will now collect acute and late RT side-effects alongside other adverse events on the toxicity form.

7.2.4 Data Collection For Palliative Radiotherapy

Details of any radiotherapy given for progressive disease should be recorded on the Additional Treatment Log and if necessary (e.g. RT for bone pain) as a Skeletal related event (SRE) on the follow-up form.

7.2.5 Data Collection for Research (M1) Radiotherapy

Arm H only: all radiotherapy and acute side-effects details will be recorded on the Radiotherapy Detail and Radiotherapy Acute Toxicity CRFs upon completion of the RT schedule; any RT late side-effects should be recorded on the Follow-up CRF under the section for RTOG Toxicities.

In those cases where RT is not given (for example, due to early metastatic progression or participant refusal), this should be stated on the Radiotherapy Detail CRF together with the reason for non-administration of the treatment.

7.2.6 Data Collection for Additional Treatments Given for Disease Progression

All treatments given for disease progression are recorded on the Additional Treatment Log. Additional treatment should not be given in the absence of disease progression. This log should be updated with all subsequent changes to treatment. Only treatments for progressive disease need to be recorded; details of supportive treatments such as pain killers or bone-strengthening agents e.g. zoledronic acid, given to relieve symptoms, do not need to be provided.

In some scenarios, SOC hormone therapies such as LHRHa or anti-androgens may be given as a treatment for progressive disease. For example, LHRHa may be re-started on relapse for participants with M0 disease who discontinued hormone therapy and commenced surveillance. In addition,

participants allocated to trandermal oestradiol may switch to LHRHa on progression. Historically, some participants progressing on LHRHa will have commenced anti-androgens (dual androgen blockade) as a treatment for progression. In all cases, if treatment is being started for disease progression, treatment data are collected on the Additional Treatment Log and the details of the progression event recorded on the Progression Log.

Please note that any change in ADT which are solely a change in the participant's long-term hormone therapy, and not for disease progression, should be reported on the SOC Hormone Therapy Log only and **not** on the Additional Treatment Log.

7.3 FOLLOW-UP PROCEDURE

Every effort should be made to follow-up all participants who have been randomised up until formal closure of a comparison. Participants should, if possible, remain under the care of an oncologist or urologist for the duration of the trial. If care of a participant is returned to the GP, it is the responsibility of the responsible clinician who obtained the participant's consent to participate in the trial to ensure that all relevant data collection forms are completed. Nurse-led follow-up is permitted and should be conducted in line with local practice and procedures. This can also be performed by a suitably qualified individual who is delegated by the Principal Investigator.

If the participant moves away from the local area, arrangements should be made for trial follow-up to be undertaken by their new local site. Details of other participating site can be obtained from the STAMPEDE Trial Team. Information on participant transfer procedures is detailed in **Section 8.2.** If the responsible clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the site.

All efforts should be made to preserve the initial participant's consent for long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Public Health England.

Please see **Section 8** for more information on early stopping of follow-up.

7.3.1 Follow-up Telephone Consultations

In certain circumstances it may be appropriate to replace hospital visits with telephone consultations providing that it is still possible to collect all the necessary follow-up information. In these instances, it is acceptable to replace appointments with telephone consultations providing the required blood results and safety tests are available to the research team. All necessary information required to complete the Follow-up CRF is still required. All details on the telephone consultation must be recorded in the participants' notes as per in person assessments.

7.3.2 Follow-up Using Electronic Healthcare Records

All participants are asked to provide consent to enable the CTU to improve the reliability of long-term follow-up data through linking to other sources of electronic healthcare data. This may include hospital based record systems, NHS digital and national registers, such as the office of national statistics or data held by public health England or other sources which hold relevant information about treatment or outcomes. To ensure study data is updated with accurate data held by others the CTU will collect direct identifiers (participant name and NHS number) and securely store this data for this purpose only, and separately from the trial database. This information will be securely transferred and used to verify the data received by the CTU.

7.4 TRIAL & COMPARISON CLOSURE

For the purpose of complying with UK the clinical regulations (UK Medicines for Human Use Act [Clinical Trials]), each comparison will only be considered 'closed' when active follow-up has ceased. Active follow-up is defined as hospital-based or telephone assessments required to be able to complete the scheduled follow-up assessments. This will be reviewed separately for each comparison after the point of the primary analysis and, if appropriate, later, updated analyses. Longer-term outcome data beyond this time point may be sought through linkage with national registers where possible (and where adequate consent has been obtained) and/or via site research teams. The end of the STAMPEDE Trial is defined as 12 months after the most recent participant, randomised to the last remaining comparison, has completed follow up. Follow-up may include the use of registry data.

7.4.1 Comparisons for which Follow-up has Ceased

In Q3-2018, active follow-up stopped for all trial participants allocated to the research arms within the "original comparisons"; this is defined as all participants allocated to arms B, C, D, E, and F together with all participants allocated to arm A recruited before 15-Nov-2011.

Active follow-up will be stopped to participants in the "M1|RT comparison" (i.e. those recruited to Arm H and the contemporaneously randomised metastatic participants allocated to Arm A), except for those participants who are in the control arm of the "enzalutamide + abiraterone comparison". This follow-up will stop between Q4-2020 and Q1-2021 after sufficient data cleaning has been completed to allow reliable publication of long-term follow-up results. Targeted lists of all participants covered by this change will be disseminated to sites when the date is confirmed.

Active follow-up is defined as hospital-based or telephone assessments required to be able to complete the scheduled follow-up assessments. It should be noted that there may still be some data collection requested from sites to support ongoing sub-studies on closed comparisons. These requests may be for confirmation of health status or data already collected at sites e.g. baseline imaging data and FFPE tumour blocks.

For M1 participants on arm C and contemporaneous arm A, the PSA at baseline will be collected retrospectively where available. Further details regarding this data collection will be disseminated to the respective sites.

Given the above, any longer term analyses of data beyond comparison closure will be performed using observational data collected through national registers and NHS Digital or other datasets, providing such data are accessible.

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access). It is permissible to archive this information providing that it can be made accessible and available to the competent or equivalent authorities, the Sponsor, and other delegated authorities with suitable notice as the data may be subject to audit or inspection from any of the above. Information must be held for 25 years after the end of the trial as per **Section 13.1.**

Table 28: Summary of timing of case report forms (CRFs)

CASE REPORT FORMS	TIMING OF ASSESSMENT AND CRF
Baseline	
Eligibility Checklist	At Randomisation
Randomisation	At Randomisation
Saliva Pathology	At randomisation or any point on trial. When saliva sample has been taken and sent to Sponsor's designated laboratory.
Treatment	
SOC Hormone Therapy Log	To be completed for participants A-K, when treatment is first started and subsequently every time there is a change in SOC hormone therapy to report (including when Arm L participants switch to SOC HT pre-progression). To be sent in with the corresponding Follow-up CRF.
SOC Systemic Therapy CRF (replaces SOC docetaxel CRF which is no longer in use)	To be completed for all participants randomised to STAMPEDE: To be sent at 20 weeks after randomisation. A form is required for all participants to confirm which treatment received, including if no SOC systemic therapy received Re-send upon completion of SOC abiraterone, enzalutamide or apalutamide treatment
Abiraterone and Enzalutamide Treatment Log (research treatment)	To be completed for participants on arms G or J, when treatment is first started and subsequently every time there is a dose change, treatment pause and re-start. To be sent in with the corresponding Follow-up CRF.
Metformin Treatment	To be completed for participants on arm K, when treatment is first started and subsequently every time there is a dose change, treatment pause and re-start. To be sent in with the corresponding Follow-up CRF.
Transdermal Oestradiol Treatment Log	To be completed for participants on arm L, when treatment is first started and subsequently when reporting change in dose or type of patch. For the transdermal oestradiol arm, the 6-week follow-up form can be completed at the same time as the 4-week visit for the hormone tests (see **Section 6.2.5.B**)
RT Detail	To be completed for all participants randomised to STAMPEDE: • Upon completion of SOC RT • If planned RT is no longer planned (at 10 months after randomisation) • Arm H participants when research RT completed • Arm A participants with newly-diagnosed M1 disease at 3 months to confirm RT was not given
Blood Form	For arm J and contemporaneous A participants only. Taken at progression and end of first line treatment and pre-progression if participant has metastatic disease. Refer to the Sample Collection and Handling Manual for time points.
Metabolic sub study sample CRF	For arm K participants at selected sites recruited on protocol v21.0 that are participating in the metabolic sub study.

CASE REPORT FORMS	TIMING OF ASSESSMENT AND CRF
Assessments	
Follow-up	To be completed at every comparison specific follow-up until comparison closure (See **Table 1** and **Table 2** for comparison specific assessment schedules)
Toxicity	Required at each follow-up until 30 days after permanent stopping of protocol treatment (IMP).
Transdermal Oestradiol Treatment Hormone Results Log	To be completed whenever there are testosterone and oestradiol test results while arm L participants are on transdermal oestradiol. For the first cohort of participants starting treatment with a combination of abiraterone, enzalutamide, or apalutamide alongside transdermal oestradiol, please immediately send the log to the CTU following any blood test in the first 3 months of treatment (see **Section 6.2.5.C**).
End of Research Treatment	To be completed when (each) allocated research treatment is permanently stopped or in the event that allocated research treatment is never started (in each case a reason for stopping/never starting should be provided).
Progression Log	To be completed at the first occurrence of each progression event (PSA, local, nodal, distant metastases) and for each method of detection (clinical/symptomatic and objective/radiological). Skeletal-related events confirmed as progression should also be reported here.
Additional Treatment Log	To be completed each time a participant who has progressed starts or completes any additional treatment for progression.
Serious Adverse Event	To be completed following any Serious Adverse Event having confirmed none of the trial specific expedited reporting exemptions are met
Death	At Death
Administration	
Consent form	At Randomisation and when re-consenting following transfer procedure
Participant Transfer Confirmation Form	To be completed when a participant is transferred to a different hospital for the administration of trial treatment and follow-up
Tissue Sample Form	To be completed when sending tumour blocks to Sponsor's designated laboratory.
Co-enrolment	To be completed when a participant is co-enrolled in a post-progression interventional prostate cancer trial. Please see **Section 5.2** for more information.

Table 29: Schedule For Completion Of Treatment Forms For All Comparisons By Arm.

TIMING FROM RANDOMISATION			TREATMENT LOG[1]
YEARS	MONTHS	WEEKS	
6-Weekly			
0	-	6[2]	G, J, K, L
-	-	12	G, J, K, L
-	-	18	G, J, K, L
-	6	24	G, J, K, L
12-Weekly			
-	9	36	G, J, K, L
1	12	48	G, J, K, L
-	15	60	G, J, K, L
-	18	72	G, J, K, L
-	21	84	G, J, K, L
-	-	96	G, J, K, L
6-Monthly			
2	24	104	G, J, K, L
	30	130	G, J, K, L
3	36	156	G, J, K, L
	42	182	G, J, K, L
4	48	208	G, J, K, L
	54	234	G, J, K, L
5	60	260	G, J, K, L
Annual			
6	72	-	G, J, K, L
7	84	-	G, J, K, L
Etc.	-	-	G, J, K, L

Key:

G = SOC + abiraterone
J = SOC + enzalutamide + abiraterone
K = SOC + metformin ± RT ± SOC docetaxel/abiraterone/enzalutamide/apalutamide
L = Transdermal oestradiol ± RT ± SOC docetaxel/abiraterone/enzalutamide/apalutamide

[1] For participants in Arm L on transdermal oestradiol, the hormone tests results are to be reported on the Transdermal Oestradiol Treatment Hormone Results Log

[2] For the transdermal oestradiol arm, the 6-week follow-up form can be completed at the same time as the 4-week visit for the hormone tests (see **Section 6.2.5.B**)

8 STOPPING OF TREATMENT OR FOLLOW-UP

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

8.1 STOPPING RESEARCH INTERVENTIONS

A participant may stop **any STAMPEDE research treatment** for the following reasons:

- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Participant refusal
- Any alteration in the participant's condition which justifies the discontinuation of treatment in the clinician's opinion

In all cases, the reason for permanent stopping of research treatment should be recorded on the End of Research Treatment CRF.

In the event of stopping research treatment, unless a participant states otherwise, consent is assumed for continued recording of trial data.

8.1.1 Stopping Research Treatment: Abiraterone, Enzalutamide + Abiraterone

For **participants randomised to Arm G or J**, research treatment should also be discontinued for the following reasons:

- Disease progression whilst on therapy. As detailed in **Section 7.1.3**, the disease event for stopping treatment may be after the first reportable Failure-Free Survival event. Treatment must be stopped once all three types (biochemical, radiological and clinical) of progression have occurred.
- Intention to commence a new systemic anti-cancer treatment due to evidence of relapse

Trial abiraterone must stop if other systemic treatments are initiated at any time for disease progression control (including chemotherapy, radium-223 etc). Anti-androgens (e.g. bicalutamide) should not be given in combination with abiraterone or enzalutamide due to the risk of toxicity. However, participants may continue on abiraterone or abiraterone and enzalutamide if they receive radiotherapy on a single occasion for a skeletal-related event. Sites must contact the STAMPEDE trial team for further guidance as appropriate.

8.1.2 Stopping Research Treatment: Metformin

For **participants** randomised to Arm K, treatment duration is detailed in **Table 9**.
Please note that in contrast to other treatments tested in STAMPEDE metformin does **not** need to be stopped following progression. Metformin treatment should aim to **continue post-progression** whilst participants continue to receive ADT.

Reasons for early stopping of metformin include:

- Decline in renal function (metformin must be stopped if GFR ≤30ml/min/1.73m^2, see **Section 6.2.4.C**)
- Decline in performance status (WHO PS >2)
- Unacceptable toxicity
- Participant refusal

- Intercurrent illness preventing continued metformin treatment
- Investigator decision e.g. administration of IMP within a CTIMP in CRPC setting

If treatment is paused for >3 months or >50% of doses are missed for any reason, it is at the discretion of site investigators as to whether it is appropriate to restart trial treatment with metformin. Contact the CTU for any advice if required.

8.1.3 Stopping Research Treatment: Transdermal Oestradiol

For **participants randomised to Arm L**, treatment with transdermal oestradiol may be discontinued for the following main reasons:

- Unacceptable toxicity
- Participant refusal
- Intercurrent illness
- Investigator decision
- Cardiovascular event (see **Section 7.1.4.A**)

For participants who stop transdermal oestradiol patches due to unacceptable toxicity or intercurrent illness, site investigators can consider changing treatment to LHRHa or allowing a break from hormone therapy. On re-initiation of hormone therapy, the investigator can choose whether it is in the participant's best interests to recommence transdermal oestradiol patches or LHRHa.

If transdermal oestradiol patches are chosen to restart, it is important to recommence with the loading regimen (See **Section 6.2.5.B**) and monitor oestradiol and testosterone levels closely. The process outlined for monitoring hormone levels and titrating doses at randomisation should be used when restarting transdermal oestradiol patches in order to ensure the correct dose is achieved.

In addition, if there is evidence of disease progression, subsequent therapy is at the discretion of the treating clinician with references to any relevant guidelines (see **Table 10**).

8.2 BREAKS IN SOC ADT

The SWOG trial (48) comparing intermittent versus continuous ADT in hormone sensitive metastatic prostate cancer did not find evidence to support that intermittent therapy was non-inferior for overall survival (hazard ratio for death with intermittent therapy 1.10; 90% confidence interval 0.99 to 1.23). Thus, STAMPEDE does not support intermittent androgen therapy as an appropriate upfront treatment approach.

Some participants will experience toxicity or report their QL is adversely impacted by ADT. In these instances we would recommend trying to ameliorate any symptoms with appropriate lifestyle or medical interventions, as per local or national guidelines. Please check that any treatment for symptoms will not interact with the trial treatment.

However, if the participant continues to struggle with ADT, treatment breaks can be considered, although this may impact the trial treatment as well – see below.

Participants who require breaks in SOC ADT due to unacceptable toxicity or an intercurrent illness can restart ADT as long as the investigators deems it is safe to do so, and as long as it remains in the participant's best interests.

All treatment stop and start dates must be recorded, with the reason for the break, on the hormone therapy and trial treatment logs so they can be considered during any data analyses.

8.2.1.A Impact on trial treatment if participant has a break in SOC ADT

Abiraterone:
Participants allocated to receive abiraterone as part of Arm G cannot continue their trial treatment whilst SOC ADT is stopped.

Abiraterone in combination with Enzalutamide, or either treatment alone:
Participants allocated to receive abiraterone with enzalutamide, or remain on either agent as monotherapy, as part of Arm J cannot continue their trial treatment whilst SOC ADT is stopped.

Metformin:
Participants allocated to receive metformin as part of Arm K should continue metformin as per the proposed treatment length at randomisation after stopping SOC ADT. This is as long as it remains in their best interests as assessed by the local clinician. See **Table 9** for specific instructions about the proposed length of metformin treatment for participants who receive radical treatment versus those who do not.

Transdermal Oestradiol:
Transdermal oestradiol patches replace SOC ADT treatment. Please see transdermal oestradiol section **8.1.3** for further details about breaks or stopping trial transdermal oestradiol patch treatment.

