MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

MAMS platform protocols:
Patient engagement in STAMPEDE and beyond

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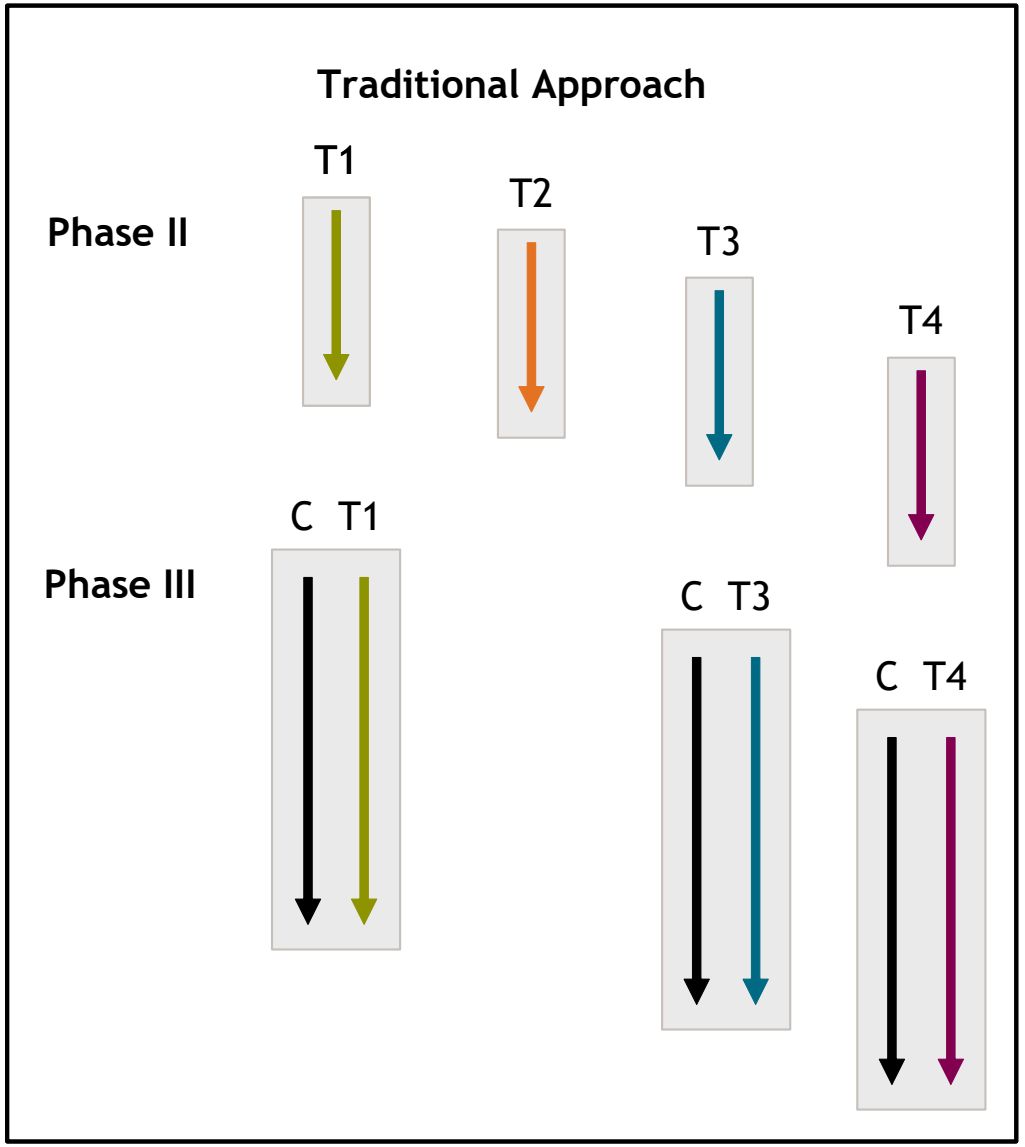
MRC CTU at UCL
Institute of Clinical Trials and Methodology
London, UK

Patient Engagement Open Forum
09-Dec-2021 (Version 2.00)

Need For New Approaches To Design

- Many approaches worthy of testing
- Each take years to confirm clinical benefit (if any!)
- Traditional designs don’t cope well

Need For New Approaches To Design



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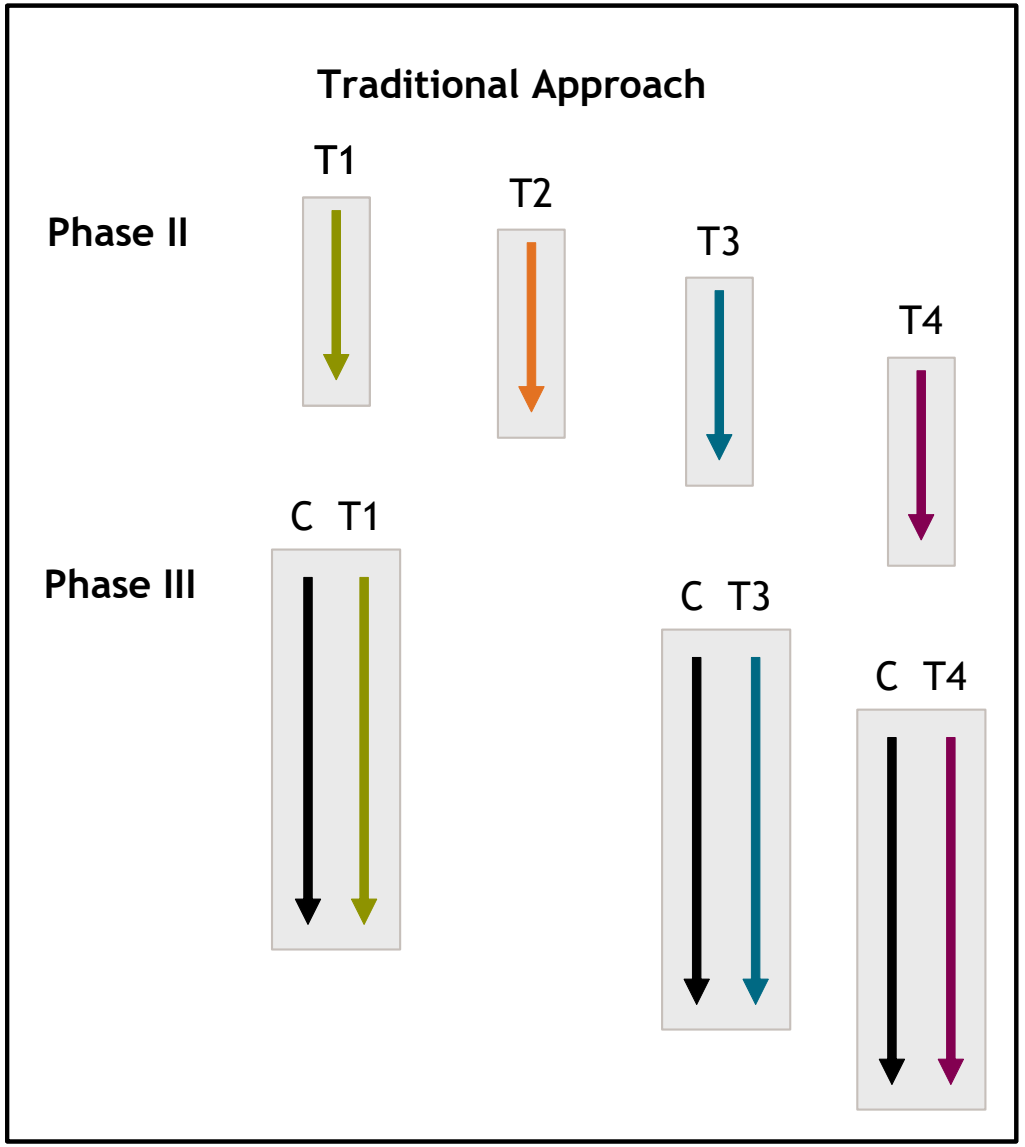
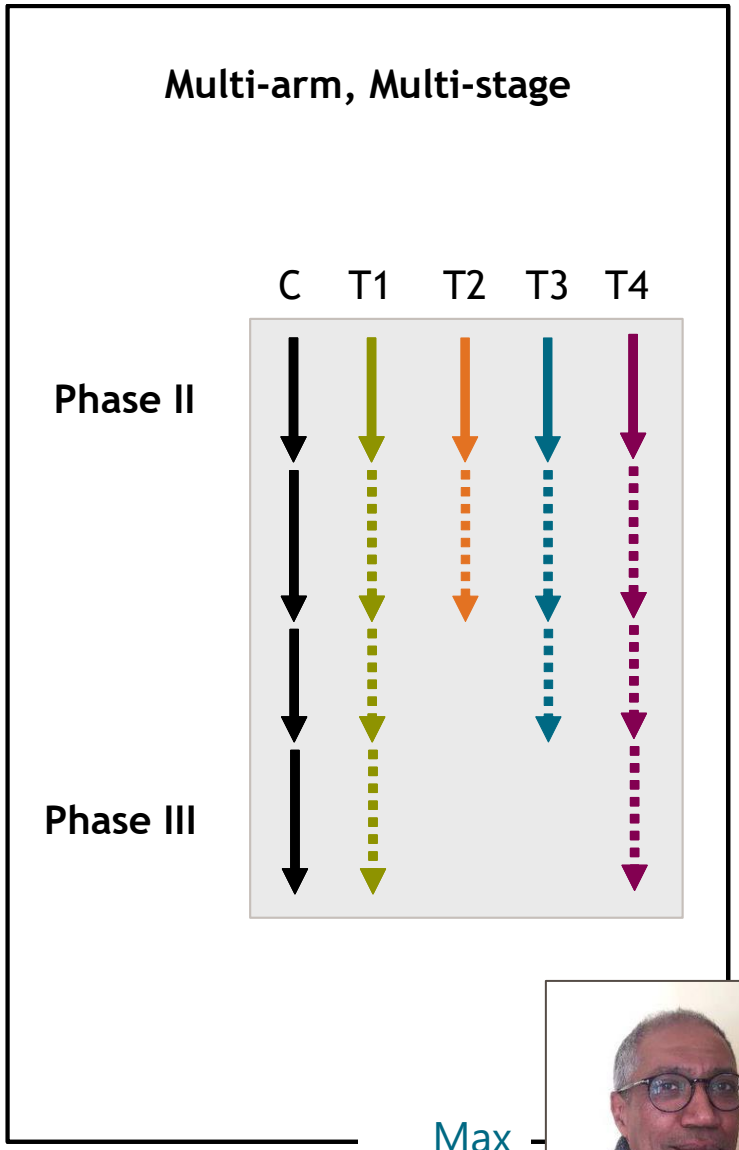
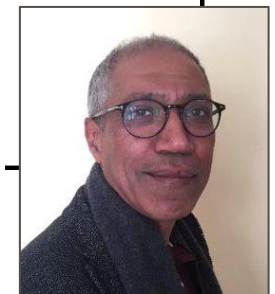
Need For New Approaches To Design





