

# STAMPEDE: “Metformin comparison”

## Pharmacy Training

- “Metformin comparison” hypothesis and trial design
- Treatment administration and duration
- IMPs overview
  - Supply
  - Accountability
  - Destruction
  - Returns
- Activation timelines and requirements
- Other pharmacy updates

# Hypotheses and rationale

# Hypothesis

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- Will the addition of metformin to the standard-of-care
  - Improve survival in hormone-naive PCa?
  - Mitigate adverse side effect linked to long-term ADT?

# Background and rationale

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- Long-term ADT
  - ↑ risk of insulin resistance
  - ↑ hyperglycaemia
  - ↑ dyslipidaemia
  - ↑ obesity
- 50% pts on ADT will develop **metabolic syndrome**
  - Cardiovascular morbidity
  - Mortality
- Metformin
  - Counteracts effects of metabolic syndrome
  - Anti-cancer effects

# Background and rationale

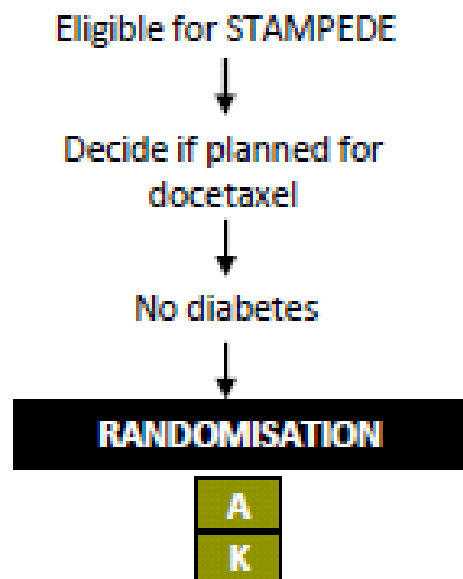
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- Full details on scientific and clinical rationale to be posted on STAMPEDE website

[www.stampedetrial.org](http://www.stampedetrial.org)

# Trial design

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## Key

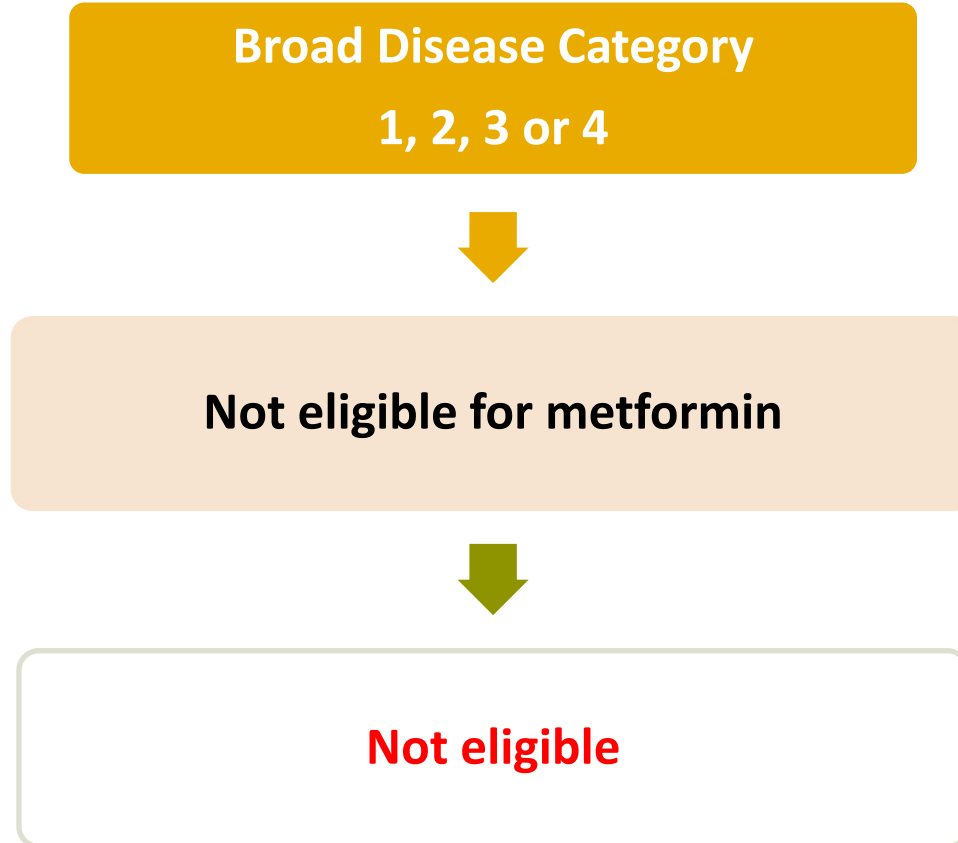
A	Standard-of-care (SOC)
K	SOC + metformin