8.3 PARTICIPANT TRANSFERS

For participants moving away from the area and planning to transfer care, every effort should be made for the participant to be followed-up at another trial site. The participant will need to sign a new consent form at the new trial site. Once this has been done, the new trial site will take over responsibility for their ongoing participation in the trial.

To document the transfer process the main contact person at both the current and receiving hospitals should complete and sign the Patient Transfer Confirmation form. A fully completed form must be returned to the CTU prior to the participant transfer and any outstanding data queries for the participant should be completed prior to transfer.

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

- Consent form
- Completed CRFs
- Any documentation relating to the participant's participation in STAMPEDE (participant names must be removed from any documentation).

8.4 EARLY CESSATION OF TRIAL PARTICIPATION

If a participant explicitly withdraws consent to have any further trial data recorded, their decision must be respected and the CTU must be informed in writing in the form of a letter, a template is available upon request. All communication surrounding the early cessation of trial participation should be noted in the participant's records. Please note, data for the participant prior to this decision will still be required.

In the majority of cases, participants continue to give permission for their data and information on their health to continue to be collected via clinical notes and national registries. Any information on the follow-up status, however minimal, would be helpful. Investigators are encouraged to facilitate ongoing collection of follow-up data for example, through considering telephone consultations (see **Section 7.3.1**).

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

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

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Participants will be randomised centrally using a computerised algorithm developed and maintained by CTU. Randomisation will be performed using the method of minimisation over a number of clinically important stratification factors with an additional random element. To decrease determinability, the factors are not listed here but can be found in the Statistical Analysis Plan.

Participants will be randomised between arms as follows:

- All participants who fulfil both comparison-specific eligibility criteria for metformin and transdermal oestradiol will be allocated between A:K:L.
- All participants ineligible for metformin, but eligible for transdermal oestradiol, will be allocated between A:L
- All participants ineligible for transdermal oestradiol, but eligible for metformin, will be allocated between A:K.

See **Appendix H** for the allocation weighting of each arm by previous protocol version; this also shows allocation weighting for research arms previously closed to recruitment.

9.2 OUTCOME MEASURES

The definitive primary outcome measure for each comparison in the trial is overall survival (all-cause mortality), unless otherwise stated. The design of the trial is such that it is important to have additional intermediate primary outcome measures to assess activity in each research arm as the trial progresses.

For comparisons involving research arms B to J the intermediate primary outcome measure is failure-free survival (FFS); this and other outcome measures are listed in **Table 30.** Note that this reflects the original analysis plan for research arm J.

Table 30: Trial Outcome Measures by Comparison Stage (Arms B-J)

COMPARISON STAGE	PRIMARY OUTCOME MEASURE	SECONDARY OUTCOME MEASURES
Pilot phase	Safety*	Feasibility
Activity Stages (AS)	Failure-free survival (FFS)†	Overall survival (OS) Toxicity Symptomatic skeletal events (SSE)
Efficacy Stage (ES)	Overall survival Metastatic progression- free-survival (mPFS) – Arm J M0	Quality-of-life Cost effectiveness Failure-free survival† Toxicity Symptomatic skeletal events (SSE)

*Based on toxicity
†Including biochemical failure (see Section 7.1.3)

For the “enzalutamide + abiraterone comparison” the original plans for the final Efficacy Stage analysis were updated in late 2019, after the earlier analysis stages had been completed. The updated efficacy stage analysis will use metastatic progression-free-survival (mPFS) as the definitive primary outcome measure for participants with baseline M0 disease, and overall survival as the primary outcome measure for participants with baseline M1 disease.

For the “metformin comparison” the intermediate and definitive primary outcome measure are the same, being overall survival; see **Table 33** for full details of all outcome measures for that comparison.

For the “transdermal oestradiol comparison”, overall survival and progression-free survival are the definitive co-primary outcome measures, and the intermediate primary outcome measure is progression-free survival (PFS); see **Table 35**. The rationale for choosing progression-free survival rather than failure-free survival as the outcome measure for this comparison is outlined in **Section 9.7.3**.

The reasons for different emphases in each recruitment stage are explained in **Section 9.3**.

9.3 SAMPLE SIZE: PRINCIPLES

The design is a multi-arm multi-stage, multi-centre, platform, randomised controlled trial. There are a number of stages for each research arm: a Pilot/Feasibility/Safety Phase, Activity Stages and a final Efficacy Stage. Full details of the methodology underlying the trial design are given by Royston et al. (49, 50) The original sample size calculations were performed using the stage2 (version 1.2.0, Mar-2002) and stagen (version 1.1.1, May-2004) programs, both implemented in Stata (Stata Corp, TX) and updated using the later nstage program (version 1.0.3, Jun-2007; version 2.1.0, Jun-2009; version 3.0.1, Sep-2014). (51)

Other than transdermal oestradiol, we have adequately powered each comparison to detect an appropriate improvement in overall survival at the final Efficacy Stage, with high power at each of the planned interim Activity Stages to detect a pre-defined target difference in the intermediate primary outcome. For example, in a cohort with 2 years median FFS and 4 years median overall survival (OS) a target HR of 0.75 for research arm relative to control would translate into an absolute improvement in FFS of 10%, from approximately 50% to 60% at two years, and in OS of 10%, from approximately 50% to 60%, at four years.

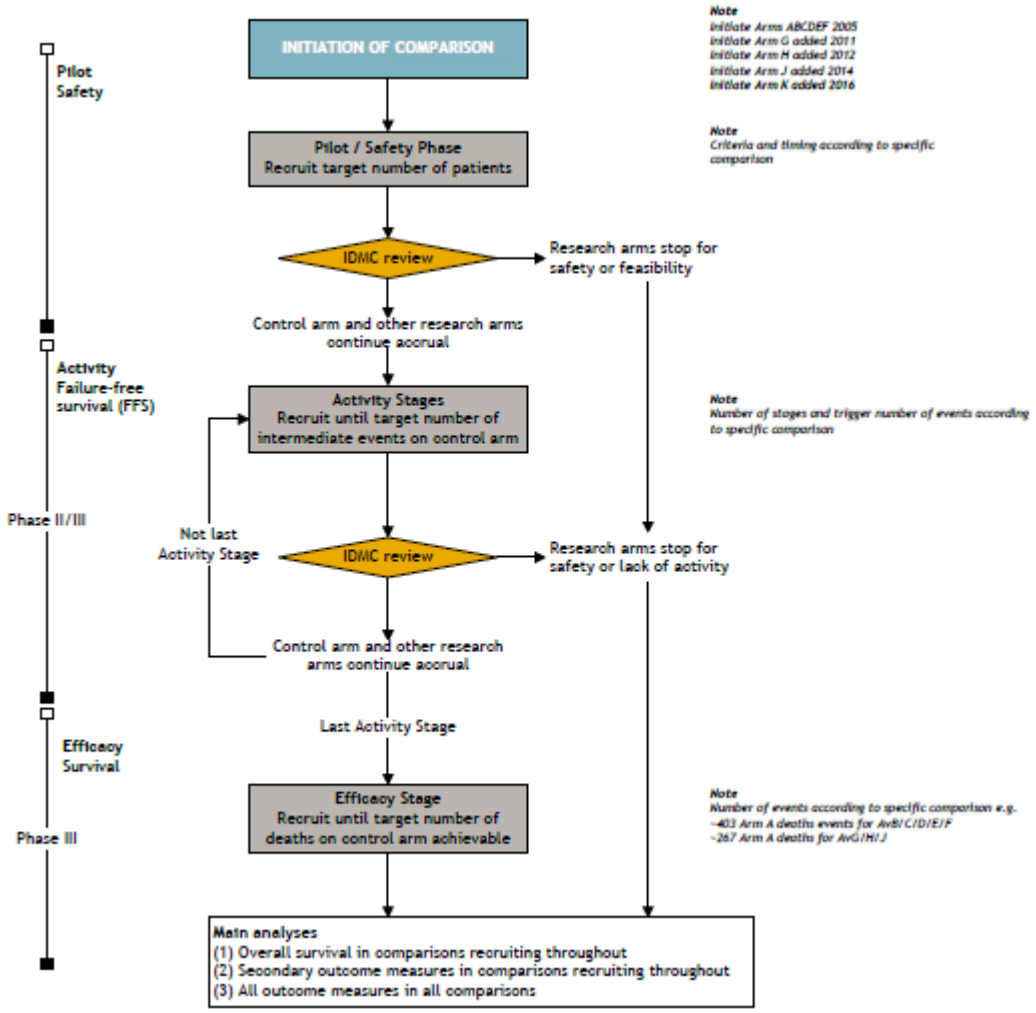
The “transdermal oestradiol comparison” is powered only for contributing to a meta-analysis of participants from the STAMPEDE “transdermal oestradiol comparison” and the PATCH trial. It will assess non-inferiority of transdermal oestradiol in terms of overall and progression-free survival which are co-primary outcome measures. For details of the sample size calculations, planned analyses and corresponding operating characteristics, see version 10 of the PATCH protocol.

As each comparison is powered to detect a relative difference in survival, the analyses will be performed when the pre-planned number of events has been reported in the control arm, rather than after a certain number of participants have been recruited to the comparison or a certain amount of time has elapsed. Further details of the sample size calculations and varying assumptions for each research comparison are summarised in the relevant **Sections 9.4-9.8** and detailed in a separate Statistical Design Document which is available on request.

As with all trials, changes in both the standard-of-care and second-line therapies over time are possible which improve outcomes and thus will affect the observed control arm event rates and

associated reporting timelines. In particular, from protocol v8.0, standard-of-care RT was mandated for all participants with N0 M0 disease and no RT contraindication (this is likely to improve outcomes for this subgroup) and standard-of-care docetaxel permitted from protocol v14.0. Further agents are starting to be licensed for participants with castrate-refractory disease which may also improve survival rates. Improved FFS rates would delay the intermediate analyses, for comparisons where FFS is the intermediate primary outcome measure; while improved OS would delay the definitive analyses. Similarly, improved PFS rates could delay both the time of intermediate and definitive analysis for the "transdermal oestradiol comparison". For each comparison event rates are estimated based on data which are publicly available at the time of design. The Statistical Design Document for arms A-K includes models where median survival is varied around such estimated rates.

Figure 4: Schema of progress of STAMPEDE through the trial*



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

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

* Except for the "transdermal oestradiol comparison"

9.4 SAMPLE SIZE ISSUES & TRIAL STAGES: ADDITIONAL RESEARCH ARM H

This is the "M1|RT comparison" and includes participants allocated to research Arm H (SOC+RT) and newly-diagnosed M1 participants with no contraindication to RT allocated to the control Arm A whilst Arm H was open to recruitment. Suitability for allocation to the comparison was assessed before randomisation to ensure comparability with contemporaneous control arm participants.

Table 31: Guidelines for stopping accrual to additional research Arm H

ACTIVITY STAGE	SIG LEVEL	POWER	TARGETED HR	NUMBER OF CONTROL ARM EVENTS	CONSIDER DISCONTINUATION IF (HROBSERVED) IS…
I	0.50	95%	0.75	~75	>1.00
II	0.25	95%	0.75	~142	>0.92
III	0.10	95%	0.75	~221	>0.89

9.4.1 Pilot Phase: Additional Research Arm H

The IDMC reviewed safety data, in the context of data from the control arm, when the first 30 participants allocated to Arm H had been on trial for around six months.

9.4.2 Activity Stages I-III: Additional Research Arm H

The same principles were applied to this new comparison as to previous comparisons and an equal allocation ratio of control arm participants to participants allocated to Arm H was employed, as for Arm G. The number of control arm events required to trigger the intermediate analyses are the same as for the "abiraterone comparison" (see **Table 31**).

9.4.3 Efficacy Stage IV: Additional Research Arm H

The analysis of Efficacy Stage IV for this comparison was planned for when ~267 deaths had been observed in the relevant control arm participants. This was to give 90% power to detect the targeted hazard ratio of 0.75 at one-sided significance level of 0.025.

9.4.4 Sample Size For Additional Research Arm H

Consideration was given to ceasing further randomisations to Arm H if it was not showing sufficient evidence of activity on the intermediate primary outcome measure (FFS), as for the other research arms. This research comparison is relevant to around 60% of participants joining STAMPEDE. At the point of the scientific approval, accrual was averaging around 80 participants per month to the trial; therefore, up to approximately 48 participants a month would be eligible for the comparison. If accrual to the trial was slower at 70 participants per month, then accrual to this comparison could be between 18 and 42 participants per month, depending on which other trial arms are open to recruitment at the time.

We were targeting a 25% relative improvement in overall survival following local radiotherapy to the prostate in this participant group. This is the same size of effect targeted with the other research arms in STAMPEDE. This relative improvement can be further justified in the light of MRC PR07 which demonstrated an improvement of this magnitude for adding radiotherapy to ADT in locally-advanced disease, with a hazard ratio for overall survival of 0.77 (95% CI 0.61 to 0.98). In that trial, fewer than half of the deaths were from prostate cancer, whereas in newly-diagnosed metastatic participants nearly all people will die of their disease. Therefore, it is relevant to note the relative benefit of radiotherapy in PR07 in terms of prostate cancer-specific survival, where the hazard ratio was 0.46 (95% CI 0.34 to 0.61) after a median follow-up time of 8 years (52).

We anticipated that around 1250 participants were required over 4 years to observe 267 control arm deaths after 5.25 years. This assumed that (i) recruitment was constantly 70 pts/m to the trial overall; (ii) the original research arms stopped accrual within 6 months after activation of the RT arm; (iii) the abiraterone arm stopped accrual around 24 months after activation of the RT arm; and (iv) a further new research arm with an equal allocation ratio was introduced 18 months after activation of the RT arm. In Protocol version 13.0, we reflected on these four points: (i) recruitment to the trial has been faster; (ii) the original research arms completed accrual 2 months after activation of the RT arm; (iii) the abiraterone arm stopped accrual 12 months after activation of the RT arm; and (iv) Arm J was activated 18 months after activation of the RT arm, Arm H.

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

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

All sample scenarios are documented in the Trial Master File.

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

For the control arm of the whole trial, we constructed sample size scenarios based on median failure-free survival being 18, 24 or 30 months; the event rate would depend on the participant mix. We now know that around 60% of participants have M1 disease at trial entry and we have reported that FFS at 24 months is 51% across the whole of the control arm participant sample.(53)

For the updated sample size calculation for the "M1|RT comparison", we based our estimates on the subgroup of participants with newly-diagnosed M1 disease in the control arm. Therefore, we

estimated median FFS for control arm participants in this comparison to be 1 year and estimated that median overall survival would be around 3.5 years.

9.5 SAMPLE SIZE ISSUES & TRIAL STAGES: ADDITIONAL RESEARCH ARM J

This is the "enzalutamide + abiraterone comparison" and includes participants allocated to research Arm J (SOC + enzalutamide + abiraterone) and participants contemporaneously allocated to the control Arm A.

Note that as of Protocol version 20.0 the details of the Efficacy Stage analysis for the "enzalutamide + abiraterone comparison" have changed to reflect separate analyses for non-metastatic (M0) and metastatic (M1) participants and a broadening of the therapeutic intervention being tested. See below for further information.

9.5.1 Pilot Phase: Additional Research Arm J

The IDMC first reviewed safety data for this combination when the first 50 participants allocated to Arm J had been on trial around 6 weeks (i.e. to the first follow-up visit).

Furthermore, an additional review of safety was performed when these 50 Arm J participants had been on trial for around 6 months. Safety is routinely reviewed at regular intervals and additional safety reviews will be performed if the IDMC raises any concerns.

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

9.5.2 Activity Stages I-II: Additional Research Arm J

The principles of intermediate analyses were applied to this new comparison as to previous comparisons, but some of the details were different, and an equal allocation ratio of control arm participants to participants allocated to Arm J was employed; as for Arms G and H. Owing to the expected accrual rate to the trial (>100 pts/m), the expected slower event rate in all participants given improvements to SOC and specifically in participants randomised to this comparison. Given the simultaneous recruitment of M1 (but not M0) participants to the "M1|RT comparison", only two activity stages were planned before accrual completed. These are set out in **Table 32**.

The IDMC intermediate activity stage reviews were completed in Nov-2015 and Mar-2016 for Arm J and recommended continuation of the comparison.

Table 32: Guidelines for stopping accrual to the additional research Arm J

ACTIVITY STAGE	SIG LEVEL	POWER	TARGETED HR	NUMBER OF CONTROL ARM EVENTS	CONSIDER DISCONTINUATION IF (HROBSERVED) IS…
I	0.40	95%	0.70	~66	>0.957
II	0.12	95%	0.70	~139	>0.869

9.5.3 Efficacy Stage III: Additional Research Arm J

The analysis of the final Efficacy Stage for this comparison was originally planned to be performed when around 267 deaths had been observed in the control arm. This would give 90% power to detect the targeted hazard ratio of 0.75 at a one-sided significance level of 0.025.

In late 2019 the plans for the Efficacy Stage III analysis of the "enzalutamide + abiraterone comparison" were updated. See section 9.5.5 for further details.

9.5.4 Sample Size For Additional Research Arm J

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

The participant mix for this comparison is likely to represent a more favourable prognosis on average than in the original comparisons, due to concurrent recruitment of M1 but not M0 participants, to Arm H.