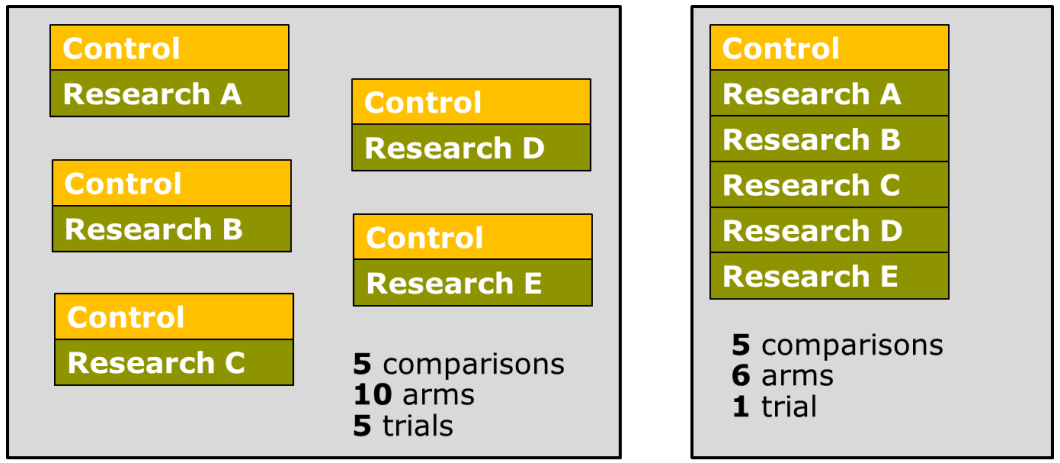
Max Parmar



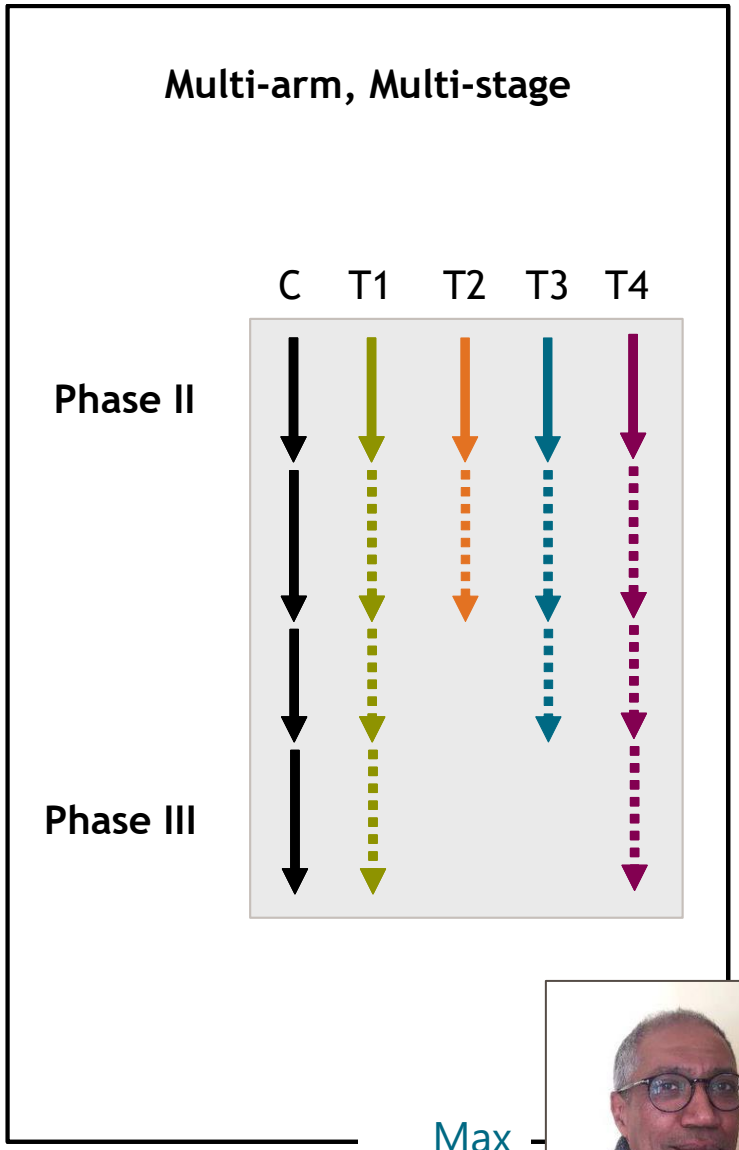
Multi-Arm Multi-Stage (MAMS) Approach

Multi-arm

- Test many relevant approaches



- Use fewer resources
- Cost per comparison is much less
- Less bureaucracy



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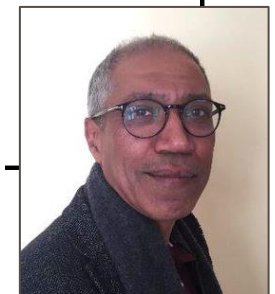


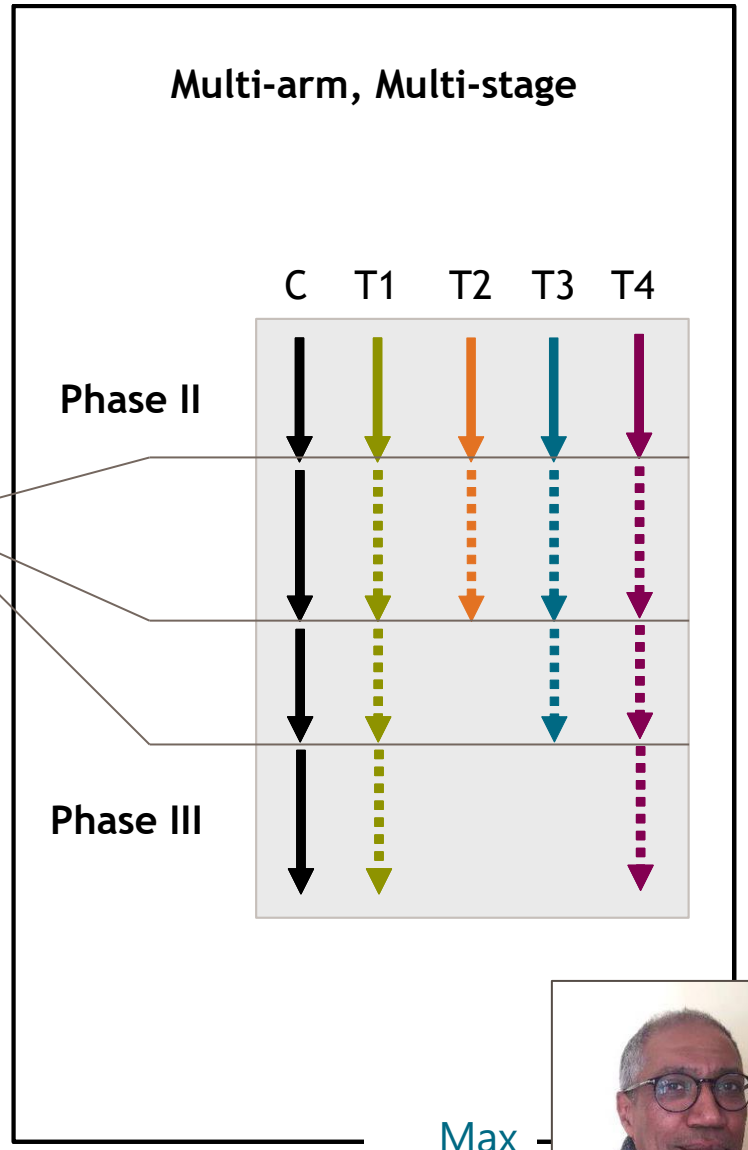
Multi-Arm Multi-Stage (MAMS) Approach

Multi-arm

- Test many relevant approaches

Multi-stage

- Using interim lack-of-benefit analyses
- Ask if reasons to *continue to* investigate an approach?



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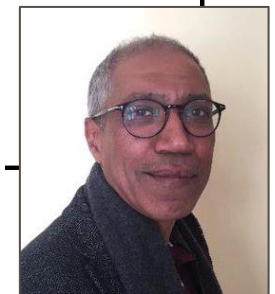

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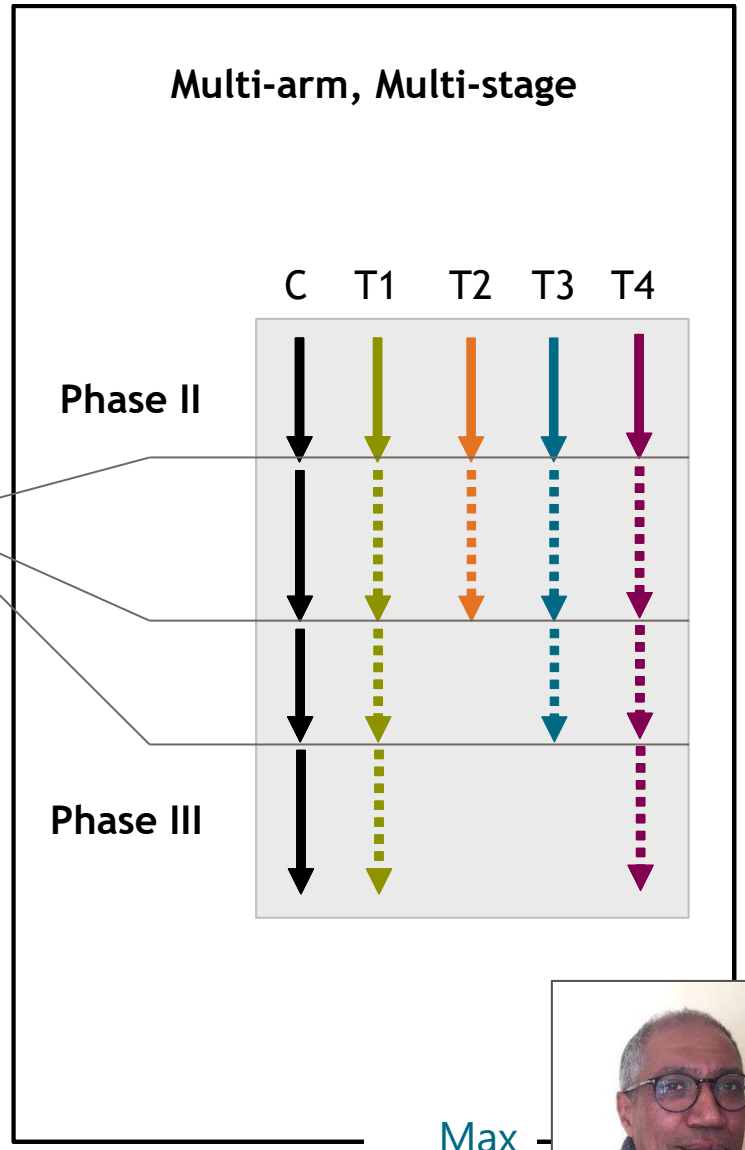

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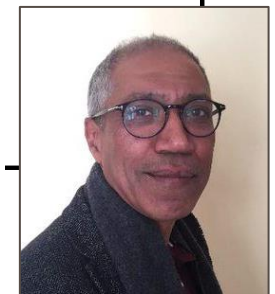
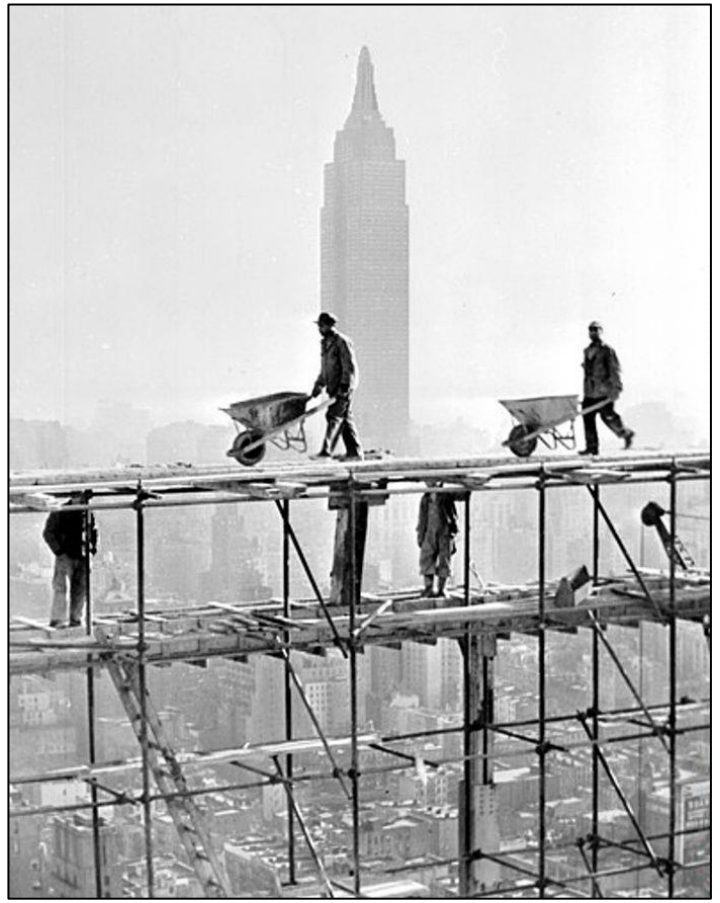


Platform (“Master” or “Living”) Protocols

- Protocols addressing many research questions in one administrative trial structure

- New important questions added later (“living” protocols)
  - eg into multi-arm trials

- Stratified trials testing biomarker-directed therapies in same disease (“master protocols”)



imi innovative medicines initiative

EU-PEARL

CLINICAL TRIALS TRANSFORMATION INITIATIVE

MHRA

NHS Health Research Authority

MRC Clinical Trials Unit

CANCER RESEARCH UK

NCRI National Cancer Research Institute

NHS National Institute for Health Research Clinical Research Network

UCL

STAMPEDE

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

A multi-arm multi-stage randomised controlled trial

Version: 19.0
Date: 01-June-2018

MRC CTU AT UCL ID:	PR08
ISRCTN #:	ISRCTN78818544
NCT #:	NCT00268476
EUDRACT #:	2004-000193-31
CTA #:	00316/0026/001-0001
MREC #:	04/MRE07/35

Authorised by:
Name: Professor Nicholas D James
Role: Chief Investigator & Comparison CI for "Abiraterone comparison"
Signature:

Name: Matthew Sydes
Role: Trial Statistician
Signature:

STAMPEDE

Clinical setting

- Prostate cancer, metastatic or high-risk non-metastatic
- Initiating long-term hormone therapy