SOC = ADT ± Docetaxel ± RT

# Trial design

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- “M1|RT comparison” closed 02-Sep-2016
- “Metformin comparison” opened 05-Sep-2016





# Inclusion criteria: metformin comparison

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- No diabetes mellitus
- HbA1c <48 mmol/mol (equivalent to < 6.5% of total Hb)
- Creatinine clearance  $\geq 60$  ml/min /m<sup>2</sup>
- No history of metabolic acidosis or pre-disposing conditions
- No current or previous treatment with metformin
- No contra-indications to metformin

# Screening

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## Imaging

- CT or MRI of pelvis and abdomen
- Bone Scan (or equivalent e.g. whole body MRI, choline PET-CT)
- Chest X-ray (only if chest not included in CT/MRI)

## Blood tests

- PSA
- Creatinine clearance
- Full blood count
- Urea and Electrolytes

- HbA1c

Mandatory

## Other

- BP
- ECG

# Health-related findings

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- Screening might detect new diagnosis of diabetes
  - New letter developed to inform GP
  - Management as per standard clinical practice



## **Framework on the feedback of health-related findings in research**

March 2014

### **Reference:**

[http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy\\_communications/documents/web\\_document/wtp056059.pdf](http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp056059.pdf)

# Baseline investigations

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- Baseline tests required
  - Within 4 weeks before or after randomisation
  - Before starting research treatment
- Testosterone (pre-ADT, if available)
- Serum corrected calcium
- Phosphate
- Magnesium
- Albumin

- Fasting glucose
  - Fasting triglycerides
  - Non-fasting total cholesterol, LDL and HDL
- } Mandatory

# Concomitant medications

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- Information on long-term (>6months) use of con-meds
  - Statins
  - Metformin
  - Aspirin
  - Bisphosphonates or Denosumab/calcium and Vitamin D
  - Opiate pain killers
  - ACE inhibitors or angiotensin II antagonist
  - Vitamin B12

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# **Trial Treatment**

# Starting trial treatment: metformin

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- Arm K patients should start metformin
  - As soon as possible after randomisation, ideally
    - $\leq 4$  weeks from randomisation
    - $\leq 12$  weeks from starting ADT
- Metformin and docetaxel can be given concurrently
  - i.e. don't wait until after chemotherapy
- Formulation
  - Immediate release (IR)
  - Sustained release (SR)
- To be taken with or after food
  - SR with evening meals
- Starting dose = 850mg OD
- If tolerated (after 1 month) = 850mg BID

# Treatment duration: M0 patients

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- Metformin should continue as long as ADT
- If ADT is stopped after 2 years
  - Metformin continues for a minimum of 3 years **OR**
  - 12 months after the last LHRH injection (whichever is longer)
- If LHRH is re-started whilst patient on metformin
  - Metformin should continue while on ADT
- If metformin stopped 12 months after last LHRH injection
  - Metformin should not be re-started



# Treatment duration: M1 patients

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- Metformin treatment continues:
  - As long as ADT
  - Post-progression
  - While on second-line treatments
    - Unless patient joining new IMP trial (CRPC setting)

# Contraindications

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- Metformin should be **permanently stopped** if
  - eGFR  $\leq 60$ ml/min/1.73m<sup>2</sup> (contradiction in protocol on page 47)
- Metformin should be **paused** if

	RISK FACTOR
Iodinated contrast agents	Pause metformin 24 hours prior to receiving contrast and re-start 48 hours post administration.
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.