We anticipated that around 1,800 participants were required within 3.5 years to observe ~267 control arm deaths within 6 years. The default scenario assumes that (i) recruitment is constantly 70pts/m to the trial overall, (ii) Arm H (M1|RT) accrues throughout and (iii) a further new research arm with an equal allocation ratio is introduced 18 months after activation of Arm J. The stopping date for Arm G is no longer an assumption.

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

Updating the standard-of-care to include docetaxel has minimal impact on the projected time to maturity of the "enzalutamide + abiraterone comparison".

9.5.5 Update to Efficacy Stage Analysis For Additional Research Arm J

In Protocol version 20.0 the planned Efficacy Stage analysis of the "enzalutamide + abiraterone comparison" was updated. This followed the larger-than-expected improvement in overall survival seen in the primary analysis of the "abiraterone comparison"; evidence from other trials combining enzalutamide with abiraterone did not result in further efficacy gains; and continued divergence in the aims of first-line therapy for patients with baseline metastatic and non-metastatic disease since the comparison was conceived.

In late 2019, the STAMPEDE TMG and TSC approved an updated analysis plan designed to test the impact of the addition of the more broadly-defined therapeutic intervention of androgen receptor (AR)-targeted therapy on patient outcomes, compared to SOC treatment alone. Patients from the "abiraterone comparison" (A vs G) and the "enzalutamide + abiraterone comparison" (A vs J) will be included in a combined analysis comparing the addition of AR-targeted therapy (abiraterone or the combination of enzalutamide and abiraterone) to SOC with SOC alone. Those with baseline M0 disease at entry to the study will be analysed separately to those with baseline M1 disease.

<u>Non-metastatic (M0) patients</u>
The Efficacy Stage analysis for these patients will test whether adjuvant AR-targeted therapy improves survival compared to SOC alone, using the primary outcome of metastatic progression-free-survival (mPFS).

A total of 1,982 patients with M0 disease were randomised to arms G or J or contemporaneously to the control arm. We plan to perform the Efficacy Stage analysis when a total of 315 mPFS events have been observed in the control arm patients for this sub-group. This will provide 90% power to

confirm a treatment effect equivalent to a HR of 0.75 for AR-targeted therapy, at the 1.25% one-sided significance level, based on an assumption of 70% survival in the control arm at 66 months.

Metastatic (M1) patients
The Efficacy Stage analysis for these patients will validate whether a new biomarker that includes lobular vs basal transcriptomic sub-classification (PAM50) is predictive of differential response to adjuvant AR-targeted therapy. Prior to the data freeze for the analysis, as many M1 patients as possible will be classified into one of two subgroups, biomarker positive (luminal B) and biomarker negative (basal), based on the results of the biomarker assay. The primary outcome measure will be overall survival.

A total of 1,916 patients with M1 disease were randomised to arms G or J or contemporaneously to the control arm. The timing and power for the planned analysis will depend on the proportion of these patients who are successfully classified using the biomarker assay. For example, if 50% of patients are classified, we expect to have 80% power to confirm an interaction between allocation to adjuvant AR-targeted therapy and biomarker classification at the two-sided 5% significance level if the analysis is performed in the spring of 2022, based on a minimum follow-up duration of 70 months. This assumes that 40% of patients will be classified as 'positive' and the remaining 60% as 'negative', with an anticipated treatment effect equivalent to a HR of 0.85 for AR-targeted therapy in the 'positive' group and a treatment effect HR of 0.45 for patients in the 'negative' biomarker group, equivalent to a hazard ratio ratio (HRR) of 1.9.

Further details of the calculations and assumptions underpinning the Efficacy Stage analysis planned for both subgroups can be found in the SAP for the "enzaluatmide + abiraterone comparison".

9.6 SAMPLE SIZE ISSUES & TRIAL STAGES: ADDITIONAL RESEARCH ARM K

This is the "metformin comparison" and includes participants allocated to research Arm K (SOC + metformin) and the equivalent non-diabetic participants with no contraindication to metformin contemporaneously allocated to the control Arm A whilst Arm K is open to recruitment. Suitability for allocation to the comparison is assessed before randomisation to ensure comparability with contemporaneous control arm participants

9.6.1 Implementation: Additional Research Arm K

The implementation of the MAMS principles are different in this comparison for the following reasons:

- Although all non-diabetic participants will be eligible for allocation to the "metformin comparison", the timing of the analyses will be driven only by the M1 participants. (See **Section 9.6.4** for discussion of the implications for power overall and in M0/M1 subgroup analyses.)

- Failure-free survival will not be used as the intermediate primary outcome measure; overall survival will be used as both the intermediate and definitive primary outcome measure. This is because we are not convinced that any comment on metformin's usefulness should be determined from an ability to act on a PSA-driven outcome measure. Furthermore, treatment with metformin is intended to continue throughout long-term hormone therapy which may include going well beyond an FFS event, particularly in M1 participants.

- The target HR is 0.80 for overall survival (a 20% relative improvement). This is a smaller relative improvement in survival than targeted for previous comparisons because of metformin's known low toxicity profile, the low cost of the drug and the potential positive

effects on metabolic parameters and morbidity; a smaller impact on overall survival may still have clinical benefit.

9.6.2 Outcome Measures: Additional Research Arm K

Table 33 lists the outcome measures for this comparison and can be compared with the outcome measures for the other comparisons in Table 30.

Table 33: Trial outcome measures by stage for the "metformin comparison"

COMPARISON STAGE	PRIMARY OUTCOME MEASURES	SECONDARY OUTCOME MEASURES
Pilot phase	Safety*	Feasibility Metabolic effects§ Cardiovascular event: major adverse cardiac events‡
Activity Stage (AS) I	Overall survival	Failure-free survival† (FFS) Symptomatic skeletal events (SSE) Toxicity Metabolic effects § Cardiovascular event: major adverse cardiac events‡
Efficacy Stage (ES) II	Overall survival	Metastatic progression-free survival (M0 participants) Progression free survival (M1 participants) Toxicity Symptomatic skeletal events (SSE) Failure-free survival† (FFS) Metabolic effects § Quality-of-life Cost effectiveness Correlative outcomes ~~A~~ Cardiovascular event: major adverse cardiac events‡

*Based on toxicity
§Including changes in: BMI; Haemoglobin A1c (HbA1c); waist circumference and a new diagnosis of diabetes mellitus
‡MACE; nonfatal MI, nonfatal stroke, & death from CVS causes
†Including biochemical failure (see Section 6.1.2 and Appendix J)
~~A~~Plasma lipid and fasting triglyceride levels, fasting plasma glucose
Sarcopenia and/or radiological progression free survival (rPFS)
Plasma insulin
AMP Kinase

Note: All arms are unblinded so primary outcome measures for this comparison are objectively measured with caution to be taken around interpretation of more subjective secondary outcome measures such as symptomatic skeletal events

9.6.3 Pilot Phase: Additional Research Arm K

The IDMC reviewed safety data for this comparison when the first 50 participants allocated to Arm K had been on trial around 12 months. Furthermore, analyses were conducted on metabolic parameters (see **Table 33**). If there was harm observed in metabolic effects, or any serious concerns regarding the toxicity profile, recruitment would be stopped; there were no formal criteria to guide this.

Safety is routinely reviewed at regular intervals and additional safety reviews will be performed if the IDMC raises any concerns.

9.6.4 Activity Stage I: Additional Research Arm K

The principles of intermediate analyses will be applied to this new comparison as to previous comparisons, but some of the details will be different, and an equal allocation ratio of control arm participants to participants allocated to Arm K is employed; as for Arms G, H and J. Owing to the expected accrual rate to the trial overall (>100 pts/m) and the interim primary outcome being overall survival, only one intermediate activity stage is planned before accrual is completed; this is set out in **Table 34**.

Although analyses are triggered by events in M1 participants, they will include all participants in the "metformin comparison"; this will have high power. A separate subgroup analysis in M1 participants (conventionally-powered) and M0 participants (limited power) will then look at consistency of effect; few deaths in M0 participants are expected at this time. The IDMC recommendation will be based on the totality of the available data, including safety, metabolic and compliance data.

The IDMC reviewed the intermediate activity stage data for Arm K in May 2020 and recommended continuation of the comparison.

Table 34: Guidelines for stopping accrual to the additional research Arm K

ACTIVITY STAGE	SIG LEVEL	POWER	TARGETED HR	NUMBER OF CONTROL ARM EVENTS	CONSIDER DISCONTINUATION IF HR_K (OBSERVED) IS…
I	0.40	92%	0.80	~121 M1 deaths	>0.965

9.6.5 Efficacy Stage II: Additional Research Arm K

The analysis of the final Efficacy Stage for this comparison will be performed when around 473 deaths have been observed for M1 participants randomised contemporaneously to the control arm. This would give 92% power to detect the targeted hazard ratio of 0.80 at a one-sided significance level of 0.025 at the final Efficacy Stage, and 86% pairwise power overall.

As with the intermediate activity, this analysis will include all participants in the comparison, with a separate subgroup analysis in M1 and M0 participants looking at consistency of effect. At this time point we predict approximately 100 control arm M0 deaths will be observed. Further subgroup analyses, defined by the stratification factors, are planned to check for consistency of effect at intermediate and final analyses. Due to this comparison being powered for overall survival in M1 patients, the relatively high OS for M0 patients means that anaysis of OS in this subgroup will not have high power. As such, an additional outcome measure of metastasis-free survival will be analysed as part of the subgroup analysis.

9.6.6 Sample Size For Additional Research Arm K

Consideration would be given to ceasing further randomisations to Arm K if it did not show sufficient evidence of improvement on overall survival at the intermediate analysis.

We anticipate that around 2,800 participants, including around 1,700 M1 participants, are required over 3 years to observe ~473 control arm M1 deaths over around 7 years. (This is a revision from the initial target – see **Section 9.6.7**). This number and time will be dependent on the observed overall survival. The default scenario assumes (i) recruitment is constantly 100pts/m to the trial overall, (ii) co-recruitment throughout of the equivalent of one other research arm, and (iii) the majority of metastatic participants will also have docetaxel but non-metastatic participants will not. Variations on these factors are documented in a Statistical Design Document. Sample scenarios are documented in the Trial Master File.

Updating the standard-of-care to permit first-line use of docetaxel was assumed within the sample size scenarios and is reflected in the projected time to maturity of the "metformin comparison".

9.6.7 Further Sample Size Issues For Additional Research Arm K

Analyses for the "metformin comparison" will be timed from randomisation. The point of randomisation compared to the start of hormone therapy may differ, depending on the planned use of docetaxel. This practical information will be reviewed by the TMG and IDMC.

For the development of Protocol v19, the sample size calculations for the "metformin comparison" were discussed by the TMG and revised to the estimates as presented in Section 9.6.4 – Section 9.6.6.

The original sample size estimates for this comparison were based on a lower target for power than the previously-added comparisons, with 90% power for the interim analysis, 85% power for the final analysis and 80% pairwise power overall. The observed accrual to the "metformin comparison" is higher than forecast. Therefore the TMG took the opportunity to revisit the sample size target for the "metformin comparison".

The revised sample size estimates aim for a higher target power of 92% at both interim and final analysis with 86% pairwise power overall, increasing the analysis power for this comparison in line with that of previous STAMPEDE comparisons. These revisions have resulted in the overall sample size for the comparison increasing from 1800 patients in Protocol v18 to 2800 patients in Protocol v19. This was determined to be achievable within the forecast timelines for recruitment i.e. by the end of 2019, and has the benefit of bringing forward the reporting timelines by approximately one year.

9.7 SAMPLE SIZE ISSUES & TRIAL STAGES: ADDITIONAL RESEARCH ARM L

This is the "transdermal oestradiol comparison" and includes participants allocated to research Arm L (transdermal oestradiol ± RT ± docetaxel) and the equivalent, eligible participants contemporaneously allocated to the control Arm A (SOC).

The phase III evaluation of the clinical efficacy of transdermal oestradiol will ultimately be based on the relevant data from this comparison within STAMPEDE and the PATCH trial, combined using an individual participant data meta-analysis. The overall evaluation is based on a non-inferiority design.

9.7.1 Implementation And Outcome Measures: Additional Research Arm L

The transdermal oestradiol evaluation is based on the following approach.

9.7.1.A Earlier Stages In The PATCH Trial

- The early stages of the PATCH trial already demonstrated the safety and early activity of transdermal oestradiol in comparison to LHRH therapy (see **Appendix I**) (31). The pilot phase (completed in 2010, n=254) showed the rates of cardiovascular events in the transdermal oestradiol and LHRH arms were similar, and the castration rates were equivalent. These results were confirmed by longer-term data including nearly 900 patients enrolled up to Oct-2015.

- A pre-planned, confidential interim analysis undertaken in Jun-2013, based on progression-free survival, at the end of the Phase II component of the PATCH trial, led the PATCH IDMC to recommend further recruitment for an extension to Phase III. That analysis included 638 patients with 206 PFS events, and reviewed data against a pre-specified non-inferiority margin hazard ratio of 1.25 with a 1-sided alpha 0.25.

9.7.1.B STAMPEDE And PATCH Meta-analysis

- To assess the clinical efficacy of transdermal oestradiol, the relevant data from the STAMPEDE "transdermal oestradiol comparison" will be combined with that data from all patients recruited into PATCH; the data from STAMPEDE will not be analysed alone.

- As the eligibility criteria with respect to the timing of start of ADT differs between the STAMPEDE "transdermal oestradiol comparison" and the PATCH trial (see **Section 4.3.1**), the "transdermal oestradiol comparison" will undergo an initial Pilot Phase to assess castration rates and safety among those participants on Arm L. This will also include a safety review of participants receiving transdermal oestradiol in combination with docetaxel. The data will be reviewed by the PATCH IDMC when there are 30 participants in Arm L who have been followed up for at least 18 weeks. A feasibility review will also be performed at the same time.

- The pre-planned Activity Stage II, on intermediate primary outcome measure progression-free survival, will take place based on combined data from the STAMPEDE "transdermal oestradiol comparison" participants and PATCH patients.

- The same approach will be used at the final Efficacy Stage, with progression-free and overall survival as definitive co-primary outcome measures (see PATCH Protocol v13.0for further details). The rationale for choosing progression-free survival as both the intermediate primary outcome measure and as part of the definitive co-primary outcome measure for the "transdermal oestradiol comparison" is outlined in **Section 9.7.3**

Table 35 summarises the outcome measures for each stage of this research comparison. The target sample size for the meta-analysis of the "transdermal oestradiol comparison" is approximately 2,500 participants, with around 700 to be recruited through the STAMPEDE "transdermal oestradiol comparison". By Feb-2017, around 1,200 patients had been recruited directly to the PATCH trial.

Table 35: Trial outcome measures by stage for the "transdermal oestradiol comparison"

COMPARISON STAGE	DATA SOURCE(S)	PRIMARY OUTCOME MEASURES	SECONDARY OUTCOME MEASURES
Pilot phase (completed 2010)	PATCH trial	Cardiovascular morbidity and mortality	Castration rates Other toxicities Metabolic effects
Activity Stage I (completed 2013)	PATCH trial	Progression-Free Survival*	Cardiovascular and other toxicities Castration rates Metabolic effects
Activity Stage II+$	PATCH and STAMPEDE trials	Progression-Free Survival*	Cardiovascular & other toxicities
Efficacy Stage III$	PATCH and STAMPEDE trials	Progression-Free Survival* Overall survival	Cardiovascular & other toxicities Prostate cancer specific survival Quality-of-life

* Defined as the earliest among biochemical failure, clinical progression (local progression, lymph node progression, distant metastases), or death from any cause (see Section 9.7.3).

+ In addition, there is Pilot Phase to assess castration rates and safety among Arm L participants within STAMPEDE, since the eligibility criteria with respect to timing of start of ADT differs between the transdermal oestradiol comparison within STAMPEDE and the PATCH trial (see Section 4.3.1).

$ The timing of these analyses is determined by when a pre-specified number of events for the primary outcome measure have been observed in the control arms for the PATCH and STAMPEDE trials combined. Please see the PATCH Protocol v10.0 for further details.

9.7.2 Additional Use of Outcome Data from the "transdermal oestradiol comparison"

Participants allocated to the "transdermal oestradiol comparison" may provide additional consent to participate in translational sub-studies, see Section 4.7 for details. Subsequent correlative analysis using outcome data from these participants will be undertaken by the STAMPEDE team and collaborators, overseen by the STAMPEDE BRG and other STAMPEDE oversight committees.

9.7.3 Definition of PFS and Use As Co-primary Outcome Measure: Additional Research Arm L

Note that the definition of progression-free survival (PFS) used within the "transdermal oestradiol comparison" analyses differs slightly to that of failure-free survival used for other research comparisons within STAMPEDE. This is because it includes death from any cause as an event- i.e. both PCa deaths and non-PCa deaths (see Appendix C for further details of the definition of progression). Progression-free survival is hence defined as time from randomisation to the first of: biochemical failure, clinical progression or death from any cause.

The use of PFS rather than FFS for the "transdermal oestradiol comparison" has no practical impact on STAMPEDE. The rationale for choosing PFS as part of the co-primary outcome measure for the "transdermal oestradiol comparison" is to capture any potential effects on survival due to the different toxicity profiles between transdermal oestradiol and LHRH.