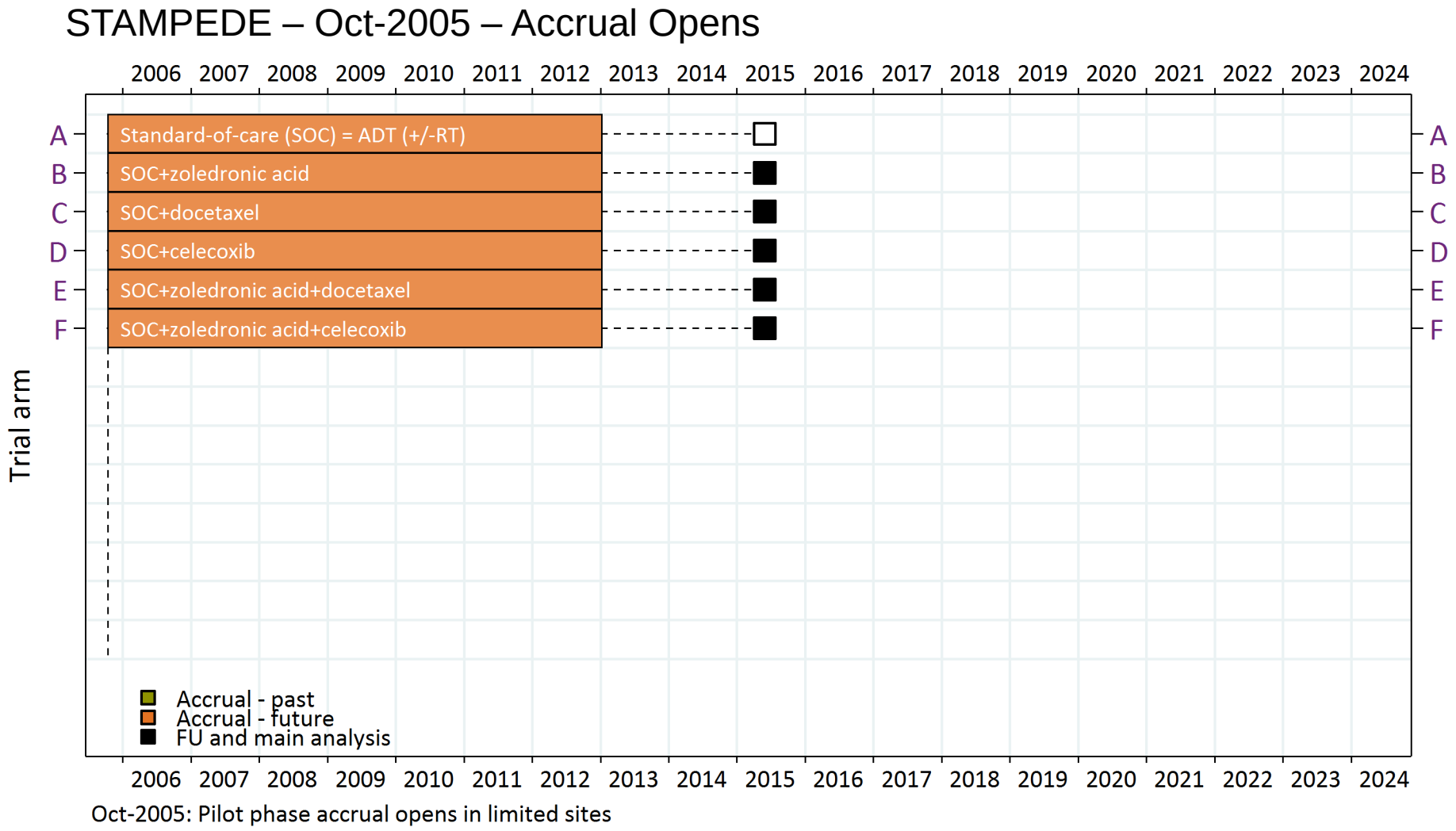
Testing setting

- Late stage, phase III
- Single randomisation

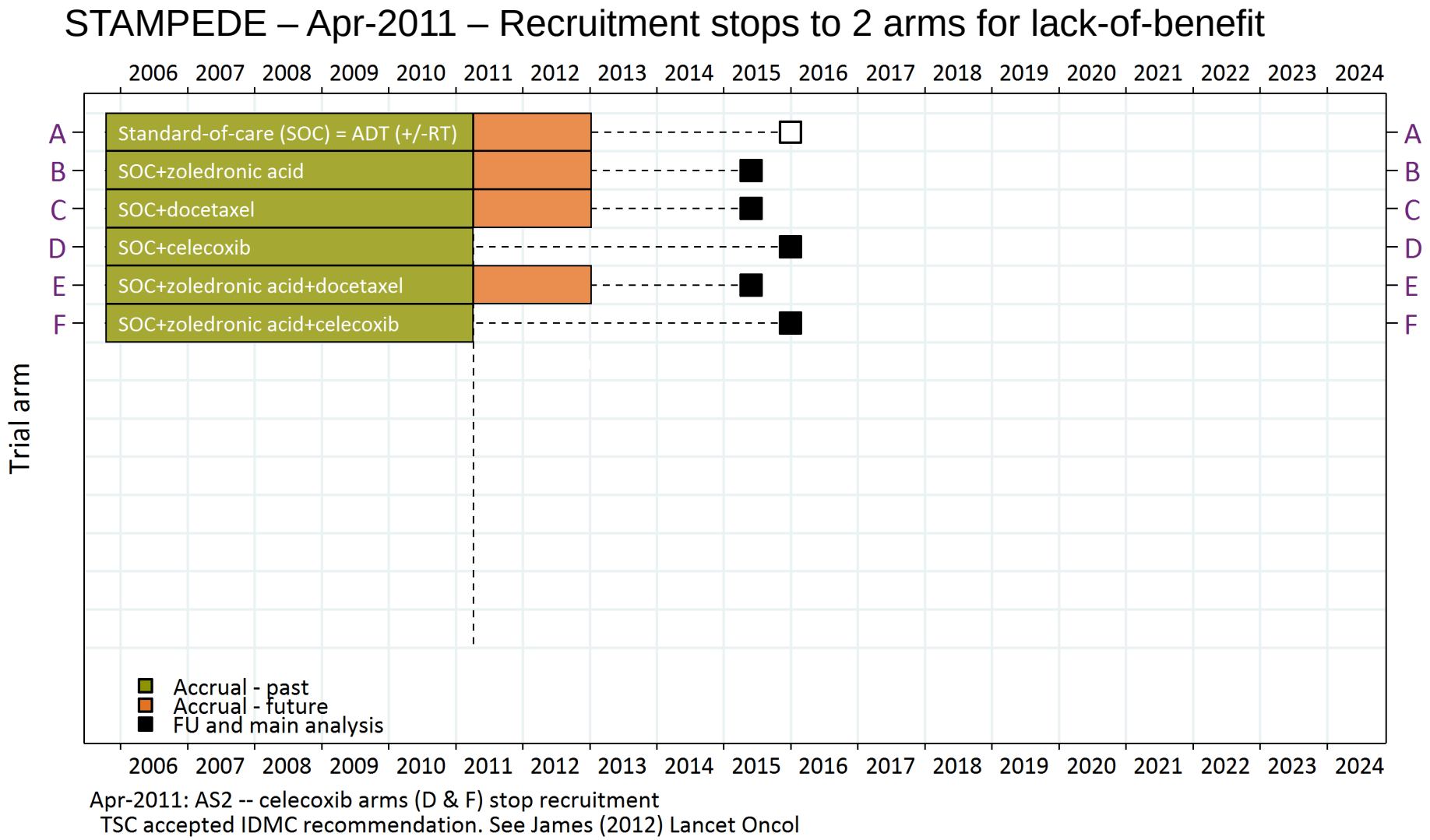
Originator:
Max Parmar

CI:
Nick James

→ Multi-arm element

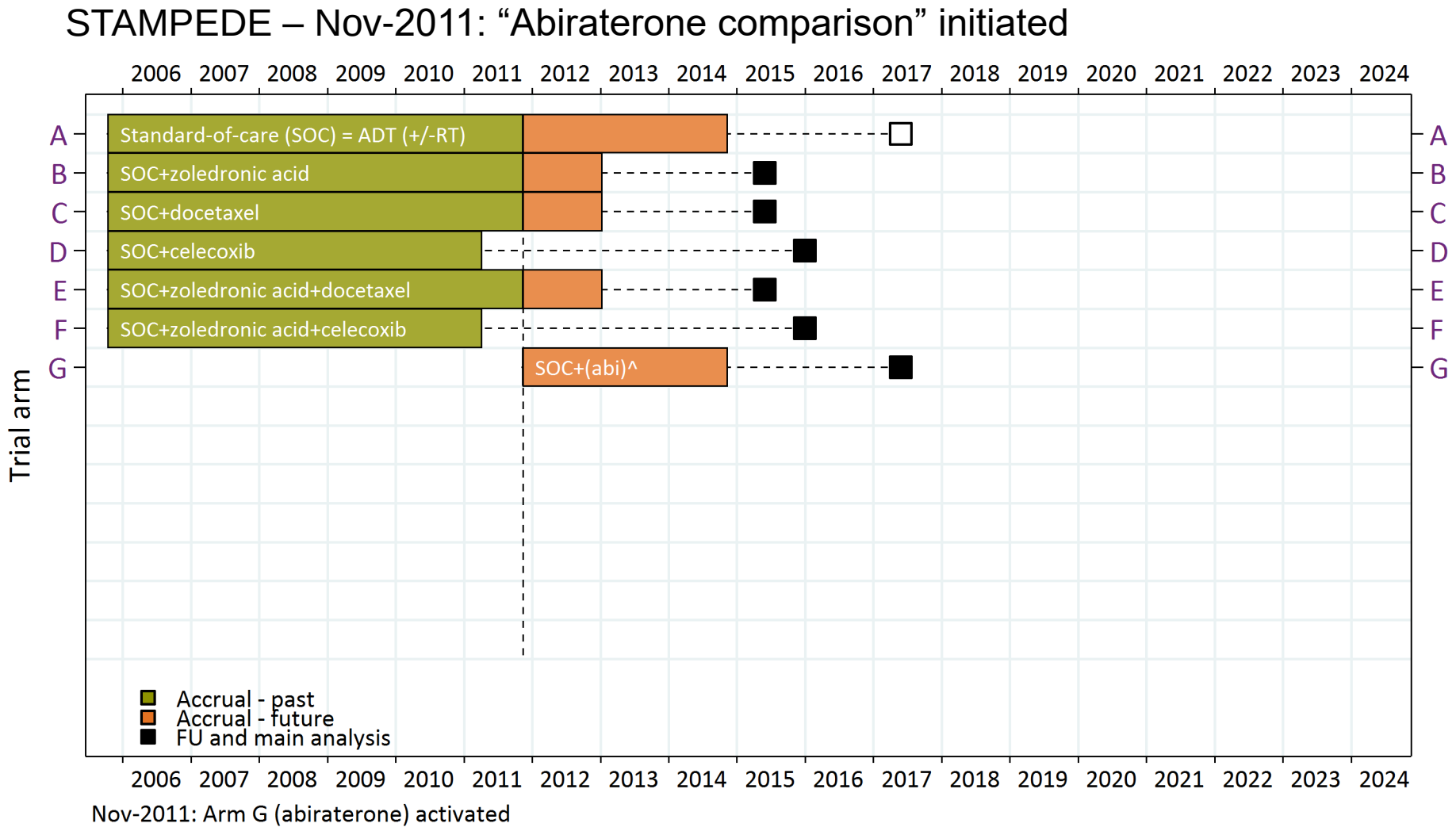


→ Multi-stage element

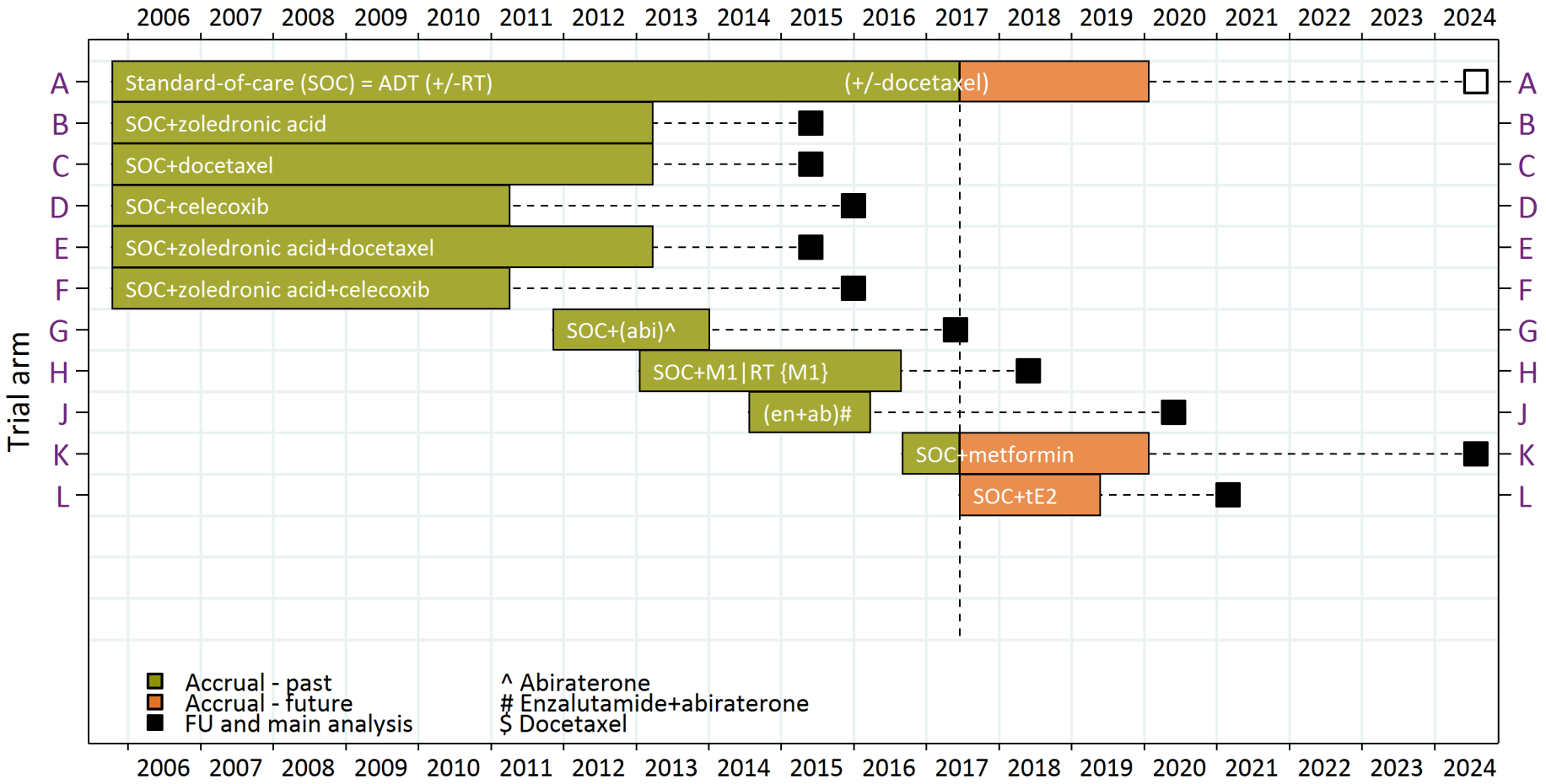


Apr-2011: AS2 -- celecoxib arms (D & F) stop recruitment
TSC accepted IDMC recommendation. See James (2012) Lancet Oncol

→ **Platform element**

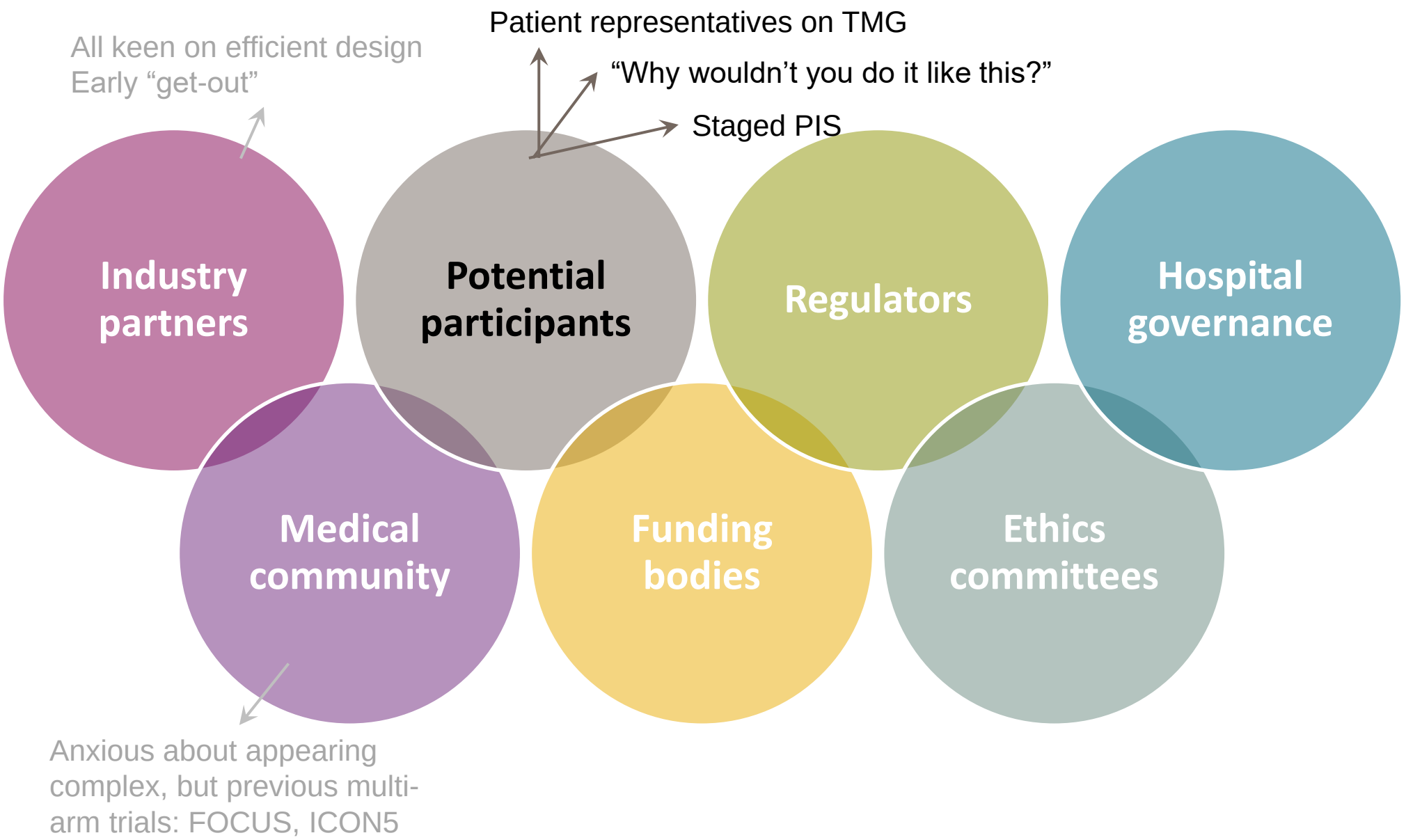


STAMPEDE – Recent activity



Include randomisation of tE2 patches for meta-analysis with PATCH
Q2-2017: launch of tE2 comparison

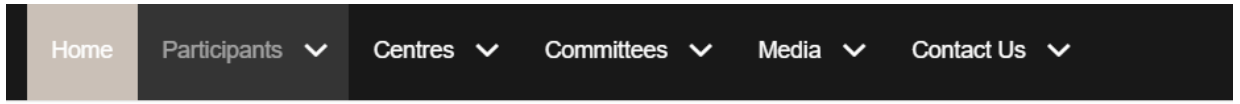
Groups to convince



Information tailored to everyone

Photo: Jay Wennington
Source: Unsplash

Groups to convince

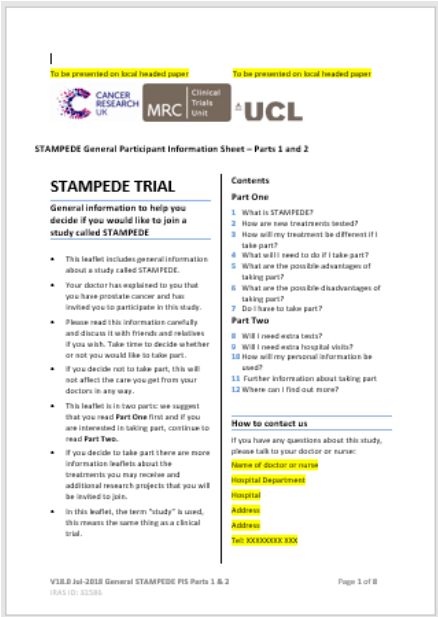


STAMPEDE: Patient Information Sheets (PIS)

What PIS?	Content	Who should read it?
General Patient Information Sheet - Part 1 & 2 (Version 18)	Overview of why the study is being done and what it involves. Details of study conduct and oversight	Everyone interested in taking part
Treatment Arm-Specific patient information sheet (PIS) **Arm A (Version 12)** **Arm K (Version 4)** **Arm L (Version 3)**	Details of treatment associated with each arm of the study	Everyone allocated to the specific treatment
Additional Research Studies Patient Information Sheet (Version 15)	Details of quality of life study and other optional studies	Everyone interested in taking part

http://www.stampedetrial.org/participants/participant-information/

Structured PIS



To be presented on local headed paper

To be presented on local headed paper

CANCER RESEARCH UK | MRC Clinical Trials Unit | UCL

STAMPEDE General Participant Information Sheet – Parts 1 and 2

STAMPEDE TRIAL

General information to help you decide if you would like to join a study called STAMPEDE

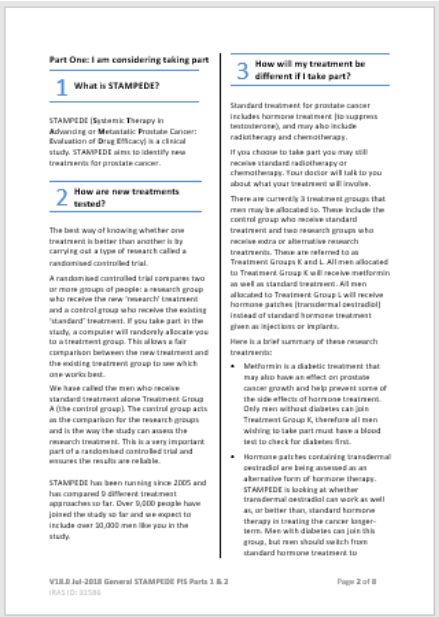
- This leaflet includes general information about a study called STAMPEDE.
- Your doctor has explained to you that you have prostate cancer and has invited you to participate in this study.
- Please read this information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not you would like to take part.
- If you decide not to take part, this will not affect the care you get from your doctors in any way.
- This leaflet is in two parts: we suggest that you read **Part One** first and if you are interested in taking part, continue to read **Part Two**.
- If you decide to take part there are more information leaflets about the treatments you may receive and additional research projects that you will be invited to join.