# Treatment breaks

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- Discuss with trial team if
  - Treatment breaks >3months OR
  - 50% doses missed
- If metformin stopped for >2wks
  - Re-start at 850mg OD
  - Escalate to full dose after 1 month

# Management of metformin-related toxicities

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- GI toxicities

TOXICITY EVENT	ACTION
Grade 1	<p>Ensure metformin is taken with or after food.</p> <p>Consider switching to 750 mg sustained release preparation if available.</p> <p>If unavailable consider a 1 week treatment pause and re-start at 850mg once daily and attempt an escalation after 1 month.</p> <p>If necessary, remain at 850mg OD.</p> <p>If unable to tolerate 850mg OD or sustained release preparations are not available consider dose reduction to 500mg OD.</p>
Grade 2 or higher	<p>Reduce to 850mg OD and if symptoms improve to grade 1 or better, re-attempt dose escalation after 1 week.</p> <p>If symptoms recur at grade 2 or higher, pause treatment for 2 weeks.</p> <p>Re-start at 850mg sustained release or if not available 500mg OD.</p> <p>Re-attempt a dose escalation 2 months later.</p> <p>Continue at the maximum tolerated dose providing symptoms <math>\leq</math> grade 1.</p>

# Management of metformin-related toxicities

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## Correction GI toxicities Table 12 Protocol v15.0

- **Grade 1 toxicity** at 850mg BID
  - A. Change to 750mg SR BID OR
  - B. 1 week treatment pause then restart 850mg OD IR & attempt an escalation after 1 month OR
  - C. Reduce to 500mg OD (IR or SR) if both A&B unsuccessful & attempt dose escalation after 1 month, aiming to continue at the maximum tolerated dose
- **Grade 2 or higher** at 850mg BID
  - A. Reduce to 500mg OD IR; re-attempt dose escalation after 1 week if symptoms improve.
  - B. Stop treatment for 2 weeks if A unsuccessful then restart 750mg OD SR after 2 weeks & re-attempt dose escalation 2 months later aiming to continue at the maximum tolerated dose

# Management of metformin-related toxicities

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- B12 deficiency
  - Start haematinics including vitamin B12
- Lactic acidosis
  - Discontinue immediately
  - Consider haemodialysis
- Overdose
  - Consider hospital admission
  - Clinical management as per standard practice

# Interactions

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Clinical use	Drug	Recommendation
Anti-hypertensives and other cardiac disease	ACE inhibitors/angiotension II receptor blockers e.g. ramipril, lisinopril, Irbesartan	Monitor renal function until confirmed to be stable and providing eGFR remains $>60\text{mls/min/m}^2$ . Repeat test if necessary
	Diuretics e.g Frusemide, budesonide	
Antibiotics	Aminoglycoside antibiotics e.g Gentamycin or amikacin	Hold metformin during treatment and re-start providing renal function confirmed to be stable and eGFR remains $>60\text{mls/min/m}^2$
Analgesia	NSAIDS e.g. Ibuprofen, diclofenac, naproxen	Avoid if possible If no alternative increase renal monitoring to until confirmed to be stable and providing eGFR remains $>60\text{mls/min/m}^2$

# Follow-up

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All patients, all research arms

- FU and PSA measurements
  - 6 weekly for first 6 months
  - 12 weekly up to year 2
  - 6 monthly up to year 5
  - Annually thereafter