Although PFS and survival are co-primary endpoints, their respective primary analyses will be triggered at different timepoints particularly because PFS is likely to contain a relatively low proportion of deaths as the contributing first PFS event.

9.7.4 Abiraterone/Enzalutamide/Apalutamide enhanced safety monitoring

Most patients with metastatic disease entering the trial prior to the COVID-19 pandemic received docetaxel as part of their standard treatment. However, following the COVID-19 pandemic, clinicians have the option to offer alternative therapies including enzalutamide, abiraterone, or apalutamide. There is no experience of combining these agents with transdermal oestradiol patches (though no significant interaction is anticipated) an enhanced safety monitoring study will be conducted. This will involve close monitoring of all patients who receive these agents in combination with transdermal oestrogen including testosterone, oestradiol, PSA levels and any events reported through SAE forms in real time.

In addition, the IDMC will formally review the enhanced safety monitoring data utilising a Simon Two Stage design, based on the castration rates at twelve weeks among patients still undergoing treatment with patches, with a significance level of 5% and power of 80%. The enhanced safety monitoring study will test a null response of 78% (P0) against an alternative response of 93% (P1), the level observed in patients receiving patches alone. The optimal design requires at least 8/10 patients to be castrate at stage I, and 37/43 patients to be castrate at stage II. Alongside efficacy data, toxicity data will undergo clinical review, and both aspects will be considered before deciding whether further patients should be treated with the combination. Any concerns raised by any aspect of the data will be discussed between the IDMC and appropriate TMG members, with any recommendations discussed with the TSC.

Clinicians have the option to treat patients with any of enzalutamide, abiraterone, or apalutamide. Initial analyses will consider patients who receive any of these treatments. If sufficient patients receive any particular one of these treatments, secondary analyses will look within each treatment.

9.8 FURTHER NOTES ON TRIAL DESIGN

9.8.1 Overall Sample Size

Given the adaptive nature of the study, there is no formal overall sample size target, but the numbers of participants required for each comparison are detailed in **Sections 9.4-9.7**. To date, more than 11,000 participants have been recruited overall.

9.8.2 Factorial Design

We note here that we did not employ a factorial design in the original design of this trial because we anticipated the possibility of synergy between SOC, zoledronic acid and docetaxel and between SOC, zoledronic acid and celecoxib.

It would not be possible to assess any such interactions reliably in a factorial trial (see the Statistical Design Document for further details).

9.9 INTERIM MONITORING AND ANALYSES

The accumulating data will be reviewed at regular intervals (approximately annually) by an Independent Data Monitoring Committee (IDMC), including pre-specified formal intermediate analyses of activity data (see also **Section 16**). These analyses will be performed by the trial team at CTU. Only participants randomised contemporaneously, and eligible for that comparison, will be included in the comparison of each research arm against control e.g. participants allocated to the control arm prior to Protocol version 15.0 will not contribute to the "metformin comparison" (Arm A vs Arm K). For the “transdermal oestradiol comparison”, the relevant STAMPEDE data will only be analysed as a meta-analysis in combination with the PATCH trial. Therefore, interim data from this comparison will be reviewed by the PATCH IDMC.

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further participants or further follow-up; guidelines for discontinuation of accrual for the relevant Activity Stages, together with results from any other relevant trials will aid them in this. A decision to discontinue recruitment, either in all participants or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians including those entering participants into the trial and the general clinical community. The intermediate stopping guidelines apply to the intermediate primary outcome measure.

To stop accrual early for benefit in any comparison would require convincing data in terms of the definitive primary outcome measure, overall survival. For example, this could be one-sided $p<0.0005$ as proposed by Haybittle-Peto.(54, 55) The use of such a guideline for stopping for benefit has a minimal impact on the operating characteristics.

If a decision is made to continue without change, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the Trial Steering Committee (TSC, see **Section 16**) as to whether the trial should continue in its present form. While the trial is ongoing the accumulating data will generally remain confidential, unless the TSC and IDMC agree that the data should be made public.

9.10 OUTLINE ANALYSIS PLAN

Analyses will be performed on an intention-to-treat basis.

For comparisons involving arms A-K, the standard unadjusted log-rank approach will be applied to analyses of intermediate and definitive primary outcome measures. The impact of potential confounders including the stratification factors used at randomisation will be considered in a Cox proportional hazards model.

Flexible parametric models will be used to calculate the absolute differences between the arms to show treatment differences over time and to estimate restricted mean “survival” times (RMST). The estimated difference in RMST will be used preferentially to compare treatment arms if the proportional hazards assumptions required for hazard ratios cannot be supported.

In the “transdermal oestradiol comparison,” a meta-analysis approach will be used to combine data from the STAMPEDE and PATCH trials. The analysis will also take into account the change in randomisation ratio partway through the PATCH trial (from 2:1 for transdermal oestradiol versus LHRH before Feb-2011, to 1:1 thereafter). In addition, as the comparison uses a non-inferiority design, sensitivity analyses will be conducted based on a number of pre-defined descriptions for the per-protocol population.

9.10.1 Pilot / Safety Phases

Feasibility of the trial originally, and now of individual research comparisons, was and still is considered in terms of acceptability of the trial randomisation, reported toxicities and adherence to trial medication. Sites participating in the Pilot Phase for the original research arms were required to keep an anonymised log of all participants assessed for trial eligibility (see protocol v2.0) so that the number of participants who did not participate in the study and the number of eligible participants who chose to not participate in the study could be summarised (reasons for non-participation were collected where the participant was willing). The anonymised logs are no longer needed for new research arms (since protocol v8.0).

For each research comparison we shall describe the incidence of expected and unexpected severe toxicities and adverse events/reactions (see **Section 11.1.1**) amongst the participants who are randomised to the comparison to decide whether to continue beyond this Pilot/safety Phase.

9.10.2 Activity And Efficacy Stages

The approach to analysis of these stages is summarised within the sample size calculations (see earlier subsections of **Section 9**). Each research arm will be compared in a pairwise fashion against the contemporaneously recruited control arm, except for the planned Efficacy Stage analyses for the "enzalutamide + abiraterone comparison", in which patients allocated to AR-targeted therapy (arms G and J) will be compared against contemporaneously recruited control arm patients.

Full details are available in the relevant Statistical Analysis Plan. See **Figure 4** for an overview of the schema of progress.

10 MONITORING AND QUALITY ASSURANCE

10.1 DATA MONITORING

To ensure patient safety and data integrity is maintained to a high standard, remote and on-site monitoring will be conducted throughout the lifetime of the study.

10.1.1 Central Monitoring Of Consent

Anonymised copies of the participant's initial consent form (including the additional research consent) should be sent to the STAMPEDE team at the CTU, as soon as randomisation has been completed. Once the consent has been received and reviewed by the CTU the participants "treatment and follow up schedule" can be released to sites.

Any subsequent re-consent forms should be sent as soon as possible to enable central monitoring and recording of consent. The dates and signatures should be visible on the copies sent to the CTU; however the name of the participant must be omitted. Any queries resulting after central monitoring will be redirected to sites for clarification. The original non-anonymised consent forms should be kept at site in the Investigator Site File.

10.1.2 Central Monitoring Of Data

Data provided to the CTU will be checked for data errors, inconsistent and missing data. The STAMPEDE team will issue data clarification requests, query reports or address issues identified via email with site staff. Data Quality and site performance sites will be reviewed, issues identified when appropriate will be fed back to sites. Sites may be identified for training or onsite monitoring through central monitoring checks.

10.1.3 Direct Access to Patient Data

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patients' consent for this must be obtained. A list of source data use for the trial and their locations should be maintained by the site.

10.1.4 Monitoring Visits to Investigator Sites

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

After the monitoring visit the monitor will complete a site visit report. Once the TMT have reviewed the report and agreed on any recommendations the monitor will finalise the report and send a copy to the Principal Investigator (PI) at the site. A copy will be kept in the CTU STAMPEDE Trial Master File.

Remote or self- monitoring could be utilised through the course of the trial. Site staff may be asked to scan and send anonymised sections of a participant's medical record to the CTU for remote verification or asked to complete a form to confirm compliance with protocol procedures.

10.2 CONFIDENTIALITY

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

Participants are asked to give their permission for information about their health status to be obtained from the Office of National Statistics (ONS), via NHS Digital (formerly HSCIC), Public Health England, National Cancer Research Advisory Service, or any similar or national equivalent. This will facilitate data collection and verification and reduce the burden on sites. In addition, participants will be asked for permission to inform their GP of their involvement in the STAMPEDE trial.

11 SAFETY REPORTING

The principles of GCP require that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol and in **Section 7.1.5**.

Further information on the expected toxicities for the protocol treatments (investigational medicinal products (IMPs)) being tested in arms on active follow-up can be found in the reference safety information (RSI) accessible via the STAMPEDE website: http://www.stampedetrial.org/centres/essential-documents/reference-safety-information-rsi/.

11.1 SAFETY REPORTING DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 36**.

Table 36: Event Terms and Definitions

TERM	DEFINITION
Adverse Event (**AE**)	Any untoward medical occurrence in a clinical trial participant to whom a medicinal product has been administered. These include occurrences which are not necessarily caused by the product.
Adverse Reaction (**AR**)	Any untoward and unintended reaction to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (**UAR**)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in reference safety information (summary of product characteristics or Investigator brochure) for that product.
Serious Adverse Event (**SAE**) or Serious Adverse Reaction (**SAR**) or Suspected Unexpected Serious Adverse Reaction (**SUSAR**)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that fulfils the definition of **serious:** • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • Other important medical condition***

Clarifications and Exceptions

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. A&E attendances are not defined as a hospitalisation unless participants are admitted. Hospitalisations for a pre-existing condition, not thought to have been exacerbated by STAMPEDE protocol treatment or IMPs (including elective procedures that have not worsened) do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the

participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.1.1 Adverse event definitions

Adverse events (AE) include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

NB: Within STAMPEDE non-melanoma skin cancers (e.g.: basal cell carcinoma and squamous cell carcinoma) are not considered important medical conditions and therefore are considered adverse events, unless they fulfil any of the other "serious" criteria – detailed in **Table 36**.

Serious Adverse Events (SAE) are AEs that fulfil the definition of serious as detailed in **Table 36.** SAEs are reported using the SAE CRF. If the event is assessed as possibly, probably or definitely related to a protocol treatment (IMP), it is categorised as a Serious Adverse Reaction (SARs). If the reaction is unexpected based on the approved reference safety information, it is categorised as a Suspected Unexpected Serious Adverse Reaction (SUSAR), see **Table 37.**

Notable Adverse Events (NAE) these include pregnancy occurring in a partner of a STAMPEDE participant. Pregnancies must be followed up until outcome, whether this is a live birth, stillbirth, or planned or spontaneous abortion. NAEs should be reported on the SAE CRF, in the same manner as SAEs.

11.1.2 Defining "treatment" for the purposes of safety reporting

STAMPEDE is an adaptive platform protocol in which research treatments are given in addition to standard-of-care (SOC) therapies, or as alternatives in the case of transdermal oestradiol. As per MHRA recommendations **all protocol treatments** (i.e. both protocol SOC and protocol research treatments) and are regarded as **investigational medicinal products** (IMPs) within the STAMPEDE platform for the purposes of safety reporting.

Protocol treatments (IMPs):

- **Protocol SOC treatments** are IMPs that are standard forms of treatment permitted as part of the STAMPEDE protocol.
    - Licensed ADT (e.g. LHRH analogues) given in the setting of hormone-sensitive prostate cancer
    - Docetaxel given in hormone-sensitive prostate cancer
    - Abiraterone given in hormone-sensitive prostate cancer
    - Enzalutamide given in hormone-sensitive prostate cancer
    - Apalutamide given in hormone-sensitive prostate cancer

Please note, if a participant allocated to transdermal oestradiol switches to standard ADT in the absence of progression, this would still be considered as being on protocol treatment (IMP).

- **Protocol research treatments** are the IMPs that are additional or alternative treatments participants allocated to research arms on active follow-up (G-L) receive as part of the STAMPEDE protocol:

- Arm G: abiraterone
- Arm J: abiraterone & enzalutamide
- Arm K: metformin
- Arm L: transdermal oestradiol

Note, the research treatment in arm H (prostate RT) is not an IMP, but safety reporting requirements to the CTU are the same.

Non-protocol treatments:

- All prostate cancer treatments commenced post disease progression (as defined in the protocol – **Section 7.1.3**).
- ADT given after progression, (e.g.: commenced in HSPC setting and now continues for the management of CRPC, or ADT given after progression after completing M0 course of treatment - See **Figure 5**).

11.2 SITE INVESTIGATOR RESPONSIBILITIES

The Site Investigator may be any medically qualified individual delegated to undertake safety reporting for the STAMPEDE trial. It is recommended that the Principal Investigator delegate safety reporting to at least one other individual in order to ensure reporting cover during their absence.

11.2.1 Notification period

All events that fall within the notification period must be reported, events outside the notification period do not need reporting.

Adverse Events (AEs): All AEs are reportable from the time of randomisation until 30 days after discontinuation of protocol treatment (IMPs)* (refer to **Section 11.1.2**). All AEs should be recorded in the participant's medical notes and on the Toxicity (AE) CRF linked to the Follow-up CRF. The Toxicity (AE) CRF should be sent to the CTU within one month of the corresponding Follow-up CRF being due.

Serious Adverse Events (SAEs): All unrelated events i.e. SAEs are reportable from the time of randomisation until the participant has progressed AND is 30 days after discontinuation of all protocol treatment (IMPs)* (refer to **Section 11.1.2**) or comparison closure (see **Section 7.4** for definition of comparison closure).

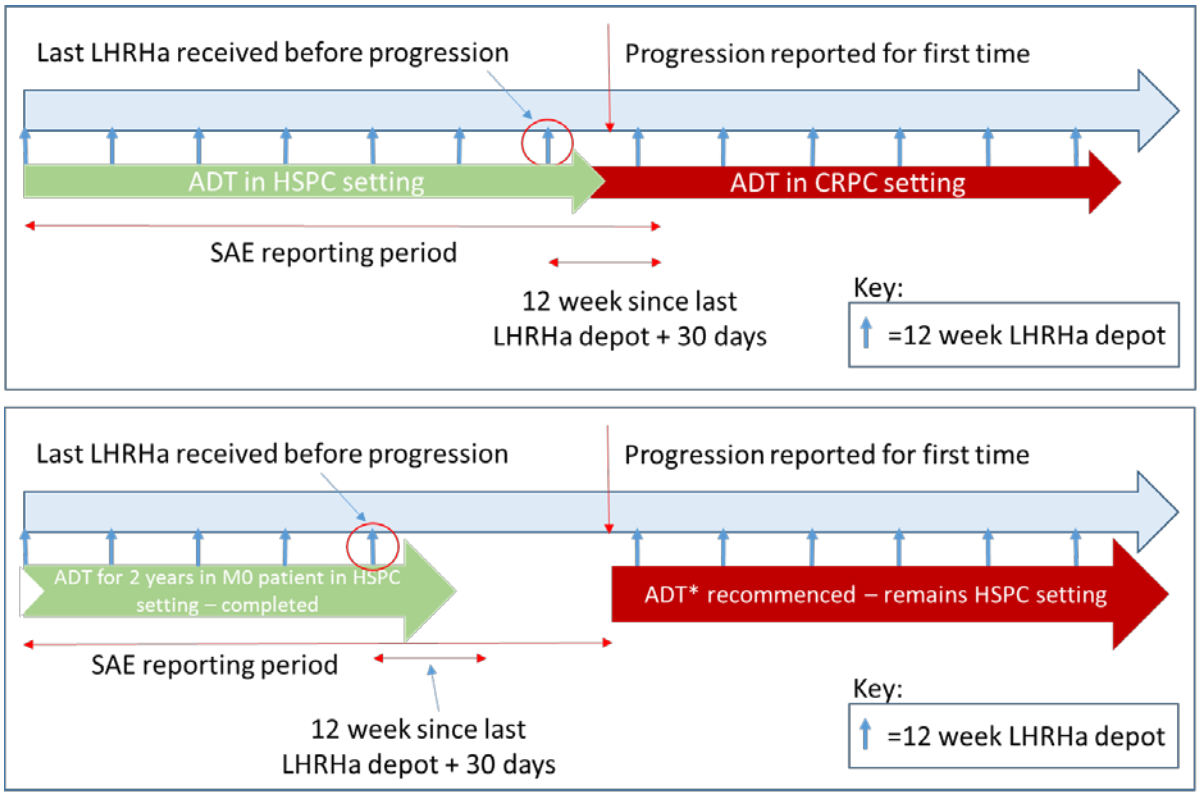
*N.B. ADT before progression is a protocol SOC treatment (IMP). However, even though ADT following progression is not protocol SOC treatment (IMP) the reporting period continues until depot expiry of the last dose before progression + 30 days is completed. Therefore when the participant is on ADT in the form of LHRHa, this is assumed to be 30 days after the depot expiration date (e.g. up to 8 weeks after administration of a 4-week depot or 16 weeks after administration of a 12-week depot) following the final dose given before progression was diagnosed (See **Figure 5**).