- In this leaflet, the term "study" is used, this means the same thing as a clinical trial.

Contents

How to contact us

If you have any questions about this study, please talk to your doctor or nurse:

Name of doctor or nurse
Hospital Department
Hospital
Address
Address
Tel: XXXXXXXX XXX



Part One: I am considering taking part

1 What is STAMPEDE?

STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) is a clinical study. STAMPEDE aims to identify new treatments for prostate cancer.

2 How are new treatments tested?

The best way of knowing whether one treatment is better than another is by carrying out a type of research called a randomised controlled trial.

A randomised controlled trial compares two or more groups of people: a research group who receive the new 'research' treatment and a control group who receive the existing 'standard' treatment. If you take part in the study, a computer will randomly allocate you to a treatment group. This allows a fair comparison between the new treatment and the existing treatment group to see which one works best.

We have called the men who receive standard treatment alone Treatment Group A (the control group). The control group acts as the comparison for the research groups and is the way the study can assess the research treatment. This is a very important part of a randomised controlled trial and ensures the results are reliable.

STAMPEDE has been running since 2005 and has compared 9 different treatment approaches so far. Over 9,000 people have joined the study so far and we expect to include over 10,000 men like you in the study.

3 How will my treatment be different if I take part?

Standard treatment for prostate cancer includes hormone treatment (to suppress testosterone), and may also include radiotherapy and chemotherapy.

If you choose to take part you may still receive standard radiotherapy or chemotherapy. Your doctor will talk to you about what your treatment will involve.

There are currently 3 treatment groups that men may be allocated to. These include the control group who receive standard treatment and two research groups who receive extra or alternative research treatments. These are referred to as Treatment Groups K and L. All men allocated to Treatment Group K will receive metformin as well as standard treatment. All men allocated to Treatment Group L will receive hormone patches (transdermal oestradiol) instead of standard hormone treatment given as injections or implants.