Arm A and K patients

- Additional metabolic and cardiovascular outcomes

Arm K patients

- 6 monthly renal function tests (U&Es)



# Cardiovascular and metabolic outcomes

OUTCOME OF INTEREST	TIMING OF ASSESSMENT	CRF
Eligibility screening		
HbA1c	Prior to randomisation	Randomisation
Baseline		
Lipid profile (cholesterol, HDL, LDL)	Randomisation	Baseline
Fasting glucose	Randomisation	Baseline
Fasting triglyceride	Randomisation	Baseline
Weight and BMI	Randomisation	Baseline
Waist circumference	Randomisation	Baseline
Follow-up		
HbA1c	6 months 12 months 24 months	FU
Fasting glucose	6 months 12 months 24 months	FU
Fasting triglyceride	6 months 12 months 24 months	FU
Lipid profile (cholesterol, HDL, LDL)	Annual	FU
Metabolic and cardiovascular events		
New diagnosis of diabetes	As and when metabolic and cardiovascular event occurs	FU
Cardiac event: myocardial infarction or revascularization (e.g PCI or CABG)	As and when metabolic and cardiovascular event occurs	FU
Stroke or transient ischaemic event	As and when metabolic and cardiovascular event occurs	FU

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# **IMP Overview**

# Metformin Hydrochloride

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- Local clinician should use stock available locally
- **Only metformin hydrochloride** permitted
  - Generic stock permitted
    - Send copy of SmPC to STAMPEDE team
- Formulation
  - Immediate
  - Sustained release
- Starting dose = 850mg OD
  - If tolerated (after 1 month) = 850mg BID

Medicine Name	Mg	Active Ingredient	Sustained Release	Form	Manufacturer
Diagemet XL Prolonged Release tablets	500	metformin hydrochloride	Yes	Tablet	Genus Pharmaceuticals
Glucient SR prolonged-release tablet	1000	metformin hydrochloride	Yes	Tablet	Consilient Health Ltd
Glucient SR prolonged-release tablets	500	metformin hydrochloride	Yes	Tablet	Consilient Health Ltd
Glucient SR prolonged-release tablets	750	metformin hydrochloride	Yes	Tablet	Consilient Health Ltd
Glucophage film coated tablets	500	metformin hydrochloride	No	Tablet	Merck
Glucophage film coated tablets	850	metformin hydrochloride	No	Tablet	Merck
Glucophage SR prolonged release tablets	500	metformin hydrochloride	Yes	Tablet	Merck
Glucophage SR prolonged release tablets	750	metformin hydrochloride	Yes	Tablet	Merck
Glucophage SR prolonged release tablets	1000	metformin hydrochloride	Yes	Tablet	Merck
Metformin tablets	500	metformin hydrochloride	No	Tablet	Aurobindo Pharma - Milpharm Ltd.

# IMP Management

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- **Ordering** → as per local procedures
- **Prescribing** → as per local procedures and commissioning arrangements
- **Labelling** → MHRA approved labels to be provided by Sponsor
  - Trial-specific labelling required before dispensing
  - Dispensing labels permitted
    - Do not obscure CT label
    - Advice to be consistent with CT label

# IMP Management

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- **Accountability** → as per local procedures and using local templates
- **Returns** → not required unless specified by local procedures
- **Destruction** → as per local procedures and using local templates

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# Activation process

# Activation process

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- Activation documentation 05-Aug-2016
- Arm H closed 02-Sep-2016
- Arm K opened 05-Sep-2016

# Activation process

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- Activation process as per previous research comparisons
  - Temporary suspension of recruitment if requirements not met by activation date
- Activation requirements
  - R&D approval
  - Amendment acknowledgment (to be signed by research team)
  - PI acknowledgment
  - Pharmacy acknowledgment
  - Training attended
- Pharmacy required to confirm SOP for IMP management is in place
- Pharmacy pack circulated to sites



# More training

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- Rationale (via website)
- Protocol Overview
- CRF training