Serious Adverse Reactions (SARs and SUSARs): All related SAEs i.e. all SARs and SUSARs are reportable from the time of randomisation until comparison closure (see **Section 7.4** for definition of comparison closure).

Notable Adverse Events: All notable adverse events are reportable from randomisation until comparison closure, using the SAE CRF. Notable Adverse Events must be reported within 24 hours of the investigator being made aware of the event using the SAE CRF.

All SAEs must be reported within 24 hours of the investigator being made aware of the event using the SAE CRF and the Investigator is responsible for providing follow up information for SAEs until resolution.

Figure 5: Diagram to show notification/reporting period for AEs and SAEs occuring on LHRHa



*Any additional treatment started at this stage eg: abiraterone would not be considered IMP

11.2.2 Trial-Specific "Expedited Reporting" Exemptions

The following events which may fulfil the definition of "serious" are exempt from expedited reporting. They are still require to be reported as an AE on the Toxicity (AE) CRF, or on an alternative CRF e.g. progression log, which will be used to report these events to the MHRA, but an SAE CRF is not required.

- **Death as a result of disease progression or disease-related deaths:** Do not complete an SAE CRF, unless death is considered to be caused by trial treatment (i.e. a SAR). The details should be reported on the Death Form.

- **Non-fatal progression events:** events that fulfil the definition of serious e.g. result in hospital admission, but are due to disease progression are exempt from reporting as an SAE, instead details should be provided on the Progression Log.

- **Elective hospitalisation** and surgery for treatment of locally-advanced or metastatic prostate cancer or its complications. These should be recorded as a non-trial inpatient admission on the follow-up form under Non-Trial visits.

- **Elective hospitalisation** to simplify treatment or procedures. If related to prostate cancer, record as non-trial inpatient admission on the follow-up form.

11.2.3 Investigator Assessment

11.2.3.A Seriousness

When an AE occurs the investigator or delegate **must** assess whether the event is serious. Refer to **Table 31** for what fulfils the criteria of serious and **Section 11.2** for a list of exemptions from expedited reporting.

11.2.3.B Grading severity of adverse event

The severity (i.e. intensity) of all AEs **must** be graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The complete CTCAE v4.03 can be found at:
http://www.stampedetrial.org/centres/tools-training/training-materials-resouces/
Any questions concerning this process should be directed to the CTU team in the first instance.

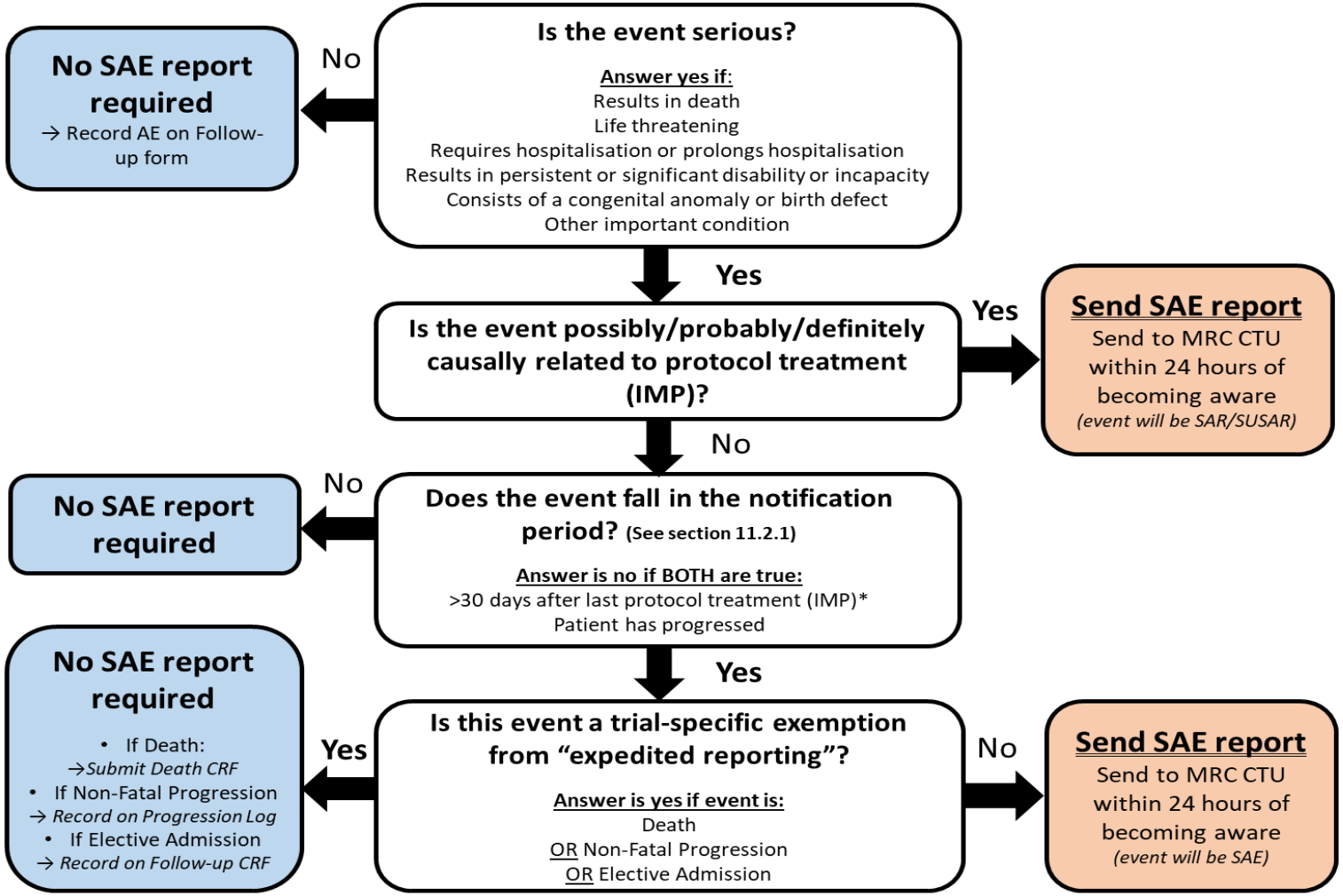
11.2.3.C Causality

The Investigator **must** assess the causal relationship of all serious events or reactions in relation to protocol treatment using the definitions in **Table 32**.

11.2.3.D Notification responsibilities for non-protocol treatments

It should be noted that ADT, docetaxel, abiraterone, enzalutamide and apalutamide may be given as non-trial treatments in the management of CRPC. It is not necessary to report AEs or SAEs relating to this non-trial use where the treatment commenced post progression. Instead the yellow card system should be used to notify the regulatory authorities of adverse drug reactions in this setting: (https://yellowcard.mhra.gov.uk/)

Figure 6: SAE reporting flowchart



**Exposure to LHRHa is assumed to be until the depot expiration date, therefore unrelated SAEs are reportable up until 8 weeks after the administration of a 4-week depot or 16 weeks after the administration of a 12-week depot.*

Box 1: SAE report notification checklist

Before sending the SAE CRF please check that the event falls within the notification period and does not meet any of the "exemption from expedited reporting criteria", see **Section 11.2**. The SAE CRF must be submitted within 24 hours of an Investigator becoming aware of the event. The following are the minimum criteria required for initial processing and review:

1. At least **two** patient identifiers
2. **One event term** that can be coded to CTCAE version 4.03
3. Indication of why the event was **serious**
4. **Grade** severity of event/reaction according to CTCAE version 4.03
5. Date of **onset** when the event met the criteria of serious. Please refer to **Table 31**
6. Provide details for **all protocol treatments (IMPs) allocated** (i.e. both protocol SOC and protocol research treatments, including any allocated protocol research treatment that has not started) whether ongoing or completed at time of event onset.
7. Assessment of **causality** in relation to **each** protocol treatment (i.e.: both protocol SOC and protocol research treatments, including any allocated protocol research treatment that has not started) – *please note this can be provided later if clinician is not available within 24 hours of becoming aware of the event. This can be completed by the trial team based on correspondence with site clinician, and signed by the clinician at a later date.*
8. **Signature** (This can be a site trial team member in the first instance to meet the reporting timelines, but the CRF must be re-sent once a clinician has reviewed and signed the form)

SAE REPORTING
Fax to 020 7670 4818 within 24 hours of becoming aware of the event
Or send via **encrypted** email to mrcctu.stampede@ucl.ac.uk

11.2.4 Event Follow-up

Participants must be followed up until clinical recovery is complete or stabilised (resolution of the event – this can include an outcome that the event is "resolved with ongoing sequela"). Follow-up should continue after completion of protocol treatment if necessary. The Investigator is responsible for providing follow up information for SAEs until resolution. Follow-up information should be updated on the original SAE CRF by ticking the box marked "follow-up" and faxing to the CTU as information becomes available. Extra information and/or copies of test results may be provided separately but must be anonymised. The participant must be identified by trial ID and initials only. The participant's name should not be used on any correspondence.

11.3 CTU RESPONSIBILITIES

The STAMPEDE trial team will acknowledge receipt of all SAEs via email. Please contact the STAMPEDE trial team if an acknowledgement email is not received within 3 working days.

At least one medically qualified person at the CTU, or comparison chief-investigator or another appropriate TMG member will review all SAE reports received. The rationale for answers provided can be discussed between the site and CTU, however, ultimately the causality assessment given by the local Investigator at the hospital cannot be overruled.

The CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (through the MHRA to competent authorities in other European member states) and the UK research ethics committees. Additionally, the CTU has sponsor oversight for reporting in other countries in which the trial is taking place. The CTU is responsible for reporting fatal and life-threatening SUSARs to the UK competent authorities within 7 days of the CTU becoming aware of the event; other SUSARs must be reported within 15 days.

SAKK (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung), the Swiss Group for Clinical Cancer Research coordinate site participation for STAMPEDE, and are responsible for reporting SUSARs to the relevant Swiss competent authority and lead ethics in accordance to their local regulations, on behalf of the CTU.

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

The CTU will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority and Ethics Committee).

Any drug companies involved will also be notified of reportable (serious and unexpected and drug-related/unknown relationship) events as per their agreement with the sponsor. CTU will also provide companies with a copy of the Annual Safety Report in the required format.

11.3.1 Sponsor (CTU) Assessment

11.3.1.A Expectedness

If there is at least a reasonable possibility of causal relationship to the protocol treatment (all IMPs i.e. SOC and research), an assessment of the expectedness of the event will be made by the Sponsor (the STAMPEDE team at the CTU). This determines whether a reaction is a SAR or SUSAR, see **Table 37**.

Expectedness is determined using the current reference safety information (RSI) (i.e. summary of product characteristics section 4.8 or current investigator brochure) approved for the trial. An event is considered unexpected if it is:

- Not listed in the RSI
- If severity exceeds that listed in the RSI
- If frequency exceeds that listed in the RSI
- If event outcome exceeds that listed in the RSI

Table 37: How causality and expectedness determine event outcome (SAE/SAR/SUSAR)

<table>
<tr><th rowspan="2">CAUSAL RELATIONSHIP (RELATEDNESS)</th><th rowspan="2">DESCRIPTION</th><th colspan="2">EXPECTEDNESS ASSESSED BY CTU</th></tr>
<tr><th>EXPECTED REACTION</th><th>UNEXPECTED REACTION</th></tr>
<tr><td>Definitely</td><td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td><td rowspan="3">SAR</td><td>SUSAR</td></tr>
<tr><td>Probably</td><td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td><td>SUSAR</td></tr>
<tr><td>Possibly</td><td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments)</td><td>SUSAR</td></tr>
<tr><td>Unlikely</td><td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).</td><td colspan="2">Unrelated SAE
No assessment required as unrelated to treatment</td></tr>
<tr><td>Unrelated</td><td>There is no evidence of any causal relationship</td><td colspan="2">Unrelated SAE
No assessment required as unrelated to treatment</td></tr>
</table>

12 ETHICAL CONSIDERATIONS AND APPROVAL

12.1 ETHICAL CONSIDERATIONS

12.1.1.A Randomisation

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

All participants, with the exception of those allocated to transdermal oestradiol (Arm L), will receive standard hormone treatment. All participants, including those allocated to Arm L, may also receive other standard-of-care (SOC) treatments such as prostate radiotherapy and/or docetaxel, abiraterone, enzalutamide or apalutamide. Use of these SOC treatments will be unaffected by trial participation and is left to the discretion of the treating clinician and participant.

Participants may be randomised to receive additional treatment (metformin) given with standard-of-care treatments, or an alternative form of hormone treatment (transdermal oestradiol). An even allocation ratio is being currently being used which means all eligible participants have an equal chance of being randomised to the control or research arms.

Through the introduction of a "transdermal oestradiol comparison" into the STAMPEDE trial platform, sufficient data will be collected to evaluate this treatment approach more rapidly. By undertaking a meta-analysis using data collected in both PATCH and STAMPEDE trials, fewer participants overall are allocated the control arm i.e. more participants gain access to novel treatments and results will be available sooner.

12.1.1.B Evaluation of Novel Therapeutic Strategies

There is some evidence to suggest that the newer treatment options may have advantages over standard treatment alone with regards to clinical outcome, but this is not confirmed and toxicity may be increased. This trial will follow a large group of people who have been randomly allocated to either the standard treatment(s) or the novel treatment strategies in order to measure the benefits of these approaches. All participants will be followed-up for toxicity and safety issues, so that any benefits can be weighed against any negative aspects, including the impact treatments have on other aspects of medical health e.g. cardiovascular disease, as well as quality-of-life and value for money (health economic analysis).

12.1.1.C Additional Tests and Hospital Visits

Trial participants will have some additional hospital visits and some extra blood samples compared with standard practice, the exact requirements depend on the allocated treatment and stage of disease. Efforts are made to reduce the burden of extra visits and tests, for example extra blood tests can be performed at a time when a blood draw would be performed as part of standard care, or participants can have the blood samples taken at their GP's surgery instead.

12.1.1.D Facilitating Participant Feedback From Investigations and Additional Analyses

For participants who choose to take part in additional sub-studies, biological samples including blood, saliva and remaining stored FFPE tumour samples will be used in research projects. These projects will enable the study of genetic factors and other biomarkers that can help identify individuals who serve to benefit most from the treatments tested in STAMPEDE, and to further understand why and how treatment resistance develops. All samples will remain anonymised and only made accessible to approved collaborators granted access by the STAMPEDE oversight

committees. We will make every effort to protect the confidentiality of this information and make sure personal identities are protected.

From protocol v16.0 onwards, participants may opt to receive feedback regarding genetic results that may arise from the research analyses of genetic material extracted from any of the biological samples collected as part of the trial e.g. saliva, FFPE tumour blocks or circulating tumour DNA extracted from blood. Only results which are of established clinical relevance and for which testing would be available under standard NHS genetic testing guidelines will be fed back. Any genetic analysis undertaken as part of additional research associated with STAMPEDE does not replace clinically indicated investigations as only a proportion of STAMPEDE participants will undergo prospective testing and therefore it cannot be guaranteed that results will be fed back in a timely fashion.

This change has been made in response to emerging data that demonstrates a small proportion of people may have genetic faults in genes such as Breast Cancer Gene 2 (BRCA2). This has implications for both participants and potentially their biological relatives. For participants and their treating clinician, knowledge of this information may facilitate access into further clinical trials and may potentially impact on the choice of treatment following progression.

Any participant who consents to receive feedback and in whom a known pathogenic mutation of clinical significance is detected on testing of research samples collected as part of STAMPEDE will be told of this. Participants will be recommended to undergo genetic counselling accessed via clinical genetics services and consider confirmatory testing. This is necessary to determine if the defect is germline (inherited) and ensures access to appropriate ongoing support. If confirmed as a germline (inherited) abnormality, this will enable biological relatives to also access appropriate genetic counselling and testing if they wish.

The introduction of the “metformin comparison” means that all participants, not known to be diabetic, will be screened for diabetes prior to trial entry. This is to enable the effect of metformin to be studied in non-diabetic participants. All participants in whom screening bloods are abnormal will be referred for confirmatory tests and further management according to local guidelines e.g. via their GP. Screening is expected to lead to a small proportion of potential trial participants receiving a new diagnosis of diabetes but will ensure appropriate management of both conditions.

12.1.1.E Considering the Impact of Emerging Data

If new information emerges during the course of the trial which may affect the treatment or follow-up of participants all Principal Investigators (PIs) will be informed of this and required to inform trial participants.

12.1.1.F Electronic health records

Participants are requested to provide consent to permit linkage of trial data to other sources of electronic health data to improve the reliability of long-term follow-up data. Explicit consent is requested for the CTU to store direct identifiers (name and NHS number) securely and seperately from anonymised trial data. This is to permit verification of the information held by others and received by the CTU, ensuring that the trial database is only updated with accurate information.

12.2 ETHICAL APPROVAL

The protocol has a Favourable Opinion from an appropriate Research Ethics Committee, according to national guidelines. Additionally, each site must also obtain management permission for research (Local R&D approval or equivalent) from the relevant host organisations before participants can be entered into the trial. The participant’s informed consent to participate in the trial should be

obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Participant information sheets and participant consent forms are available on the STAMPEDE website (www.stampedetrial.org).