Here is a brief summary of these research treatments:

- Metformin is a diabetic treatment that may also have an effect on prostate cancer growth and help prevent some of the side effects of hormone treatment. Only men without diabetes can join Treatment Group K, therefore all men wishing to take part must have a blood test to check for diabetes first.
- Hormone patches containing transdermal oestradiol are being assessed as an alternative form of hormone therapy. STAMPEDE is looking at whether transdermal oestradiol can work as well as, or better than, standard hormone therapy in treating the cancer longer-term. Men with diabetes can join this group, but men should switch from standard hormone treatment to

alternative patches soon after hormone treatment is first started.

All participants will be randomly allocated to any of the groups that they are eligible to join. On average, for every 3 men joining the study, 1 will be allocated to Treatment Group A (the control group), 1 to Treatment Group K, and 1 to Treatment Group L.

Where it can be accessed, some people may be offered abiraterone instead of chemotherapy. Your doctor will discuss this with you. If you receive abiraterone as part of your standard treatment this will mean that you cannot currently be allocated to Treatment Group L.

Your doctor or nurse will discuss which Treatment Groups you may be suitable for; you will then be randomly allocated to any of these. Further details about these treatments are given in the treatment specific patient information sheets.

For your information, this study previously looked at other treatments (Groups B, C, D, E, F, G, H and I). It is no longer possible to join these groups as we already have enough men to test these treatments. Some results are already known and you can find out more on the study website www.stampedetrial.org or by asking your research team.

4 What will I need to do if I take part?

You will need to attend clinic regularly so that you medical team can assess how you are responding to treatment and update the STAMPEDE researchers about your progress.

If you are allocated to receive metformin or transdermal oestradiol (hormone patches) you will need to have some extra blood tests too.

5 What are the possible advantages of taking part?

We hope that you will be helped by taking part in this study, but we cannot guarantee this. We hope that the new treatments will help control prostate cancer better than the current standard approach; however, we don't know this for sure which is why it is being testing in this study.

It is possible that the results may not help you individually but the information we get from this study will help us improve treatments for people like you in the future.

6 Where are the possible disadvantages of taking part?

If you take part you will need to visit the hospital more often and you are likely to need some extra blood tests. You may have different or extra side effects. The most common unwanted side effects are described in the **Treatment Specific Information Sheets**.

7 Do I have to take part in the study?

No, it is up to you if you want to take part. If you decide not to take part this will not affect the standard of care you receive.

If you think you might be interested in taking part, please carry on reading. More information is included in **Part 2**.

Part Two: I would like to know more

8 Will I need extra tests?

If you are considering joining STAMPEDE you will need to have some extra blood tests. If you do not have known diabetes then you will need to have a blood test to check this first.

If your blood tests are abnormal you will be referred to your GP to discuss this further. Not all people with diabetes have symptoms and therefore it is possible that this will be picked up early. This will enable you to receive appropriate advice and treatment. Should you have diabetes, you will not be able to join the metformin treatment group.

If you are allocated to Treatment Group L (transdermal oestradiol) you may need an extra blood test to check your hormone levels.

Extra blood tests are also required to check sugar and cholesterol levels. These are checked more regularly than they might be in standard clinical practice because we want to find out if the treatments being tested help prevent problems like diabetes or raised cholesterol from developing. These extra tests can be checked at the same time as routine blood tests but may require you to have not eaten for around 8 hours beforehand. Your research team will discuss with you when this is needed.

9 Will I need extra hospital visits?

In order to assess the long-term effects of treatment your medical team will need to keep the STAMPEDE researchers updated as to your progress.

Whichever Treatment Group you join, this will likely mean a hospital visit at least every 6 weeks for 6 months, then about every 3 months for the next 2 years and then every 6 months. Once you've been part of the study for 5 years the research team will only need to review your progress once a year. However, if you are receiving metformin or transdermal oestradiol, you will need to attend more regularly in order to pick up your medication.

10 How will my personal information be used?

The STAMPEDE study aims to test if different ways of treating prostate cancer can improve disease control, reduce relapse and improve life expectancy. The Medical Research Council is the sponsor for this study, based in the United Kingdom. University College London (UCL), through the MRC Clinical Trial Centre at UCL, will be using information from you and your medical records in order to undertake this study and will act as data controller for this study. UCL will be responsible for looking after your information and using it properly. UCL will keep identifiable information about you for 25 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information at www.ctu.mrc.ac.uk/general/privacy-policy

How will your data be stored and collected?

Your site will collect information from you and your medical records for this research study in accordance with our instructions.

Your hospital will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your hospital will pass your name, postcode and NHS number to UCL along with the information collected from you and your medical records. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Your hospital will keep identifiable information about you from this study for at least 25 years after the study has finished.

UCL will collect information about you, for research, from your hospital site, NHS Digital, Public Health England (PHE,) and the National Cancer Registration and Analysis Service (NCRAS). This information will include your name, postcode and NHS number and health information. This health information is regarded as a special category of information as defined by the General Data Protection Regulation (GDPR). We will use this information to track your long term health status (https://digital.nhs.uk/).

Where information could identify you, the information will be held securely with strict arrangements about who can access the information.

Future Research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with relevant legislation, ethics and NHS research policy requirements.

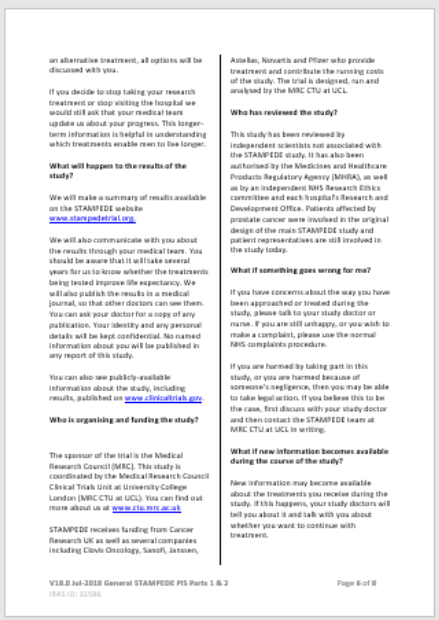
We won't share information with others that can identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. If there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee. You will be specifically asked about whether you want your data to be used in future research. If you say no you will still be able to participate in STAMPEDE.

11 Further information about taking part

Can I stop taking part after I have joined the study?

You can stop taking part in all of this study, or any part of it at any time and without giving a reason. But you must talk to your study doctor or nurse first. They can advise you about any concerns you may have.

Whichever treatments you receive, the aim is to control your cancer and help you feel well for as long as possible. If your doctor believes that you would be better helped by



an alternative treatment, all options will be discussed with you.

If you decide to stop taking your research treatment or stop visiting the hospital we would still ask that your medical team update us about your progress. This longer-term information is helpful in understanding which treatments enable men to live longer.

What will happen to the results of the study?

We will make a summary of results available on the STAMPEDE website www.stampedetrial.org.

We will also communicate with you about the results through your medical team. You should be aware that it will take several years for us to know whether the treatments being tested improve life expectancy. We will also publish the results in a medical journal, so that other doctors can see them. You can ask your doctor for a copy of any publication. Your identity and any personal details will be kept confidential. No named information about you will be published in any report of this study.

You can also see publicly-available information about the study, including results, published on www.clinicaltrials.gov.

Who is organising and funding the study?

The sponsor of the trial is the Medical Research Council (MRC). This study is coordinated by the Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL). You can find out more about us at www.ctu.mrc.ac.uk

STAMPEDE receives funding from Cancer Research UK as well as several companies including Clovis Oncology, Sanofi, Janssen, Astellas, Novartis and Pfizer who provide treatment and contribute the running costs of the study. The trial is designed, run and analysed by the MRC CTU at UCL.

Who has reviewed the study?

This study has been reviewed by independent scientists not associated with the STAMPEDE study. It has also been authorised by the Medicines and Healthcare Products Regulatory Agency (MHRA), as well as by an independent NHS Research Ethics committee and each hospital's Research and Development Office. Patients affected by prostate cancer were involved in the original design of the main STAMPEDE study and patient representatives are still involved in the study today.

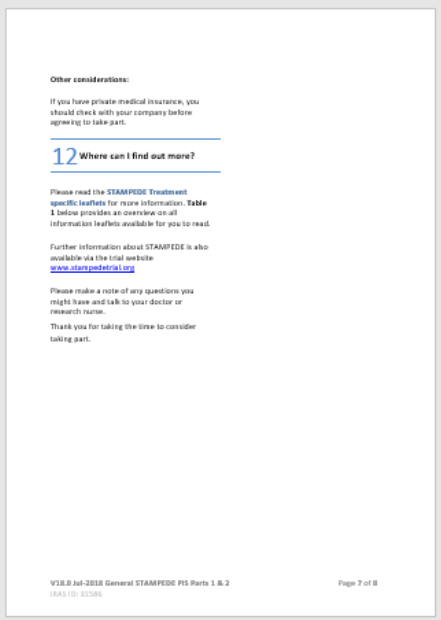
What if something goes wrong for me?

If you have concerns about the way you have been approached or treated during the study, please talk to your study doctor or nurse. If you are still unhappy, or you wish to make a complaint, please use the normal NHS complaints procedure.

If you are harmed by taking part in this study, or you are harmed because of someone's negligence, then you may be able to take legal action. If you believe this to be the case, first discuss with your study doctor and then contact the STAMPEDE team at MRC CTU at UCL in writing.

What if new information becomes available during the course of the study?

New information may become available about the treatments you receive during the study. If this happens, your study doctors will tell you about it and talk with you about whether you want to continue with treatment.



Other considerations:

If you have private medical insurance, you should check with your company before agreeing to take part.

12 Where can I find out more?

Please read the **STAMPEDE Treatment specific leaflets** for more information. **Table 1** below provides an overview on all information leaflets available for you to read.

Further information about STAMPEDE is also available via the trial website www.stampedetrial.org

Please make a note of any questions you might have and talk to your doctor or research nurse.

Thank you for taking the time to consider taking part.

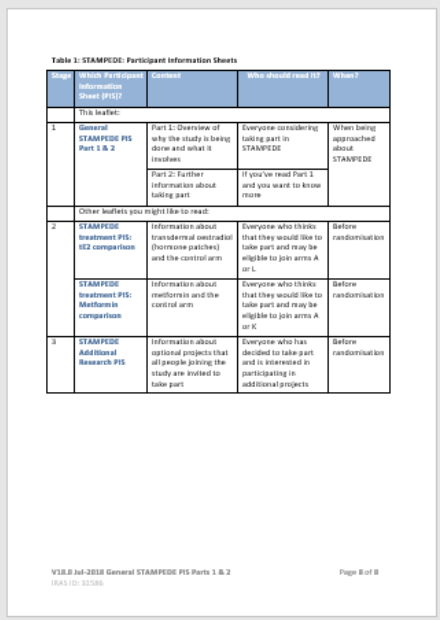
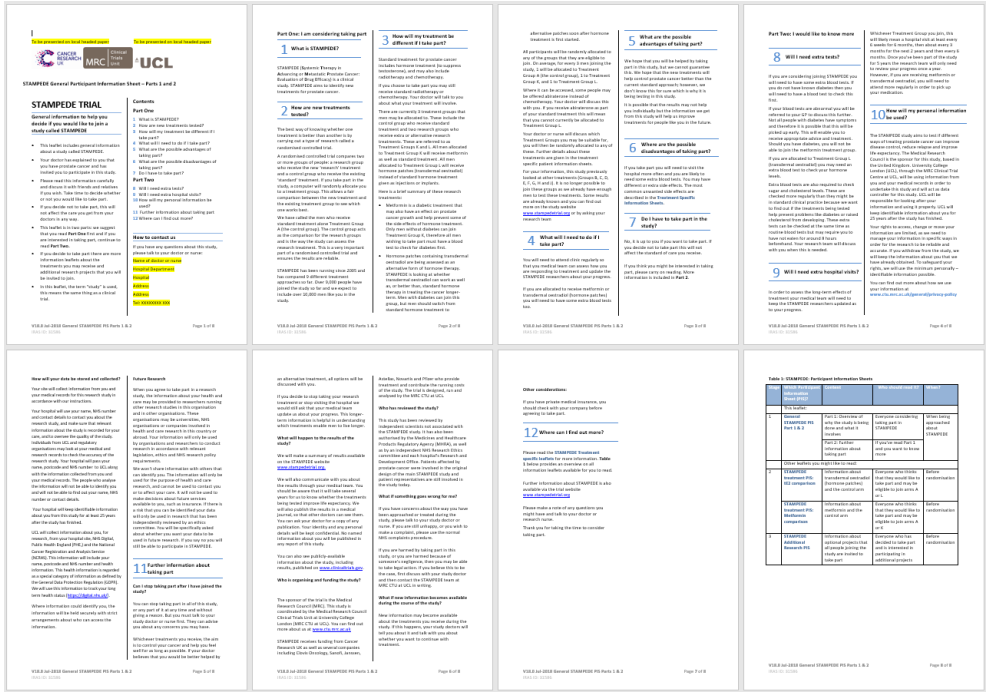


Table 1: STAMPEDE: Participant Information Sheets

Stage	Which Participant Information Sheet (PIS)?	Content	Who should read it?	When?
	This leaflet:			
1	**General STAMPEDE PIS Part 1 & 2**	Part 1: Overview of why the study is being done and what it involves	Everyone considering taking part in STAMPEDE	When being approached about STAMPEDE
		Part 2: Further information about taking part	If you've read Part 1 and you want to know more	
	Other leaflets you might like to read:			
2	**STAMPEDE treatment PIS: tE2 comparison**	Information about transdermal oestradiol (hormone patches) and the control arm	Everyone who thinks that they would like to take part and may be eligible to join arms A or L	Before randomisation
	STAMPEDE treatment PIS: Metformin comparison	Information about metformin and the control arm	Everyone who thinks that they would like to take part and may be eligible to join arms A or K	Before randomisation
3	**STAMPEDE Additional Research PIS**	Information about optional projects that all people joining the study are invited to take part	Everyone who has decided to take part and is interested in participating in additional projects	Before randomisation

Structured PIS



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STAMPEDE General Participant Information Sheet – Parts 1 and 2

STAMPEDE TRIAL

General information to help you decide if you would like to join a study called STAMPEDE

- This leaflet includes general information about a study called STAMPEDE.
- Your doctor has explained to you that you have prostate cancer and has invited you to participate in this study.
- Please read this information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not you would like to take part.
- If you decide not to take part, this will not affect the care you get from your doctors in any way.
- This leaflet is in two parts: we suggest that you read **Part One** first and if you are interested in taking part, continue to read **Part Two.**
- If you decide to take part there are more information leaflets about the treatments you may receive and additional research projects that you will be invited to join.
- In this leaflet, the term "study" is used, this means the same thing as a clinical trial.

