

The UK Clinical Trial Machinery: The Stampede Model

Christie Hospital 
NHS Foundation Trust

Salford Royal 
NHS Foundation Trust

University Teaching Hospital


The University of Manchester

NW Clarke

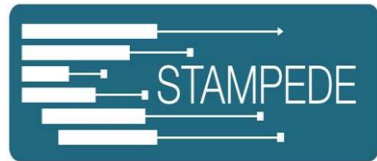
Urological Surgeon

Professor of Urological Oncology

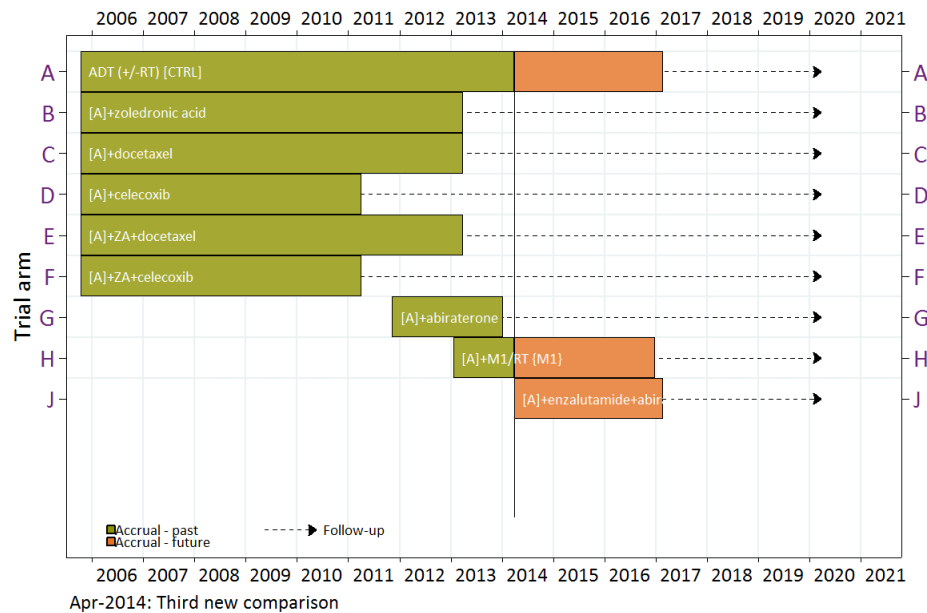
Manchester UK



The UK Clinical Trial Machinery: The Stampede Model



STAMPEDE: Enzalutamide + abiraterone comparison to be activated



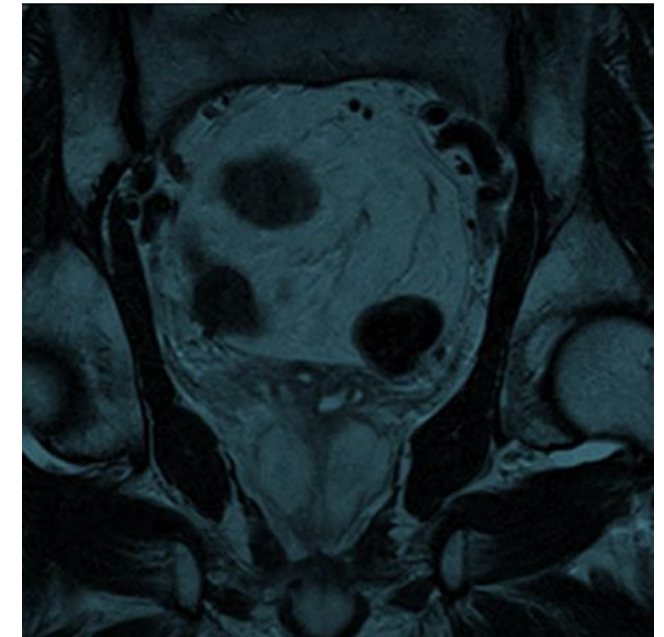
www.thestampedetrial.org



NPCA
National Prostate Cancer Audit

Annual Report 2021

Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2019 to 31 March 2020 and the Impact of COVID-19 in England during 2020 (published January 2022)