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

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (http://www.mrc.ac.uk). In addition, the MRC and the Wellcome Trust framework on the feedback of health-related findings in research is readily available (https://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf/) and has been used when developing the trial specific processes.

13 REGULATORY APPROVAL

This trial has been approved in the UK by the MHRA and will be conducted under a Clinical Trials Authorisation CTA 20363/0404/001 in the UK.

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

13.1 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 25 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, and other delegated authorities with suitable notice as it may be subject to audit or inspection from any of the above.

14 INDEMNITY

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

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

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

15 FINANCE

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

Funding arrangements for research arms and sub studies now closed to recruitment can be found in earlier protocols.

Standard therapies including **ADT**, **prostate radiotherapy** and **docetaxel** will be administered as per routine clinical care using local NHS supplies.

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

If abiraterone is required to be given to participants as standard of care, funding will not be provided and the drug should be administered as per routine clinical care using local NHS supplies.

Enzalutamide is manufactured by Astellas Pharma. They have agreed to provide free drug and funds to distribute drug to participating sites and to help support the conduct and management of the trial.

If enzalutamide is required to be given to participants as standard of care, funding will not be provided and the drug should be administered as per routine clinical care using local NHS supplies.

Metformin will be administered using local NHS supplies.

Transdermal oestradiol will be administered as either Progynova TS 100 patches, manufactured by Bayer, or Femseven 100 patches, manufactured by Theramex who have agreed to supply these patches at a trial-specific discounted price. All accredited STAMPEDE sites will be able to order Progynova for use in the STAMPEDE trial through Alliance Healthcare Ltd wholesalers and Femseven patches through AAH Pharmaceuticals Ltd wholesalers.

Apalutamide given to participants as standard of care will be administered using local NHS supplies.

16 TRIAL COMMITTEES

16.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) has been formed comprising: the Chief Investigator; each comparison lead investigator; other co-investigators and members of MRC CTU at UCL internal Trial Management Team. The membership of the TMG may be expanded if other groups of trialists wish to participate. It will also be amended during the trial if other circumstances require e.g. retirement.

The TMG will be responsible for the day-to-day running and management of the trial. The TMG will meet by teleconference at least on a monthly basis where possible and in person as needed.

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

16.2 TRIAL STEERING COMMITTEE (TSC)

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

The relationship of the TSC with the other STAMPEDE working groups is detailed in **Figure 7**. Further details of TSC functioning are provided in the TSC charter (available on request).

16.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) has been formed. The IDMC will be the only group who sees the confidential, accumulating data to the trial. Reports to the IDMC will be produced by the CTU. The IDMC will meet within 6 months of the trial opening with the frequency of meetings dictated by the IDMC. The IDMC will consider data in accordance with the analysis plan (see **Section 9**) and will be advisory to the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm is discontinued.

From protocol v8.0 onwards, any recommendation from the IDMC to stop recruitment to one or more trial arms will be acted upon immediately, pending ratification from the TSC. As this period between meetings should be very short, sites would not be notified until after the TSC have made a decision. IDMC recommendations based on emerging safety issues will be discussed with sites promptly.

The relationship of the IDMC with the other STAMPEDE working groups is detailed in **Figure 7**. Further details of IDMC functioning and the procedures for interim analysis and monitoring are provided in the IDMC charter (available on request).

Data from the “transdermal oestradiol comparison” are viewed by the PATCH IDMC, in meta-analysis with PATCH, rather than by the STAMPEDE IDMC. Recommendations of any actions relating to STAMPEDE would be made to the STAMPEDE TSC.

16.4 TMG SUB-GROUPS AND EXPERT PANELS

The trial has a number of TMG sub-groups and expert panels, each comprising of specific members of the TMG, MRC CTU at UCL, field experts and other STAMPEDE clinicians and site staff. The groups are all chaired by TMG members and report directly into the TMG.

- The **Biological Research Group** (BRG), the **Bone and Imaging Group** (BIG) and the **Metabolic Translational Group** (MTG) all input and provide expert oversight of relevant translational aspects of the trial and associated sub-studies.
- The **STRATOSPHere Consortium Management Group** (STRATOSPHere: STratification for RAtional Treatment-Oncomarker pairings of STAMPEDE Participants starting long-term Hormone treatment) coordinates the parallel translational programme funded by Prostate Cancer UK.
- The **Comparison Management Groups** (CMGs) were developed to input into the running of each comparison and to propose, plan and develop new comparisons as required. The CMGs are comprised of:
    - Arm G – Abiraterone CMG
    - Arm H – M1|RT CMG
    - Arm J - Abiraterone and Enzalutamide CMG
    - Arm K – Metformin CMG
    - Arm L – tE2 CMG
    - Future proposals CMG
    - Original comparisons CMG
- The **Site Advisory Team** (SAT) includes STAMPEDE site research staff to provide advice to the TMG concerning the running of the trial, including how proposed amendments to the protocol and CRFs directly affect staff practices.
- The **Outcome Review Group** (ORG) conducts cause of death reviews as required for secondary end point analysis.
- The **Clinical Safety Committee** (CSC) review all SAEs of STAMPEDE participants and provide guidance to site clinicians and research staff in regards to clinical safety aspects of the trial.
- The **Genetic Sub-Group** (GSG) provides oversight of all results arising from genetic testing.
- The **Quality of Life** group (QOL group) will advise on how to optimise use of QOL data within the STAMPEDE trial

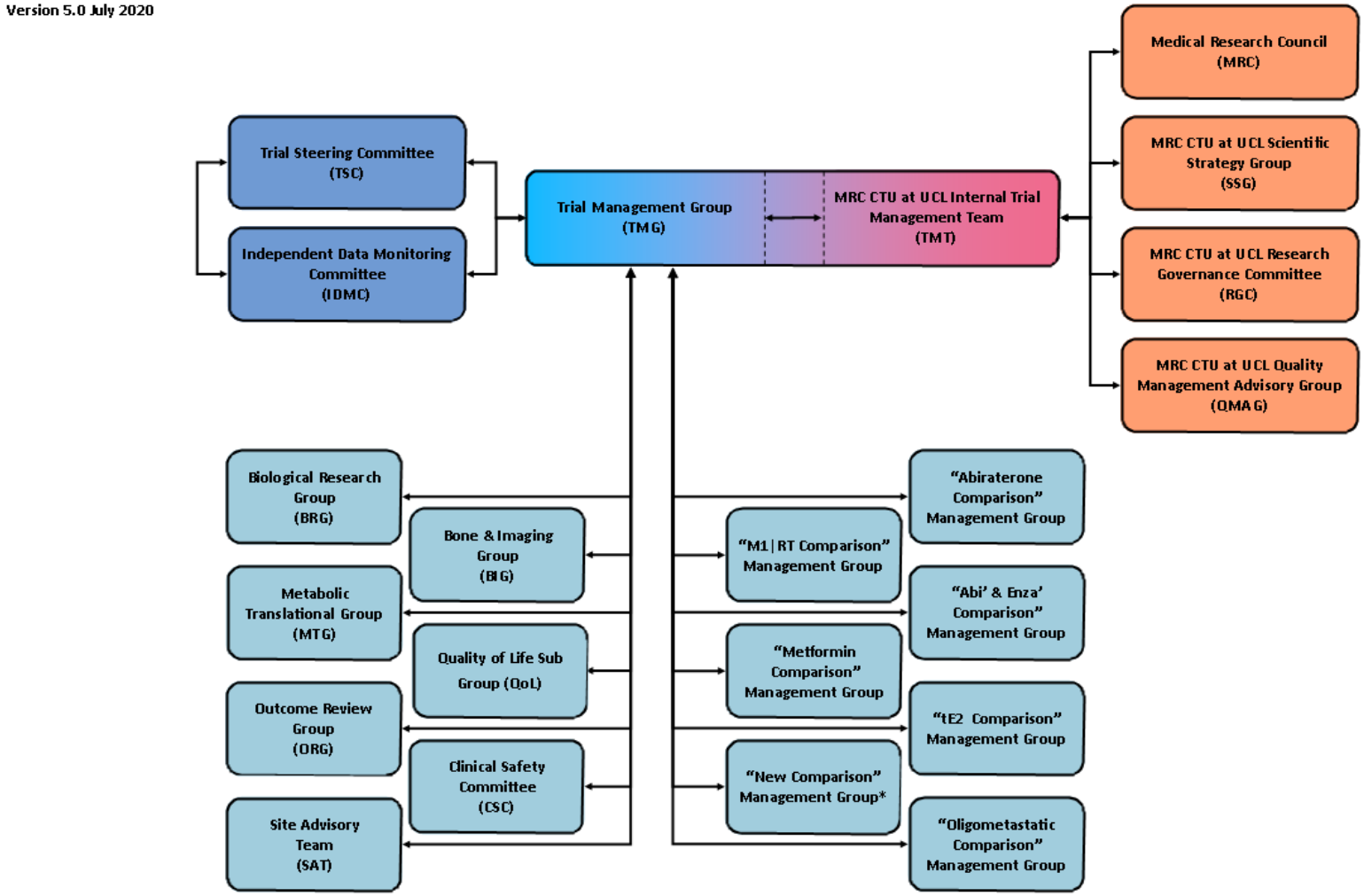
The relationship of each of these groups with the other STAMPEDE working groups is detailed in **Figure 7.**

16.5 MRC CTU AT UCL INTERNAL GROUPS

CTU requires a number of internal working groups to run a platform protocol. These internal groups assist the TMG in the operation of STAMPEDE, providing guidance on scientific strategies of research and publication, research governance in regulatory information and protocol review and the management of research quality within the STAMPEDE trial.

The relationship of each of these groups with the other STAMPEDE working groups is detailed in **Figure 7**.

Figure 7: Organigram of the relationships between STAMPEDE working groups



*The number and timeline of current and planned comparisons will dictate the need for the number of CMGs in operation. At any point there may be one or more.

17 ANCILLARY STUDIES

17.1 PATIENT REPORTED OUTCOMES

STAMPEDE collects patient reported outcomes in the form of the EORTC QLQ-30 Quality of Life form and the EQ-5D Health Economics Form.

The research nurse should approach participants at appropriate clinical visits to complete a questionnaire. If no clinical visit is scheduled for the participant (with a window of 4 weeks around the expected date) the nurse should organise the completion of the questionnaire e.g. by post or secure e-mail.

Questionnaires should be self-administered; participants should be encouraged to complete the questionnaires without conferring with friends or relatives and all questions should be answered even if the participant feels them to be irrelevant. The research teams should encourage the participants to answer all questions but should not review the responses as these should remain confidential. Copies of questionnaires should not be retained at site.

17.1.1 Quality of life (QL)

The EORTC QLQ-C30 with the prostate-specific module QLQ PR25 will be used. Key items for assessment are pain reduction for participants with metastatic disease and urinary symptoms for participants with locally-advanced disease. In addition, specific hypotheses will be generated for each of the research arms.

17.1.1.A Changes in QL data collection from protocol v19.0 onwards

Initial participation in the QL sub-study was limited to the first 700 participants recruited (this was reached in Sep-2008). After a pause, the QL sub-study re-opened from the implementation of protocol version 8.0 (Nov 2011 onwards).

From protocol v19.0, QL and HE data collection changed, as laid out in **Table 33.** QL and HE collection stopped for most participants but continued as planned in participants in the “abiraterone comparison” and “abiraterone and enzalutamide comparison” and became lifelong in participants in the “metformin comparison”. HE collection (without QL) also continued in participants in the “M1|RT comparison” randomised after Apr 2016.

Table 33 summarises the participant reported outcome data collection (QL and HE) by comparison. Going forward, for each new comparison within STAMPEDE, a pre-defined sample size for the participant reported outcomes will be described and a sampling approach considered where appropriate.

17.1.2 Health Economics

The EuroQol (EQ-5D) will be used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences. This data will be used to calculate quality-adjusted life-years as part of the economic evaluation. Healthcare resource use will be collected at each follow-up. This includes non-trial inpatient days, non-trial outpatient, GP visits and data on concomitant medications. Information on participants’ use of primary care and community-based services will also be collected as additional questions in the questionnaire. Costs will be calculated on the basis of representative UK unit costs at the point of analysis. A cost-effectiveness analysis will compare all regimens that continue to recruit into their final Efficacy Stage. For further details please refer to **Appendix G**.

Table 38: Patient reported outcome data collection by comparison

COMPARISON	PARTICIPANT DETAILS	COLLECTION OF PATIENT REPORTED OUTCOMES E.G. EORTC QLQ-C30, EQ-3D
"Original"	Arms B, C, D, E, F and Arm A recruited between trial start (2005) and 15-Nov-2011	No further collection of participant reported outcomes as comparisons have closed to follow-up
"Abiraterone"	Arms A and G randomised between 15-Nov-2011 and 17-Jan-2014	Data collection to continue until disease progression or 5 years post randomisation (i.e. all data collection stops 17-Jan-2019).
"Abiraterone and enzalutamide"	Arms A and J randomised between 29-Jul-2014 and 31-March 2016	Data collection to continue until disease progression or 5 years post randomisation whichever occurs first.
"M1|RT"	Arms A and H randomised between 22-Jan-2013 and 02-Sep-2016	From protocol v19.0 QL and HE data collection will stop for all participants recruited to Arm H prior to April-2016. From protocol v21.0 HE (EQ-5D) data collection will stop along with active follow up for all A and H participants randomised between Apr-2016 to Sep-2016.
"Metformin"	Arms A and K randomised since 05-Sep-2016	From protocol v19.0 the QL and HE sub-studies are closed to newly randomised participants. For all existing arm A and K participants (i.e. randomised prior to activation of protocol v19.0) data collection continues at each follow-up lifelong.
"Transdermal oestradiol"	Arms A and L randomised since 20-Jun-2017	From protocol v19.0 the QL and HE sub-studies are closed to newly randomised participants within this comparison. QL data will be collected through the PATCH trial.

17.2 TRANSLATIONAL SUB-STUDIES

Samples obtained from consenting STAMPEDE participants are analysed as part of separate translational sub-studies. These are conducted through collaborations with other academic and industry partners. All applications for collaboration and sample access are reviewed by the STAMPEDE oversight committees and overseen by the STAMPEDE BRG. For details on eligibility criteria for each translational sub-study refer to **Section 4.7.** For details regarding sample collection refer to the **Sample collection and handling manual** available via the website.

17.2.1 Germline DNA Analysis

DNA is being extracted from saliva samples provided by consenting participants enrolled in STAMPEDE. The purpose of this sub-study is to examine the germline (inherited) genetic changes present in people with high-risk localised or metastatic prostate cancer. The aim is to determine the prevalance of germline genetic aberrations present pre-diagnosis and to correlate prostate cancer risk single-nucleotide-polymorphisms (SNP) genetic profiles, identified in Genome-wide Association Studies (GWAS) and other sequence variants from next generation sequencing (NGS), with duration of response to ADT and the experimental treatments tested in STAMPEDE.

All newly randomised trial participants who join arms A, K or L are eligible to join this sub-study. For details relating to Saliva sample collection and shipping refer to the **Sample collection and handling manual.**

17.2.2 Circulating Tumour-DNA Analysis (Sequential Blood Samples)

The aims of this analysis include identification of molecular subgroups with differential treatment effects and, through sequential sampling, identification of molecular changes associated with disease progression to explore resistance mechanisms and early detection of treatment failure.

Sequential samples are required in order to detect genetic changes within tumours over time. The most important sampling timepoint is at progression, as it is hoped this can inform the potential mechanisms of treatment resistance. The sampling schedule is different for M0 and M1 participants and is detailed in the **Sample collection and handling manual**.

For details relating to blood sample collection including eligibility criteria and shipping refer to the **Sample collection and handling manual.**

17.2.3 Tissue Sample Analysis (FFPE Blocks)

As the clinical outcome data matures for several of the treatments comparisons evaluated within STAMPEDE, correlative analysis of the archival formalin-fixed paraffin-embedded (FFPE) tumour tissue will be undertaken, aiming to identify if genetic mutations present in prostate cancer cells pre-treatment predict how well each treatment works. In addition, projects providing preliminary prevalence and feasibility data to inform future biomarker-directed randomisations will be conducted.

From 2016 onwards, the CTU has been coordinating the retrieval of archival tumour blocks from selected consenting STAMPEDE participants. These samples are usually stored as FFPE tissue blocks at the hospital where the procedure was performed. Randomising sites will be asked to assist in the retrieval of FFPE samples when these are requested. Research teams will be required to confirm sufficient consent has been provided and to provide an anonymised copy of the relevant consent form. If not done so already, an anonymised copy of the consent form should also be sent to the CTU, as per **Section 10.1.1.**

For further details on where to check sufficient informed consent, sample processing and shipping and reimbursement, see the **Sample collection and handling manual.**

17.2.4 Biomarker-Screening Pilot

A biomarker-screening pilot was conducted in a subset of STAMPEDE sites. This ran from Dec 2017 to Jun 2018 and has now been completed.

17.2.5 Informed consent to receive results arising from genetic sub-studies

The consent process was updated for participants joining the trial from protocol v16.0 onwards (activated June-2017). Trial participants are asked to provide explicit informed consent if they wish to receive feedback of any results that arise from research analyses of genetic material extracted from any of the biological samples collected as part of the trial e.g. saliva, FFPE tumour blocks or circulating tumour DNA extracted from blood.