Contents

How to contact us

If you have any questions about this study, please talk to your doctor or nurse:

Name of doctor or nurse
Hospital Department
Hospital
Address
Address
Tel: XXXXXXXX XXX

Slides from PPI rep – David Matheson

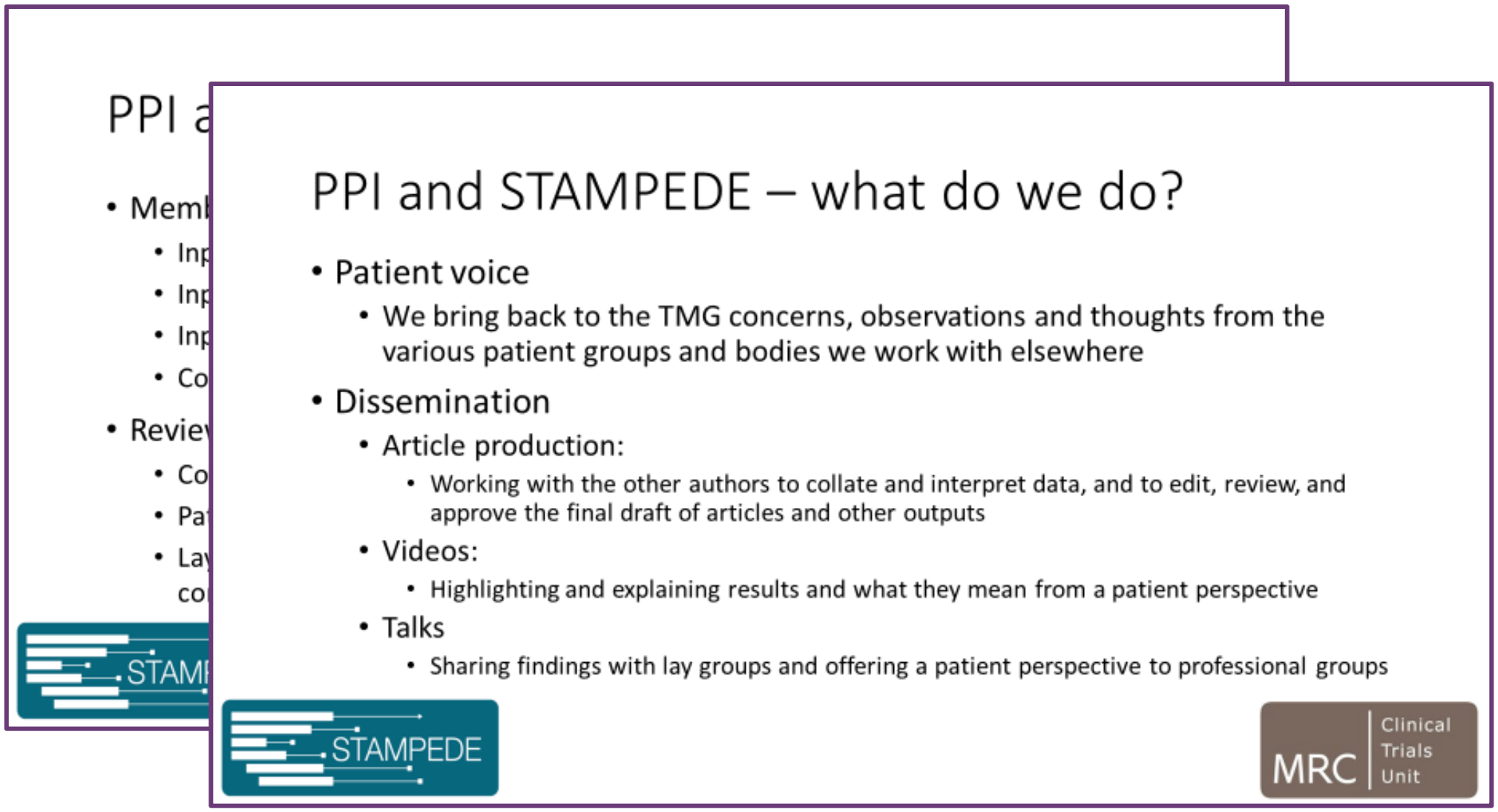
PPI and STAMPEDE – what do we do?

- Members of the Trial Management Group and various working groups
  - Input into prioritising and defining questions
  - Input into oversight and TMG
  - Input into interpretation and dissemination, inc. co-author abstracts and papers
  - Commenting / advising on communications with trial participants
- Review all patient interface documentation
  - Consent forms – keeping layout as simple and understandable as possible
  - Patient information sheets – paying special attention to avoiding cognitive overload
  - Lay summaries – emphasising clarity and ease of comprehension without compromising content