Only results which are of established clinical relevance and for which testing would be available under standard NHS genetic testing guidelines will be fed back e.g. pathogenic BRCA2 mutations. Any genetic analysis undertaken as part of additional research associated with STAMPEDE does not replace clinically indicated investigations as only a proportion of STAMPEDE participants will undergo prospective testing. Analyses are conducted on a purely research basis and it cannot be guaranteed that results will be fed back immediately.

STAMPEDE investigators are strongly recommended to refer all participants in whom a clinically relevant genetic result is detected during research analyses to a clinical geneticist. This is to facilitate access to genetic counselling and the required confirmatory testing. This is also necessary in order to offer appropriate advice to biological relatives in the event of confirmatory testing detecting a germline (inherited) abnormality. The list of clinically relevant gene mutations to be fed back will be based on current clinical guidelines. The STAMPEDE Biological Research Group will review this periodically to ensure it remains current and to oversee this process.

Information provided to STAMPEDE participants who joined the trial prior to Protocol version 16.0, stated that any subsequent genetic results would not be linked to them or their families and therefore results will not be provided in this instance. It is possible for trial participants to update their consent by re-consenting to the current Additional Research Consent Form. This should be anonymised and sent to the CTU as per standard procedures, see **Section 10.1.1.**

17.3 DISEASE VOLUMETRIC ANALYSIS SUB-STUDY

Baseline imaging obtained from STAMPEDE participants are accessed and analysed as part of the trial data collection. Collection and analysis will be undertaken in collaboration with partners on the TMG, initially, in ordered to determine disease volume. For details partaking to retrospective imaging centralisation and image handling, please refer to the individual sub study Working Practices available from the CTU. All subsequent applications for collaboration and imaging access are reviewed by the STAMPEDE oversight committees following the usual processes.

17.4 USING ROUTINE DATA TO IDENTIFY CLINICAL TRIAL OUTCOMES

This sub-study is developing methods to explore whether routine data can be used to quickly and accurately capture trial-related events in centrally-held datasets. These methods need to be developed and validated using different sources of routine data and to identify different types of events. These data sources include, but are not limited to, data from the Public Health England (PHE) National Cancer Registration and Analysis Service (NCRAS), the National Radiotherapy dataset (RTDS)

and the Systemic Anti-Cancer Therapy dataset (SACT) and NHS Digital, Hospital Episode Statistics (HES), and Office of National Statistics (ONS) data.

The overall aim of this sub-study is to develop a clinically useable tool, to accurately identify disease driven events and trial outcomes, to help reduce the burden of collecting trial data from traditional participant-investigator contact. By using data that has already been accurately collected in patients that have given appropriate consent, or for whom the appropriate permissions are in place (e.g. via the Confidentiality Advisory Group), it may be possible to improve timeliness, reduce costs and save resources. Development of enhanced ways to obtain trial data is being undertaken, to recalculate analyses already carried out but also to perform secondary analyses not possible with conventionally collected trial data. The projected aim is to utilise validated methods for routine follow-up and/or analysis in the future, as outlined in the protocol, longer term outcome data may be sought via routine data sources.

17.5 METFORMIN METABOLIC SUBSTUDY

The aim of this project is to explore the heterogeneity of metabolic changes associated with ADT and the effect that metformin has on these changes. Multiple blood markers of metabolic and disease status and sarcopenia assessed by cross-sectional imaging will be examined and linked with baseline characteristics and clinical outcomes.

ADT is standard of care for patients with advanced prostate cancer. It is effective but has side effects, one of them being metabolic dysfunction including obesity, sarcopenia, hyperinsulinemia, and insulin resistance. We will assess whether metformin will alter the percentage of patients with a poor prognostic lipid signature. We will explore whether adding metformin improves oncological outcomes through metabolic reprogramming of the host. In addition we want to determine whether the side effects of ADT can be mitigated by metformin, thus potentially decreasing cardiovascular morbidity and mortality. If we find a decrease in sarcopenia by adding metformin this will also be of importance since sarcopenia does not only affect the self-esteem of men, but also correlates with increased morbidity and mortality.

If metformin is associated with an improvement in metabolic parameters or sarcopenia, it could change clinical standard of care very rapidly, even independently of a benefit in cancer-specific or overall survival.

From protocol v21.0 we will collect sequential blood samples at baseline, regular time points throughout the trial and at progression. In addition we will request CT scans and FFPE tissue blocks from sites. The metabolic sub-study will be for participants allocated to the “metformin comparison”.

For eligibility criteria for the metabolic sub-study refer to **Section 4.7.4**.

For details relating to blood sample collection and shipping, please request the **Metabolic Sub-study Sample Collection and Handling Manual** from the CTU.

18 PATIENT AND PUBLIC INVOLVEMENT

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of a trial's participants in guidance or oversight of a trial.

18.1 POTENTIAL IMPACT OF PPI

PPI is in place to have constant patient overview and investment to guide research. Ultimately STAMPEDE has been created to test whether alterations in treatment help to improve outcomes and quality of life of patients. It is essential to have patients' input as they understand what other patients are going through

The nature of STAMPEDE is such that, even after a main analysis of a comparison has been performed, other participants are still being recruited to other arms. We have a duty to participants and the public to disseminate findings and results, both negative and positive. With this in mind, participants are periodically provided with study findings and updates. Study findings are also presented at conferences.

18.2 PATIENT REPRESENTATIVES

Patient representatives are actively involved in the management of STAMPEDE including updates and alterations. Part of their role is to review all material that will enter the hands of a patient or family member. This is to ensure all documentation used is clear, concise and has wording that is appropriate for everyone, as well as conveying the intended information. Patient representatives sit on the Trial Management Group (TMG).

19 PUBLICATIONS

The results from different sites will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG together with the STAMPEDE collaborators will form the basis of the writing committee and decide on the nature of publications.

For the "transdermal oestradiol comparison", as the efficacy analyses will based on relevant data from the STAMPEDE and PATCH trials, TMGs for the two studies will form the writing committee. Any release, of efficacy or safety data, presentation or publication will be agreed with the TSC according to the terms of their charter.

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

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

In the presentations, this list of sites will also be shown. The term "the STAMPEDE investigators" will clearly be stated and relevant names included in the presentation credits.

A detailed **Publication Plan** is documented separately.

20 DATA AND/OR SAMPLE SHARING

Data will be shared according to the CTU's controlled access approach and Standard Operating Procedure, based on the following principles:

- No data should be released in response to a data release request that would compromise an ongoing trial, unless specifically for safety reasons.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing on successful request and after the main publication for each comparison. Researchers wishing to access STAMPEDE data should contact the TMG via the CTU team in the first instance. All requests must be reviewed and approved by the TMG and TSC prior to release of data. Investigators should in term ensure the CTU team are regularly updated on the progress of their project and any presentation and publication must be in accordance to the agreements in place.

21 PROTOCOL AMENDMENTS

21.1 PROTOCOL

21.1.1 Amendments Made To Protocol Version 1.0 (May-2004)

Administrative changes such as typos, word change etc.

Name additions/changes to:

TMG members

TSC members

IDMC members

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

Section 1.2 – Figure 1, Celecoxib duration amended

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

Section 2.3 – Docetaxel information updated

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

Section 3 – Title change and content updated

Section 4.2 – New exclusion criteria added

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

Section 6.1.4 – Celecoxib duration amended

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

Section 6.1.6 – Celecoxib duration amended

Section 6.2.2 – additional docetaxel information

Section 6.2.3 – addition of CVS event history

Section 11 – Safety reporting updated

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

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

21.1.2 Amendments Made To Protocol Version 1.1 (May-2005)

Section 6.2 Administration and Dose Modifications, subsection 6.2.1 Zoledronic Acid

21.1.3 Amendments Made To Protocol Version 2.0 (Jun-2005)

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

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

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

Section 1.3 Trial Documentation updated to include new table detailing trial documentation ahead of accreditation, the inclusion of the radiotherapy forms and correct case report form timings

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

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

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

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

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

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

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

Section 4.3.1 – Additional information regarding the use of NSAIDs and cox-2-inhibitors before coming on to the STAMPEDE study and once commenced on study treatment

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

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

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

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

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

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

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

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

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

Chapter 11 – Safety reporting section updated

Section 17.3 – Increase in amount of blood needed & additional tissue sample request.

21.1.4 Amendments Made To Protocol Version 3.0 (Jul-2006)

Front Cover - NCRN logo added for accuracy

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

Front Cover - Clarification that it is a 6 arm trial

General Information section - MRC CTU staff section updatedyyyy

Section 1.2 – Statistics section updated.

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

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

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

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

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

Section 2.5 - Sub-headings numbered for consistency

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

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

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

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

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

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

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

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

Sections 6.1.2-6.1.6 - Androgen Suppression replaced with hormone therapy for consistency of terms

Section 6.2.2 - '(Taxotere)' Removed for consistency

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

Section 7.1 - Page number reference updated

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

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

Section 8 - Rewording for clarification of definition of trial withdrawal

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

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

Section 8.2- Information added in regard to patient transfers

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

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

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

Section 11.2 – Reference to toxicity grading website added

Section 11.2.1 - Reference to table in appendix G added

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

Section 13 - CTA reference added

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

21.1.5 Amendments Made To Protocol Version 4.0 (Dec-2007)

General Information Section - Randomisation and SAE reporting details sections clarified

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

Section 1.2 - Follow schedule corrected

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

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

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

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

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

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

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

Section 6.6.4 - Information on radiotherapy data collection added

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

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

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

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

Figure 4 - Note added to include palliative radiotherapy CRF

Section 11.3 - SAE reporting information updated

Section 19 - Protocol amendments list updated

21.1.6 Amendments Made To Protocol Version 5.0 (Aug-2008)

1. General Information Section – Randomisation phone line number updated – non UK extension added

2. Section 3 – Information about QL study removed to reflect closure of QL study after first 700 patients

3. Section 4.2 – Exclusion criteria clarified to explain that only patients with severe poor cardiovascular history should be excluded

4. Section 4.3.1 – Information on co-administration of NSAIDS with celecoxib changed based on clinical advice.

5. Section 5 - Randomisation phone line number updated – non UK extension added

6. Section 6.2.1. – Information added to clarify that patients who develop an osteonecrosis of the jaw should stop zoledronic acid treatment

7. Section 6.2.3 – 'severe' text added to accurately reflect which patients should be excluded based on their cardiovascular history

8. Section 7.1.2 – Definition of disease progression extended for clarity

9. Figure 3 – Updated to include reference to newly created skeletal related event form

10. Figure 4 – Previous error in table amended to show that the 4th Zoledronic Acid form that is submitted contains information about 3 cycles rather than 2 as previously indicated

11. Table 4 – 'Other important medical condition' added to definition of serious in the SAE section, to accurately reflect SAE form and current practice

12. Section 11.1 – Information added on reporting or pregnancies

13. Section 17 - Information about QL study removed to reflect closure of QL study after first 700 patients

21.1.7 Amendments Made To Protocol Version 6.0 (Jul-2009)

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

Co-Investigator

Patient Representatives

Trial Manager

Data Manager

General Information Section - Coordinating Centre – address change

General Information Section – change of Sponsor address

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

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

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

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

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

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

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

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

Section 3 – SSA Favourable Opinion removed

Section 4.2 – Exclusion criterion xiii greyed out

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

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

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

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

Section 6.2.3 – recruitment note added

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

Section 7.1.2 – removal of reference to SRE- specific CRF

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

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

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

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

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

Section 12.2 – Reference to SSA removed

Section 16.3 – Statement added regarding actioning IDMC recommendation ahead of TSC ratification

21.1.8 Amendments Made To Protocol Version 7.0 (Jul--2011)

1. General Information Section- SAE reporting fax number corrected

2. Section 11- SAE reporting fax number corrected

21.1.9 Amendments Made To Protocol Version 7.1 (Jul-2011)

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

General Information Section – contact details updated

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

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

General Information Section – Abbreviations list updated

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

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

Section 1.1 – Information about new IMP, Abiraterone inserted

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

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

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

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

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

Section 2.1 – Wording related to hormone therapy updated for clarity

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

Section 2.2 – Updated references added

Section 2.3 – Updated references added

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

Section 2.6.1 – Updated references added

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 6.1.1-6.1.6 – References to further sections updated

Section 6.1.7 – Section added to describe abiraterone treatment

Section 6.2.4 - Section added to describe abiraterone treatment

Section 6.6 - Section added to give information regarding radiotherapy treatment

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

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

Section 7.1.2 – Wording updated regarding skeletal-related events for clarity

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

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

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

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

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

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

Section 8.1 – Definition of progression for abiraterone patients added.

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

Section 11 – Safety reporting wording updated for clarity

Section 11 – SAE reporting fax number updated

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

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

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

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

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

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

Section 16 – Reference to trial committee charters added for information

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

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

Section 18 – Information on publication policy expanded for clarity

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

Section 20 – References extensively updated

21.1.10 Amendments Made To Protocol Version 8.0 (Sep-2011)

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

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

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

General Information Section – Abbreviations list updated

Section 1.1 – Information regarding the new research radiotherapy treatment inserted

Section 1.1 – Information regarding docetaxel updated

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

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

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

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

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

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

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

Section 4.2 – Clarification added on cardiovascular exclusion criteria

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

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

Section 4.4.1 – Clarification added regarding pre-randomisation checks

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

Section 4.4.5 – Information added regarding starting research radiotherapy treatment

Section 4.4.6 – Information updated on concomitant medications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 9.8 – Clarification on intermediate stopping guidelines

Section 9.9 – Clarification on the outline analysis plan

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

Section 11 – Clarification added regarding arm A safety reporting timelines

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

Section 14 – Indemnity section updated to reflect current MRC policy

Section 16 – Clarification regarding TMG membership

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

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

Section 20 – References updated

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

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

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

Section 1 – Figure added and clarifications added to each figure

Section 2 – Previous reference 8 removed

Section 4 – Clarification of acceptable alternatives to bone scans

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

Table 4 – Dose-volume objectives corrected: order swapped

Table 5- Correction CRFs names

Section 17.3.2 – Clarification that DNA may be extracted

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

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

Throughout protocol – typos have been corrected

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

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

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

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

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

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

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

Throughout protocol – typos have been corrected

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

Section 1.2 – Enzalutamide added as trial treatment

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

Section 2.10 – Rationale for the combination of enzalutamide and abiraterone

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

Section 4.4.2 – Wording clarified

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

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

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

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

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

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

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

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

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

Section 12.1 – Wording clarified

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

Section 19 - Amendments made to protocol updated

Reference list updated

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

Throughout protocol – typos have been corrected

Section 4.4.2. Wording clarified

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

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

Section 6.11.4.A. Correction of CTCAE version

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

Section 9.6. Sample size increase for M1|RT comparison

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

Section 17. Addition of saliva samples collection for DNA analysis

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

21.1.15 Amendments Made To Protocol Version 13.0 (Feb-2015)

Throughout protocol – typos have been corrected

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

Table of contents updated to reflect any changes to the protocol

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

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

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

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

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

Section 4.2. Clarification of Exclusion criteria XIII and XVI

Section 4.4.2. Clarification on HT prior to randomisation

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

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

Section 4.5. Clarification provided on tissue block collection

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

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

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

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

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

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

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

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

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

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

Table 1. Table updated to remove repetition

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

Table 15. Table updated to include only active trial treatments

21.1.16 Amendments Made To Protocol Version 14.0 (Oct-2015)

Throughout protocol – typos have been corrected

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

Table of contents updated to reflect any changes to the protocol

Section 1. Wording added throughout section to include reference “metformin comparison”

Section 2. Section updated to include reference “metformin comparison”

Section 4.2. Exclusion criteria review to reflect Arm J closure and instruction of “metformin comparison”

Section 4.3. Clarification of comparison specific eligibility (M1|RT and metformin)

Section 4.5.7. Clarification on concomitant medication and contra-indicated concomitant medications

Section 6. Treatment sections improved throughout

Section 6.11. Section updated to include details on metformin treatment

Section 6.12. Amendment throughout sections and sub-sections for metformin treatment

Section 6.13. Amendment throughout sections and sub-sections for metformin treatment

Section 6.13. Improvement throughout sections and sub-sections for abiraterone and enzalutamide treatment

Section 7.0. Amendment throughout sections and sub-sections to include assessment and procedures specific to “metformin comparison”

Section 9.0. Section updated and streamlined to capture statistical considerations on each comparison

Section 9.0. Details on “metformin comparison” added

Section 11. Safety processes updated and clarified

Section 16.0 Membership to oversight groups updated

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

21.1.17 Amendments Made To Protocol Version 15.0 (Mar-2017)

Throughout protocol – re-structure of the treatment-related information for ease of use

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

Throughout protocol – typos have been corrected

Addition of TMG members

Table of contents updated to reflect any changes to the protocol

New section for summary of trial added in table format

Section 1. Revised format for the summary of treatment groups, with the new transdermal oestradiol arm also added

Section 2. Clarification regarding research treatments that have previously reported or completed recruitment, section updated to include the "transdermal oestradiol comparison"

Section 3. New sections added for the "transdermal oestradiol comparison" and future planned biomarker-selected comparisons

Section 4.1.4. Change in definition of adequate renal function

Section 4.3. New section added for the biomarker screening pilot, selection criteria removed for "research RT comparison"

Section 4.4.1. Change in definition of adequate renal function

Section 4.4.2. New section added for the patient selection criteria specific to the "transdermal oestradiol comparison"

Section 4.5. Screening procedure tables and figure added for clarification.