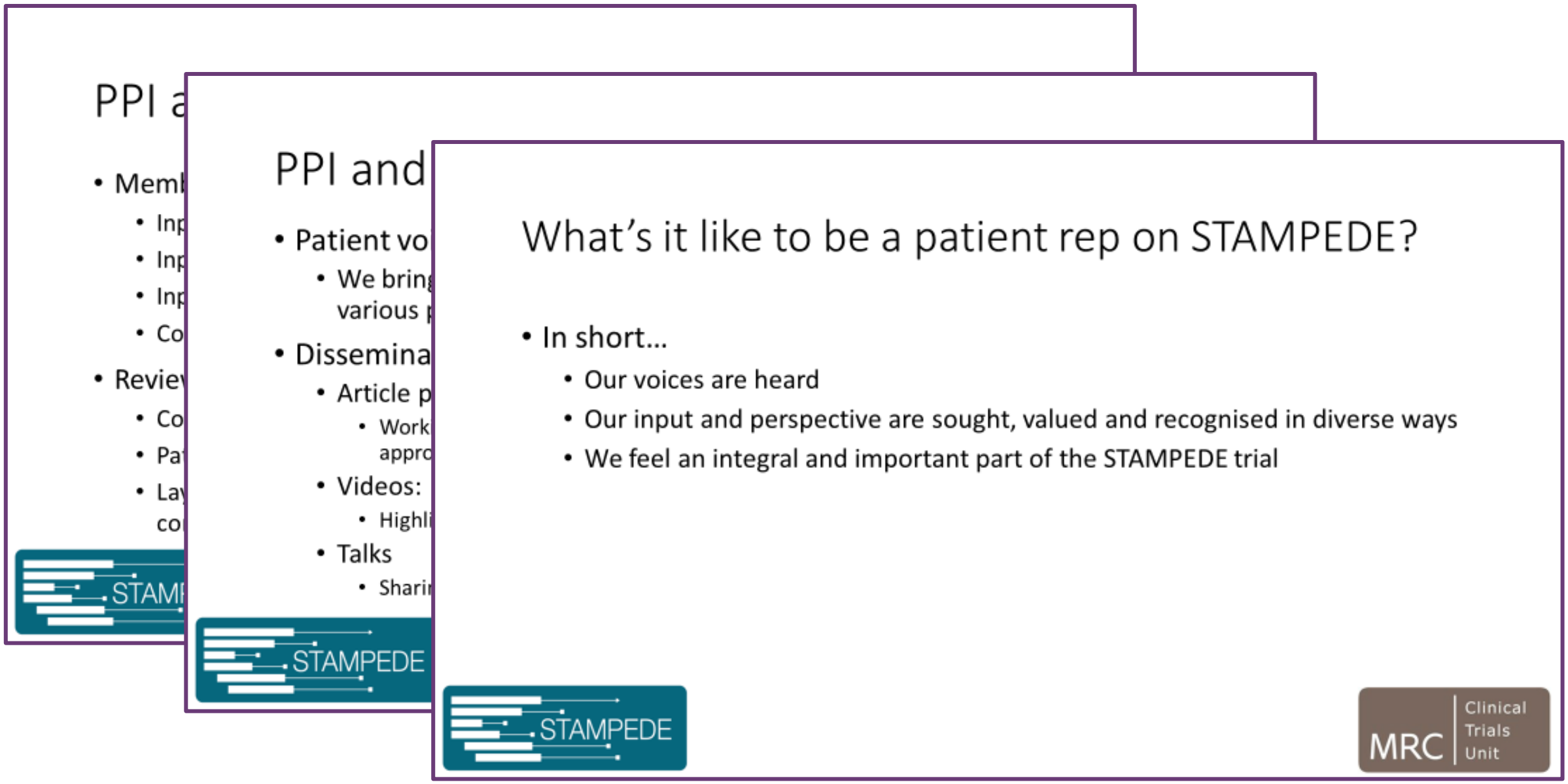
STAMPEDE

MRC Clinical Trials Unit

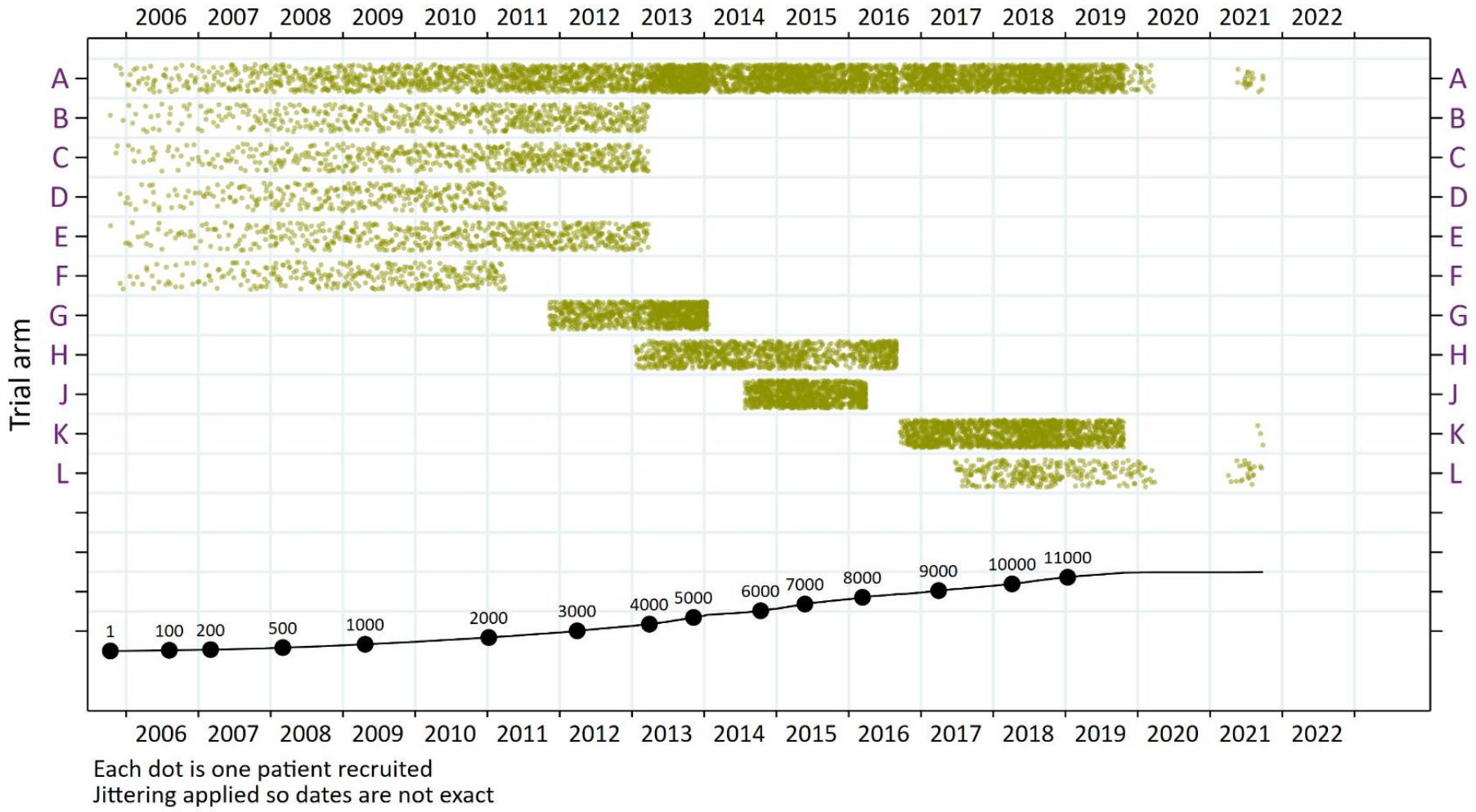
Slides from PPI rep – David Matheson



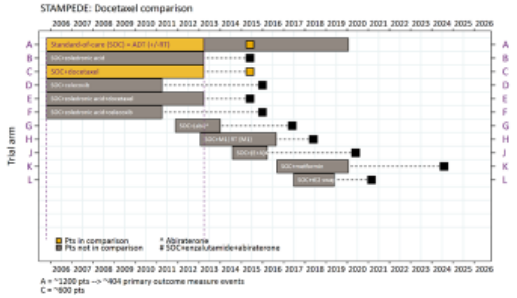
Slides from PPI rep – David Matheson

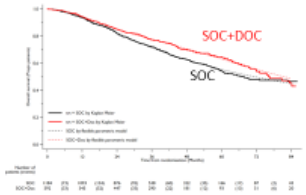


STAMPEDE – Accrual over time



Practice-changing findings 1: SOC+DocP vs SOC





HR (95%CI) **0.78** (0.66, 0.93)
P-value **0.006**

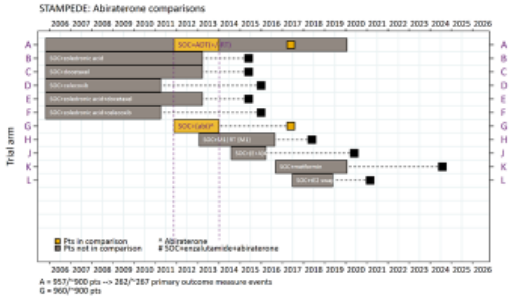
Recruitment: Oct-2005 to Mar-2013
Reported: ASCO 2015
Published: Lancet 2016

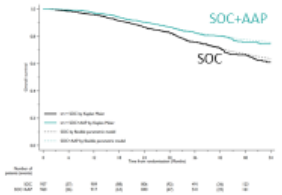
Patients: 1184 SOC
592 SOC+DocP

Allocation ratio: 2:1

doi: 10.1016/S0140-6736(15)01037-5
doi: 10.1016/S1470-2045(15)00489-1

Practice-changing findings 2: SOC+AAP vs SOC





HR (95%CI) 0.63 (0.52, 0.76)
P-value 0.00000115

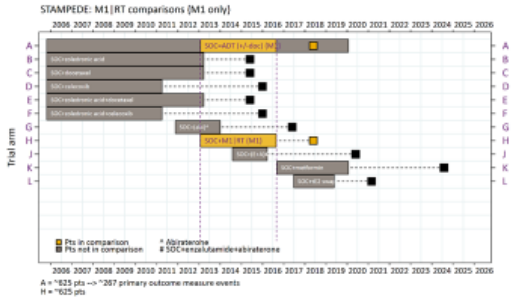
Recruitment: Nov-2011 to Jan-2014
Reported: ASCO 2017
Published: NEJM 2017

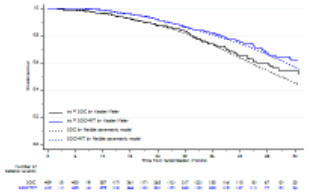
Patients: 957 SOC
960 SOC+AAP

Allocation ratio: 1:1

doi: 10.1016/S0140-6736(15)01037-5
doi: 10.1016/S1470-2045(15)00489-1

Practice-changing findings 3: SOC+RT vs SOC





Low metastatic burden

HR (95%CI) **0.68 (0.52, 0.90)**
p-value **0.007**

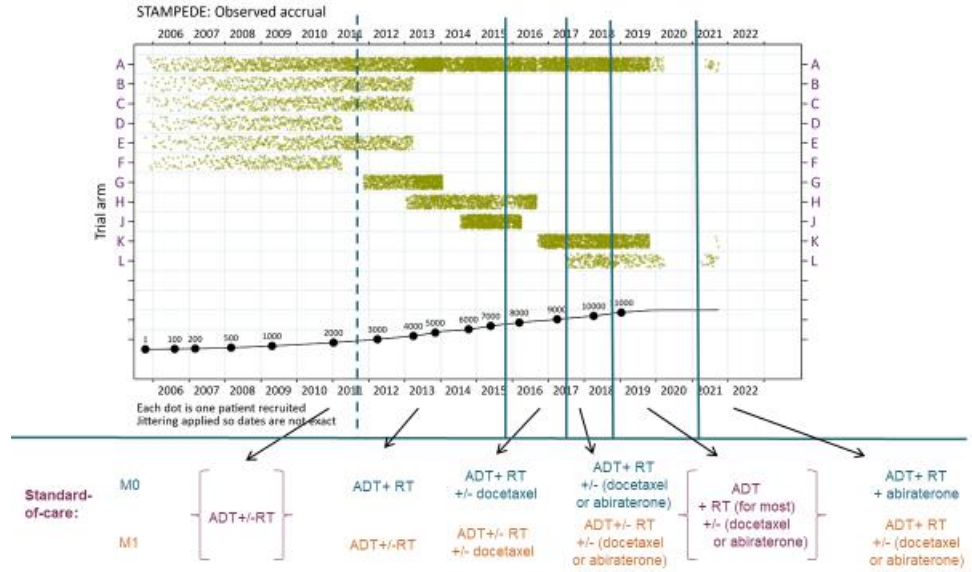
Recruitment: Jan-2013 to Sep-2016
Reported: ESMO 2018
Published: Lancet 2018

Patients: 1029 SOC
1032 SOC+DocP

Allocation ratio: 1:1

doi: 10.1016/S0140-6736(18)32486-3

STAMPEDE by 2021:
Updated standard-of-care 5 times

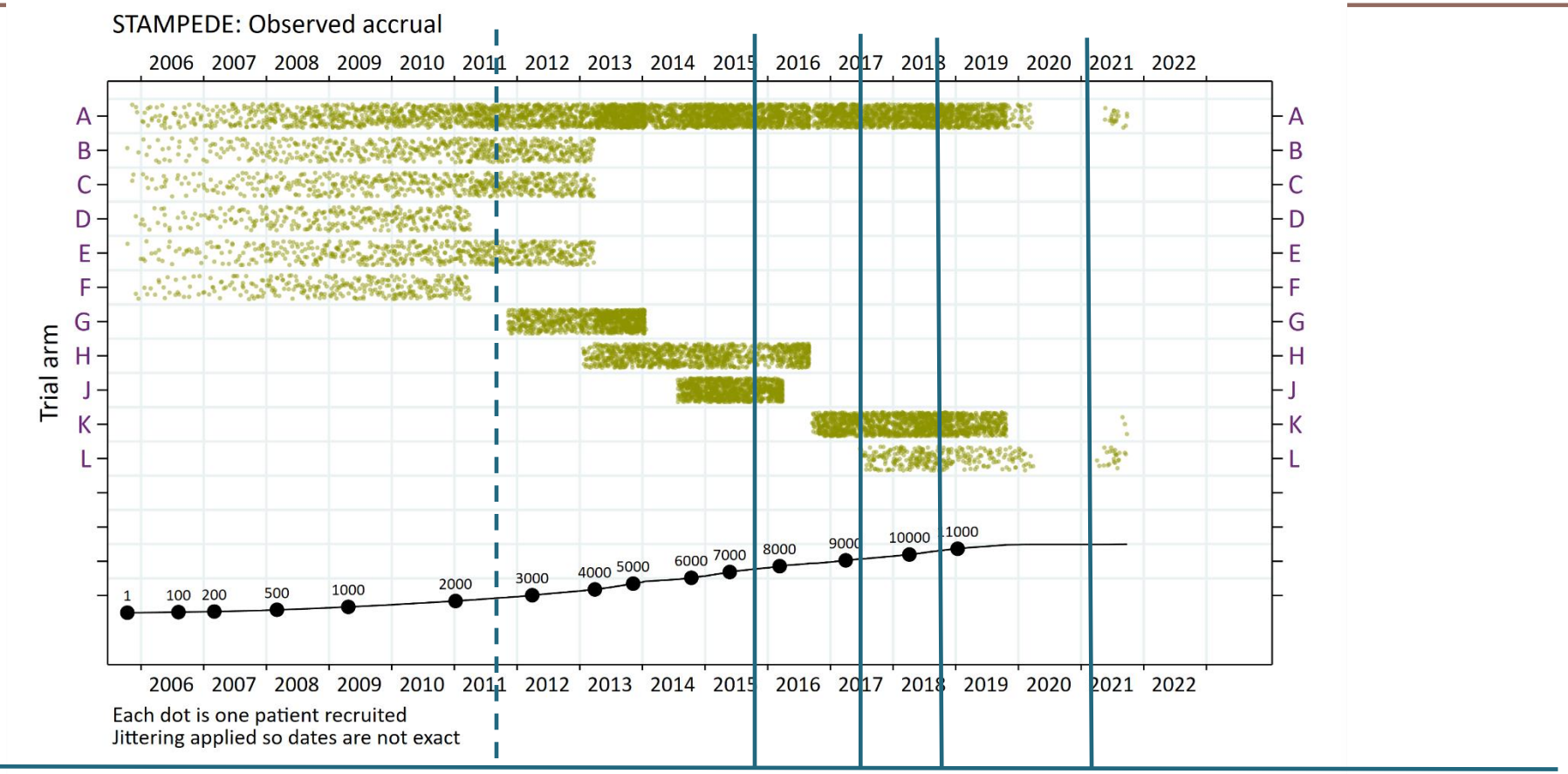


Explaining findings and design

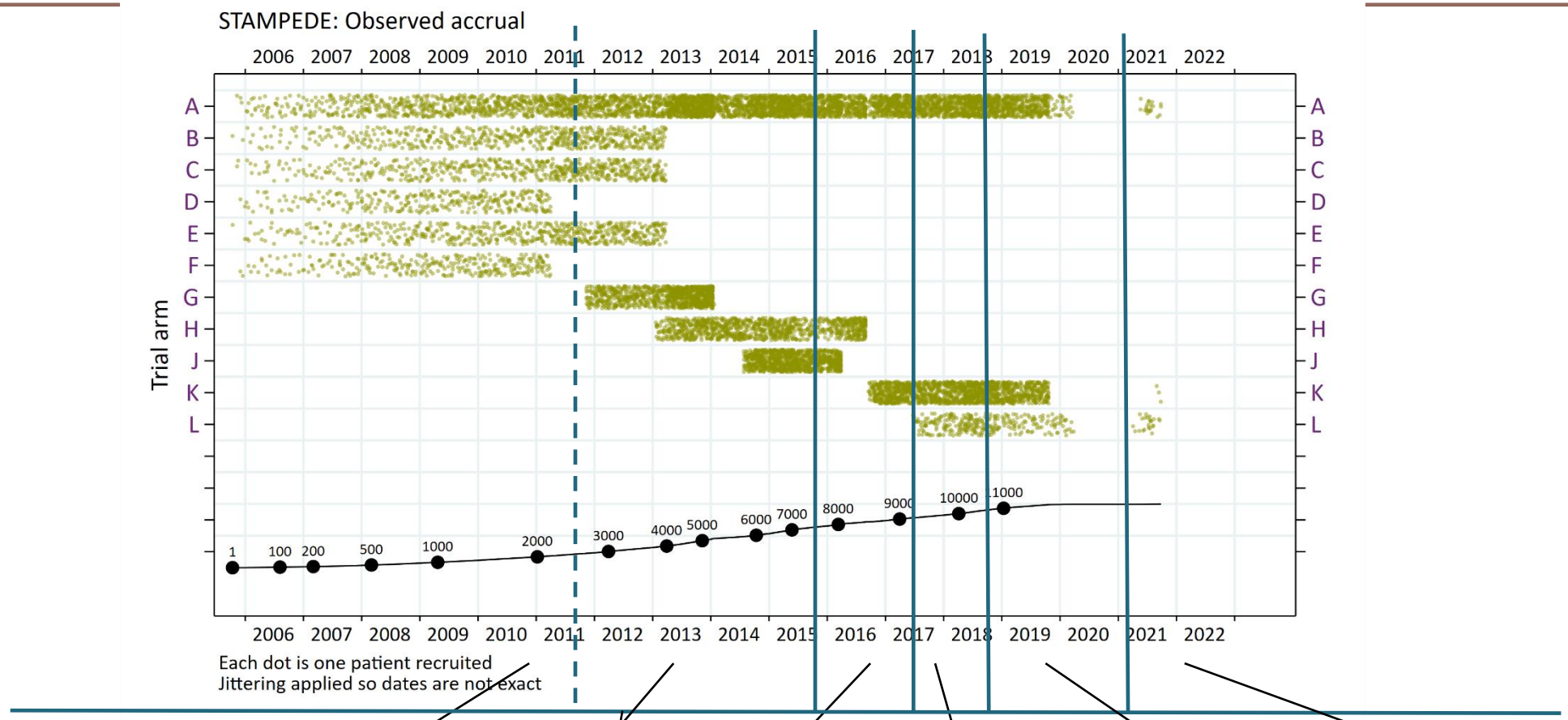
https://vimeo.com/220031463

https://vimeo.com/171900048

https://vimeo.com/335419982


STAMPEDE: Observed accrual
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Trial arm
A
B
C
D
E
F
G
H
J
K
L
1 100 200 500 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000 11000
Each dot is one patient recruited
Jittering applied so dates are not exact

STAMPEDE by 2021: Updated standard-of-care 5 times



Standard-of-care:

M0	ADT+/-RT	ADT+ RT	ADT+ RT +/- docetaxel	ADT+ RT +/- (docetaxel or abiraterone)	ADT + RT (for most) +/- (docetaxel or abiraterone)	ADT+ RT + abiraterone
M1		ADT+/-RT	ADT+/- RT +/- docetaxel	ADT+/- RT +/- (docetaxel or abiraterone)		ADT+ RT +/- (docetaxel or abiraterone)

Sharing Experiences of MAMS Platform Protocols


Trials

Methodology

Open Access

Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial

Matthew R Sydes*, Mahesh KB Parmar, Nicholas D James, Noel W Clarke, David P Dearnaley, Malcolm D Mason, Rachel C Morgan, Karen Sanders and Patrick Royston

Abstract

Background: The multi-arm multi-stage (MAMS) trial is a new paradigm for conducting randomised controlled trials that allows the simultaneous assessment of a number of research treatments against a single control arm. MAMS trials provide earlier answers and are potentially more cost-effective than a series of traditionally designed trials. Prostate cancer is the most common tumour in men and there is a need to improve outcomes for men with hormone-relapsing, advanced disease as quickly as possible. The MAMS design will personally facilitate evaluation and testing of new therapies in this and other diseases.

Methods: STAMPEDE is an open-label, 5-stage, 4-arm randomised controlled trial using MAMS methodology for men with prostate cancer. It is the first trial of this design to use multiple arms and stages synchronously.

Results: The practical and statistical issues faced by STAMPEDE in implementing MAMS methodology are discussed and contrasted with those for traditional trials. These issues include the choice of intermediate and final outcome measures, sample size calculations and the impact of varying the assumptions, the process for moving between trial stages, dropping arms at each trial arm and overall, and issues around perceived trial complexity.

Conclusion: It is possible to use the MAMS design to initiate and undertake large scale cancer trials. The results from STAMPEDE will not be known for some years but the lessons learned from running a MAMS trial are shared in the hope that other researchers will use this exciting and efficient method to perform further randomised controlled trials.

Trial registration: ISRCTN78818544; NCT00268476.

Page 1 of 16

Initial statistical in implementing MAMS

doi: 10.1186/1745-6215-10-39

Max Parmar


CLINICAL TRIALS

Testing many treatments within a single protocol over 10 years at MRC Clinical Trials Unit at UCL: Multi-arm, multi-stage platform, umbrella and basket protocols

Mahesh KB Parmar, Matthew R Sydes, Fay H Cafferty, Babak Choodari-Oskooei, Ruth L Langley, Louise Brown, Patrick PJ Phillips, Melissa R Spears, Sam Rowley, Richard Kaplan, Nicholas D James, Timothy Maughan, Nicholas Paton and Patrick J Royston

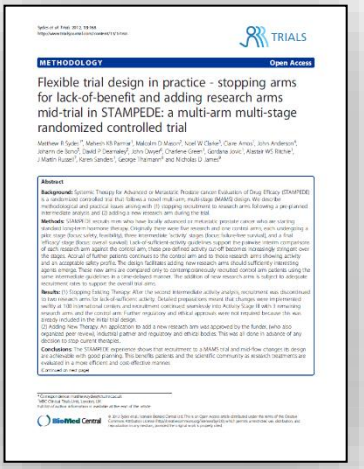
Abstract

Keywords

Introduction

10yrs experience at MRC CTU at UCL

doi: 10.1177/1740774517725697


TRIALS

METHODOLOGY

Open Access

Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial

Abstract

Practicalities in stopping & adding arms

doi: 10.1186/1745-6215-13-168

Trial management conduct experiences

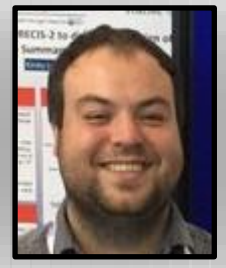
Riya Bathia

Francesca Schiavone

doi: 10.1186/s13063-019-3216-8

Data management services conduct experiences

Lindsey Masters



Stephen Townsend

Dom Hague

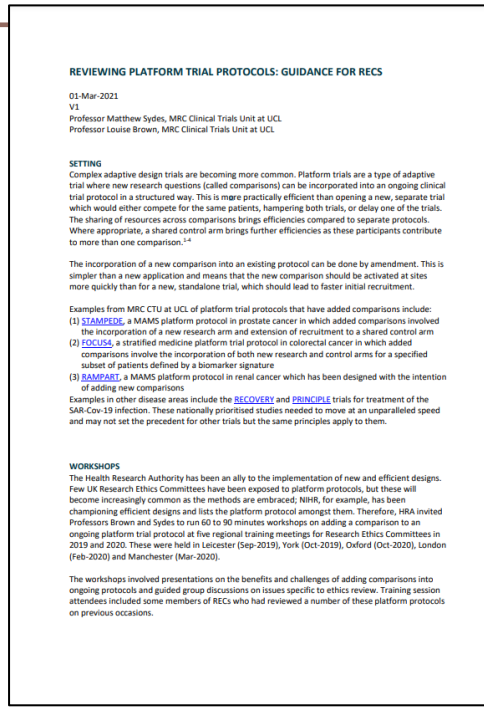
doi: 10.1186/s13063-019-3322-7

Forthcoming

~50 recommendations from 15 platform trials at 8 UK CTUs to be submitted end December 2021

Ethics Committee workshops

www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/


REVIEWING PLATFORM TRIAL PROTOCOLS: GUIDANCE FOR RECS

01-Mar-2021
V1
Professor Matthew Sydes, MRC Clinical Trials Unit at UCL
Professor Louise Brown, MRC Clinical Trials Unit at UCL

SETTING

Complex adaptive design trials are becoming more common. Platform trials are a type of adaptive trial where new research questions (called comparisons) can be incorporated into an ongoing clinical trial protocol in a structured way. This is more practically efficient than opening a new, separate trial which would either compete for the same patients, hampering both trials, or delay one of the trials. The sharing of resources across comparisons brings efficiencies compared to separate protocols. Where appropriate, a shared control arm brings further efficiencies as these participants contribute to more than one comparison.[1-4]

The incorporation of a new comparison into an existing protocol can be done by amendment. This is simpler than a new application and means that the new comparison should be activated at sites more quickly than for a new, standalone trial, which should lead to faster initial recruitment.

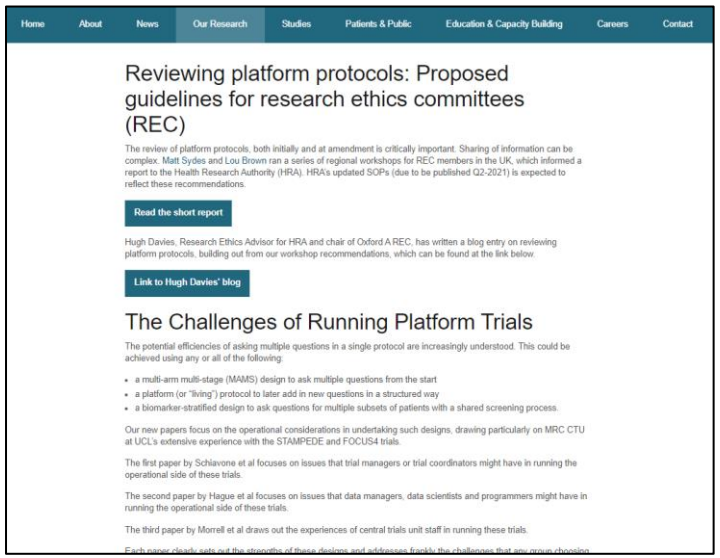
Examples from MRC CTU at UCL of platform trial protocols that have added comparisons include:
(1) STAMPEDE, a MAMS platform protocol in prostate cancer in which added comparisons involved the incorporation of a new research arm and extension of recruitment to a shared control arm
(2) FOCUS4, a stratified medicine platform trial protocol in colorectal cancer in which added comparisons involve the incorporation of both new research and control arms for a specified subset of patients defined by a biomarker signature
(3) RAMPART, a MAMS platform protocol in renal cancer which has been designed with the intention of adding new comparisons
Examples in other disease areas include the RECOVERY and PRINCIPLE trials for treatment of the SAR-Cov-19 infection. These nationally prioritised studies needed to move at an unparalleled speed and may not set the precedent for other trials but the same principles apply to them.

WORKSHOPS

The Health Research Authority has been an ally to the implementation of new and efficient designs. Few UK Research Ethics Committees have been exposed to platform protocols, but these will become increasingly common as the methods are embraced; NIHR, for example, has been championing efficient designs and lists the platform protocol amongst them. Therefore, HRA invited Professors Brown and Sydes to run 60 to 90 minutes workshops on adding a comparison to an ongoing platform trial protocol at five regional training meetings for Research Ethics Committees in 2019 and 2020. These were held in Leicester (Sep-2019), York (Oct-2019), Oxford (Oct-2020), London (Feb-2020) and Manchester (Mar-2020).

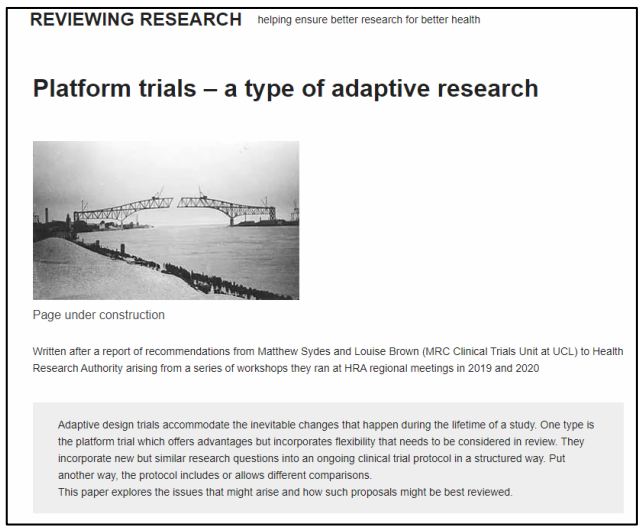
The workshops involved presentations on the benefits and challenges of adding comparisons into ongoing protocols and guided group discussions on issues specific to ethics review. Training session attendees included some members of RECs who had reviewed a number of these platform protocols on previous occasions.

www.ctu.mrc.ac.uk/our-research/methodology/conduct/practical-implementation-of-new-trial-designs/



Short Report at www.ctu.mrc.ac.uk/media/1948/guidance_for_recs_2021-03-01_v1.pdf

http://www.reviewingresearch.com/platform-trials/



Conclusions

PPI involvement in clinical trial is important & helpful to production of high-quality, relevant trials

MAMS platform trials are a key tool in efficiently improving outcomes for patients & the public

Good PPI involvement in MAMS platform trials is key

MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

MAMS platform protocols:
Patient engagement in STAMPEDE and beyond

Professor Matthew Sydes
MRC CTU at UCL
Institute of Clinical Trials and Methodology
London, UK

Patient Engagement Open Forum
09-Dec-2021 (Version 2.00)