Section 4.5.1. New section added for biomarker screening pilot investigations prior to randomisation.

Section 5.1.1. New section added for the biomarker screening pilot registration.

Section 6. New sections added for the "transdermal oestradiol comparison"

Section 7. Amendment throughout sections and sub-sections to include assessment and procedures specific to "transdermal oestradiol comparison"

Section 7.1.4.B. Section added on cardiovascular outcomes for the "transdermal oestradiol comparison"

Table 18. Table added to clarify follow-up assessments

Section 8. Section updated for "transdermal oestradiol comparison"

Section 9. Section updated for "transdermal oestradiol comparison"

Section 12.1.1.D. Section added on participant feedback from investigations and additional analyses

Section 15. Section updated for "transdermal oestradiol comparison" and biomarker screening pilot

21.1.18 Amendments Made To Protocol Version 16.0 (Oct-2017)

Summary of trial- Table 1: Schedule of Assessments has been added

Abbreviations & Glossary- new terms have been added

Section 1- Table 4: Abiraterone information updated as results of primary analysis published

Section 4.3 - Biomarker timelines redefined, the length of prior hormone therapy has increased to reflect change in turnaround time for testing

Section 4.6 - Biomarker screening information updated

Section 6.2 – Clarification on safety monitoring required for patients receiving trial abiraterone added . Abiraterone overdose information altered for clarity.

Section 6.3.4 - Drug interactions updated to specify that tamoxifen is contraindicated in combination with abiraterone, enzalutamide and transdermal oestradiol.

Section 6.5 – Detail on requirements at site to demonstrate compliance with per-protocol required safety monitoring added

Section 7 – Schedule for assessments updated, removal of table 19

Section 7.1 - Clarification on additional safety monitoring required for patients receiving trial abiraterone added

Section 7.4 - Table 20 QL information removed and added to Table 1: Schedule for Assessments

Section 10.1.1- Central monitoring of consent information added

Section 11 – Re-structured and re-worded for clarity on reporting requirements for safety data captured on the SAE CRF. Explanation provided for exempted events and definitions added. Table 28 and Box 1 updated and Figure 1 added.

Section 11.2- Updated SAE exceptions, SAE flow chart added for clarity

Section 11.3 - Update of investigator assessments and notification checklist for expedited safety reporting

Section 11.4 - Update of wording of CTU responsibilities

Section 17.4 - Sub-study information added to include Disease Volumetric sub-study

21.1.19 Amendments Made To Protocol Version 17.0 (Feb-2017)

Throughout protocol - Typos have been corrected, abbreviations & glossary & table of contents updated

Throughout protocol - Addition of abiraterone as SOC & original comparisons closed to active follow-up

Throughout protocol – Update of and removal of biomarker pilot information now randomisation to the rucaparib comparison is to be activated

Trial administration – Information updated, full contact list linked to website, all comparison chief-investigators added as co-signatories

Summary of trial – Updated, “rucaparib comparison” added and “original comparisons” closed to active follow-up; figure 1 updated with new randomisation schema and S-STAMPEDE Cohort study

Schedule of Assessments updated– Table 1a removed, Tables 1, 2 and 3 added

Lay Summary – Re-drafted, “rucaparib comparison” added

Section 2 – Role of SOC abiraterone added, reported comparisons updated and rationale for comparisons that have completed recruitment removed. Rational for the “rucaparib comparison” added

Section 3.1 – Addition of site and investigator criteria

Section 4 – Complete restructuring of section, addition of biomarker screening and registration information.

Section 4.2 – Additional information about proposed approach to staged informed consent

Section 4.4 – Clarification as to required pre-randomisation screening by comparison

Section 4.5.4 – Detail regarding SOC abiraterone (permitted in metformin comparison only)

Section 4.9.3 – Eligibility to be randomised to the “rucaparib comparison” added

Section 4.10 - Sub-study eligibility criteria clarified; new germline blood sub-study added (PAXgene for S1A and S1M) and stratified – STAMPEDE cohort study added

Section 5 – additional information relating to registration and randomisation to the “rucaparib comparison” added

Section 6.1.4- SOC abiraterone detail added

Section 6.2.7.C – Table 19: Additional assessments required following change of transdermal oestradiol patch or dose added

Section 6.2.9 - Rucaparib treatment specific information added

6.3 – Concomitant medications updated: clarification that spironalactone is contraindicated with abiraterone and rucaparib drug interactions added

Section 7.1 – Table 27: summary of follow-up schedules by participant group added

Section 7.1.5.D – Additional Safety assessment required for participants receiving rucaparib added

Section 7.2.3 – Data collection for SOC abiraterone clarified

Section 7.2.8 & 7.3.2 - Data collection & Follow-up procedures for S-STAMPEDE Cohort participants described

Section 7.3.3 – Clarification added regarding procedures to use linked follow-up information obtained from sources of electronic health data

Table 29 and 28 updated with new CRFs

Section 8.1.4 – Reasons to stop rucaparib

Section 9.8 – addition of statisitcal considerations relating to the “rucaparib comparison”

Section 11 – Stopping of SARs and SUSARs reporting for “original comparisons” closed to active follow up and addition of rucaparib-specific notable events

Section 12- ethical considerations updated with detail relating to data to permit linkage with sources of electronic health data

Section 13 – Data archiving and retention guidance added

Section 16 – Updates of STAMPEDE oversight committees including expanded TMG sub-groups

Section 17.1.1 A- Closure of HE & QL sub-studies to new participants and stopping of data collection for several comparisons; summarised in Table 40.

Section 17.2 – S-STAMPEDE cohort study & additional germline data collection added

Section 17.4 – New sub-study: Using routine data to identify clinical trial outcomes added

Section 18 – New section regarding patient and public involvement in STAMPEDE added

Section 20 - New section regarding data and sample sharing added

21.1.20 Amendments made to Protocol Version 18.0 (Jun-2018)

Throughout protocol: Removal of "rucaparib comparison" information

Throughout protocol: Redraft of biomarker screening pilot study into ancillary studies section

Summary of Trial – Figure 1 updated; removal of registration information for S-STAMPEDE Cohort study

Schedule of Assessments – Removal of registration from figure 1; Table 2 updated to include PSA within 8 weeks of randomisation; Table 3 S-STAMPEDE Schedule of Assessments removed

Abbreviations & Glossary - Terms relating to the "rucaparib comparison" have been deleted

Section 1 – Lay summary "rucaparib comparison" information removed

Section 2 – Rationale for incorporating molecular stratificaion and "rucaparib comparison" removed

Section 3.2 – "Rucaparib comparison" comparison-specific site accreditation removed

Section 4 – Removal of biomarker screening and registration information

Section 4.2 – Removal of staged informed consent process

Section 4.3 – Removal of biomarker screening eligibility information

Section 4.4.3 – Removal of "rucaparib comparison" screening investigations prior to randomisation

Section 4.5 – Removal of prior permitted SOC treatments for "rucaparib comparison"

Section 4.7 – Removal of and clarification to the general inclusion & exclusion criteria of Serum Pottasium & Cardiovascular disease respectively.

Section 4.9.3 – Removal of "rucaparib comparison" specific eligibility criteria

Section 4.10 – Addition of information regarding biomarker pilot screening

Section 4.10.1 – Removal of S-STAMPEDE Cohort sub-study

Section 4.10.2 – Removal of PAXgene sample collection

Section 5 – Removal of information relating to registration and randomisation to the "rucaparib comparison"

Section 6.2.6.B – Addition of additional metformin dose reduction stages

Section 6.2.9 – Removal of "rucaparib comparison" research treatment information

Section 6.3.1 – Removal of "rucaparib comparison" therapeutic interactions information

Section 7 - Table 30 removal of "rucaparib comparison" specific CRFs; table 31 – removal of arm S1M schedule for completion of treatment forms

Section 7.1.5.D – Removal of rucaparib additional safety assessments

Section 7.2.8 – Removal of data collection for S-STAMPEDE Cohort participants

Section 7.3.2 – Removal of follow-up for S-STAMPEDE cohort participants

Section 8.1.1 – Clarification of metformin, abiraterone and enzalutamide use post progression

Section 8.1.4 – Removal of "rucaparib comparison" stopping trial treatment information

Section 9.6.7 – Revised sample size for "metformin comparison"

Section 9.8 – Removal of statistical consideration relating to the "rucaparib comparisons"

Section 10.1.1 – Updated central monitoring of consent process

Section 11 – Removal of rucaparib-sepcific notable events

Section 11.1.1 – Clarification of trial-specific exemptions and notable adverse events

Section 16 – Addition of Genetic Sub-Group

Section 17.1.1.A – Clarification of Qulaity of Life and Health Economics data collection

Section 17.2 – Details of biomarker screening pilot study information moved here

Section 17.2.1 – removal of S-STAMPEDE Cohort study information

21.1.21 Amendments made to Protocol Version 19.0 (Aug-2020)

Throughout protocol: Section headings and table numbers renumbered, references updated, Centre changed to Site for consistency

General information - Sponsor updated to UCL, Trial contacts updated, Glossary updated

Summary of Trial – M1RT status updated, transdermal oestradiol number of participants updated

Figure 1 updated to include new SOC options and clarify options based on HbA1c level.

Figure 2 updated to reflect extended recruitment in metformin and te2 comparisons

Schedule of Assessments –remove height and upadte footnotes

Abbreviations – minor updates

Section 1 – updated comparisons closed to recruitment – addition of Arm H. Arms E and F added to Table 6.

Section 2.1.3 – Addition of new SOC options abiraterone, enzalutamide and apalutamide

Section 2.3 – Addition of M1RT results

Section 2.5.2.B – Updated target recruitment for “transdermal oestradiol” comparison

Section 3.1.2 – Addition to recommend additional investigators be delegated for safety reporting to cover absences

Section 4.2 – Minor rewording clarification

Section 4.1 – Update to screening investigations, addition of timeframes in days, M1 imaging clarified, several baseline investigations moved to pre-randomisation. ECG removed, option for no fasting glucose added.

Section 4.3 – Table 8 - Addition of new SOC options abiraterone, enzalutamide and apalutamide

Section 4.3.2 – Added oligometastatic disease

Section 4.3.3 –Clarification SOC docetaxel cannot be given if SOC abiraterone, enzalutamide and apalutamide is planned

Section 4.3.4 – New section for SOC abiraterone, enzalutamide and apalutamide. Addition of enhanced monitoring for “transdermal oestradiol” comparison

Section 4.4.4 – General inclusion criteria III removed, haematological value thresholds clarified

Section 4.5 – General exclusion criteria II added (consolidates previous VII-IX), clarification where both AST and ALT results required, VI clarified exclusion is for unhealed surgical wounds rather than surgerical intervention

Section 4.6.1 – Added metabolic substudy to “metformin“ comparison requirements

Section 4.6.2 – Added eligibility criteria for participants not yet started on SOC abiraterone, enzalutamide and apalutamide

Section 4.7.2 – Clarification circulating tumour DNA sub study not recruiting

Section 4.7.4 – New section for Eligibility for metformin sub study

Section 5.1 – Addition of new instruction to provide randomisation documents to CTU after randomisation.

Section 5.2 – Clarification of wording for co-enrolment in other trials (interventional and non-interventional)

Section 6 – Reformatted throughout, new subheadings and layout, multiple new tables inserted

Section 6.1 –Addition of SOC combination table to replace text list

Section 6.1.1 – Section renamed Androgen Deprivation Therapy (previously Hormone Therapy)

Section 6.1.2 – Updated wording on Radiotherapy for M0 participants

Section 6.1.2.C – New section for oligometastatic participants

Section 6.1.3 – Administration of SOC RT moved up from 6.7

Section 6.1.5 – New title SOC upfront systemic therapy – addition of SOC abiraterone, enzalutamide and apalutamide

Section 6.2 –Research treatment broken down per IMP instead of per comparison.

Section 6.2.1 – Addition of Table 9 treatment duration for all research treatments and Table 10 management of trial treatment post progression

Section 6.2.2 – Some text now in tables. Updated wording about associated toxicities and contraindications

Section 6.2.3 – Some text now in tables. Updated wording about associated toxicities and contraindications

Section 6.2.3.C – New table for hypertension monitoring.

Section 6.2.4 - Some text now in tables. Updated wording about associated toxicities and contraindications

Section 6.2.5 - Reformatted, some text now in tables. Updated wording about associated toxicities and contraindications. Additional detail on moving from induction to maintenance dose on oestradiol level, and changing brands of patches

Section 6.3 – Clarification of wording. Details of drug interactions and additional safety monitoring moved up to sections 6.2.2, 6.2.3, 6.2.4 and 6.2.5 respectively

Section 7 – Added Figure 3 - PSA progression example scenarios

Section 7.1.4 – Clarification added to explain rationale for continuing to collect metabolic test results post progression

Section 7.1.3.A –Addition of Figure 3 example progression schenarios

Section 7.1.4 – Addition of rationale for continuing metabolic tests beyond progression

Section 7.1.5.A Clarification of required tests for abiraterone and enzalutamide, specifically when one or the other is discontinued.

Section 7.1.5.C - Addition of real time monitoring of hormone results for te2 participants to check safety of combination with new SOC abiraterone, enzalutamide and apalutamide

Section 7.2.3 – Addition of SOC systemic therapy log

Section 7.2.4 – Addition of requirement to submit radiotherapy CRF even if radiotherapy not given

Section 7.3 – Nurse led follow up expanded to allow for other appropriately qualified individuals

Section 7.3.1 – Minor changes

Section 7.4.1 – Table 28 updated with new CRFs for SOC systemic therapy, and metabolic sub study CRF. Removal of baseline form, bone density risk factor. Blood form moved. Updated key for Table 29.

Section 8.1 – Clarification of consent for data collection

Section 8.1.3 – Additional wording on stopping te2 and options for pausing, switching and restarting.

Section 8.2 – New section about permitted breaks in SOC ADT treatment

Section 9.2 – Additional wording regarding analysis of “enzalutamide + abiraterone comparison”

Section 9.5 – Additional wording regarding analysis of “enzalutamide + abiraterone comparison”

Section 9.7.4 – New section detailing enhanced safety monitoring of combination new SOC and transdermal oestradiol

Section 9.10 – removal of Mann-Whitney test as relevant for original comparisons now closed.

Section 9.10.2 - Additional wording regarding analysis of “enzalutamide + abiraterone comparison”

Section 10.1 – Minor clarification to wording

Section 10.1.2 – Clarification of central monitoring processes

Section 10.1.3 – Wording updated in line with current protocol template

Section 11.1.1 – Clarification of notable events (NEs) to be collected, new cancers no longer included.

Section 11.1.2 – Addition of new SOC enzalutamide and apalutamide

Section 11.2 – Update to add requirement for investigator absence cover, updated AE, SAE and NE notification period. Figure 5 added.

Section 11.2.2 – Updated expedited reporting exemptions

Section 11.2.3.C – Expectedness removed from site investigator responsibilities. Table 37 updated

Section 11.2.3.D – Figure 6 updated. Box 1 updated

Section 11.3 – Updated process for causality queries. Clarification of Swiss reporting responsibilities

Section 11.3.1 – Expectedness added to sponsor responsibilities

Section 12.1.1.A – Updated with new SOC enzalutamide and apalutamide

Section 13 – CTA number updated

Section 15 - Clarification for SOC enza and addition of SOC apalutamide

Section 16.2 - Clarification on frequency of TSC meetings

Section 16.4 – subgroups updated

Section 16.5 – Figure 7 updated

Section 17.1 – Addition that secure email now permitted for sending CRFs

Section 17.2.2 – Minor changes, sub study is now closed

Section 17.2.4 – Removed details of biomarker sub study as now closed

Section 17.5 – New section added for metformin metabolic sub study

Section 20 – Clarification that any data released must be approved by TMG, TSC and subject to agreements

Section 22 – References updated, removal of several references linked to protocol v18 which was not released to sites

21.1.22 Amendments made to Protocol Version 20.0 (Oct-2020)

Minor amendment to correct typograhical, spelling, formatting and cross-reference error, or clarify wording throughout.

Minor updates to Summary of Trial table

Table 2 – ECG removed from Cardiac asseessment row, weight added to waist measurement row

4.2.2 – Timeframe for pre - SOC docetaxel bloods updated from 4 months to 16 weeks in line with other timeframes.

4.4 Header title changed

4.6 Footnote 1 restored

5.2 Wording revised to allow participants to continue on STAMPEDE research treatment while co-enrolled in IMP trial, providing no interactions.

6.1.2 Header title changed

6.1.3.A Header title changed

6.2 Footnote 2 removed from Table 10

6.2.3.C – Restoration of Table 11, deleted in error when accepting tracked changes. Table 11 outlines 3 monthly blood pressure monitoring as specified in section 7.1.5.B

6.3 Header title changed

11.2.2 – Correction to bullet list exemption, text removed

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