www.npca.org.uk

Rational for the STAMPEDE Model

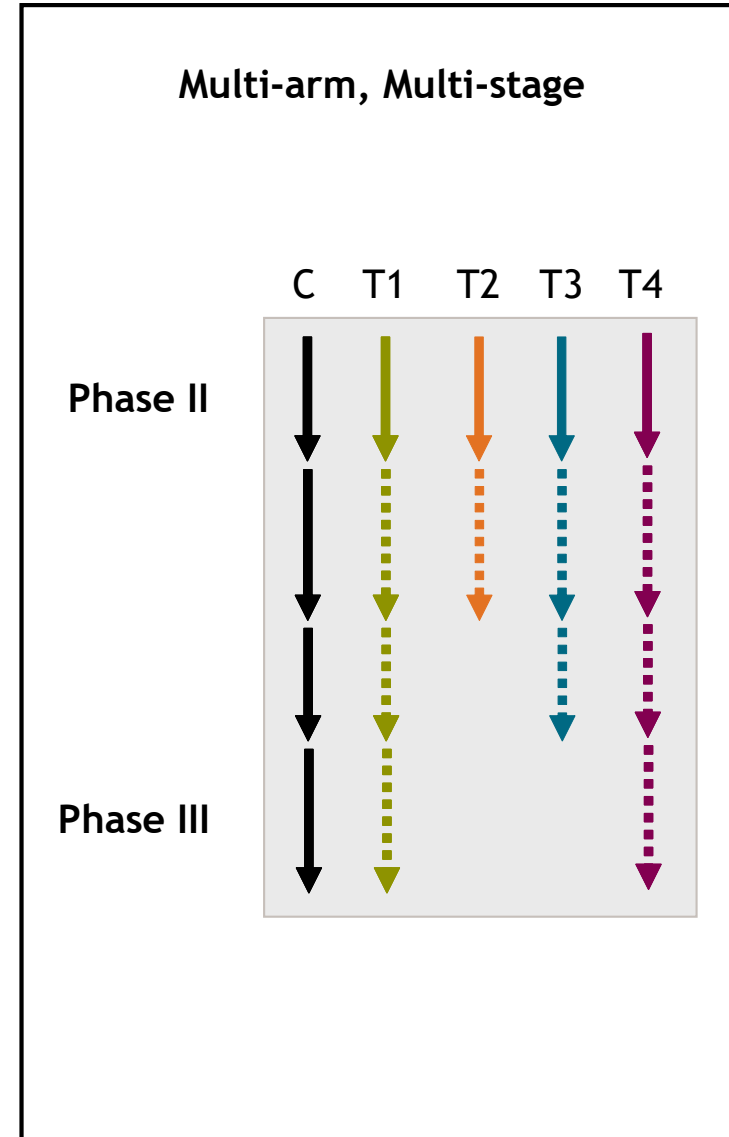
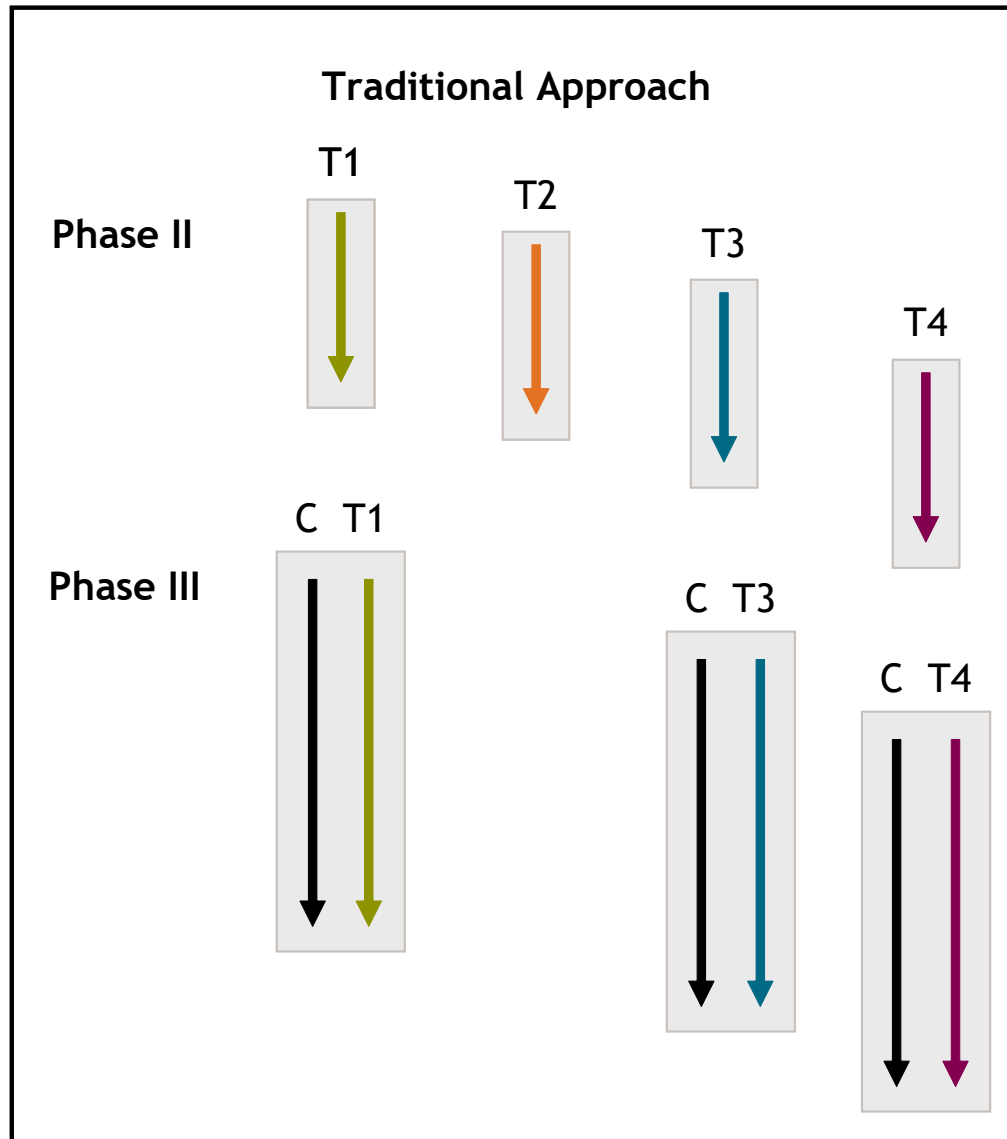
Can We Improve Outcomes Using New Treatments in Combination in High Risk Prostate Cancer ?

Flexible trial design in practice – dropping and adding arms in STAMPEDE: a multi-arm multi-stage randomised controlled trial (MRC PR08, CRUK/06/019)

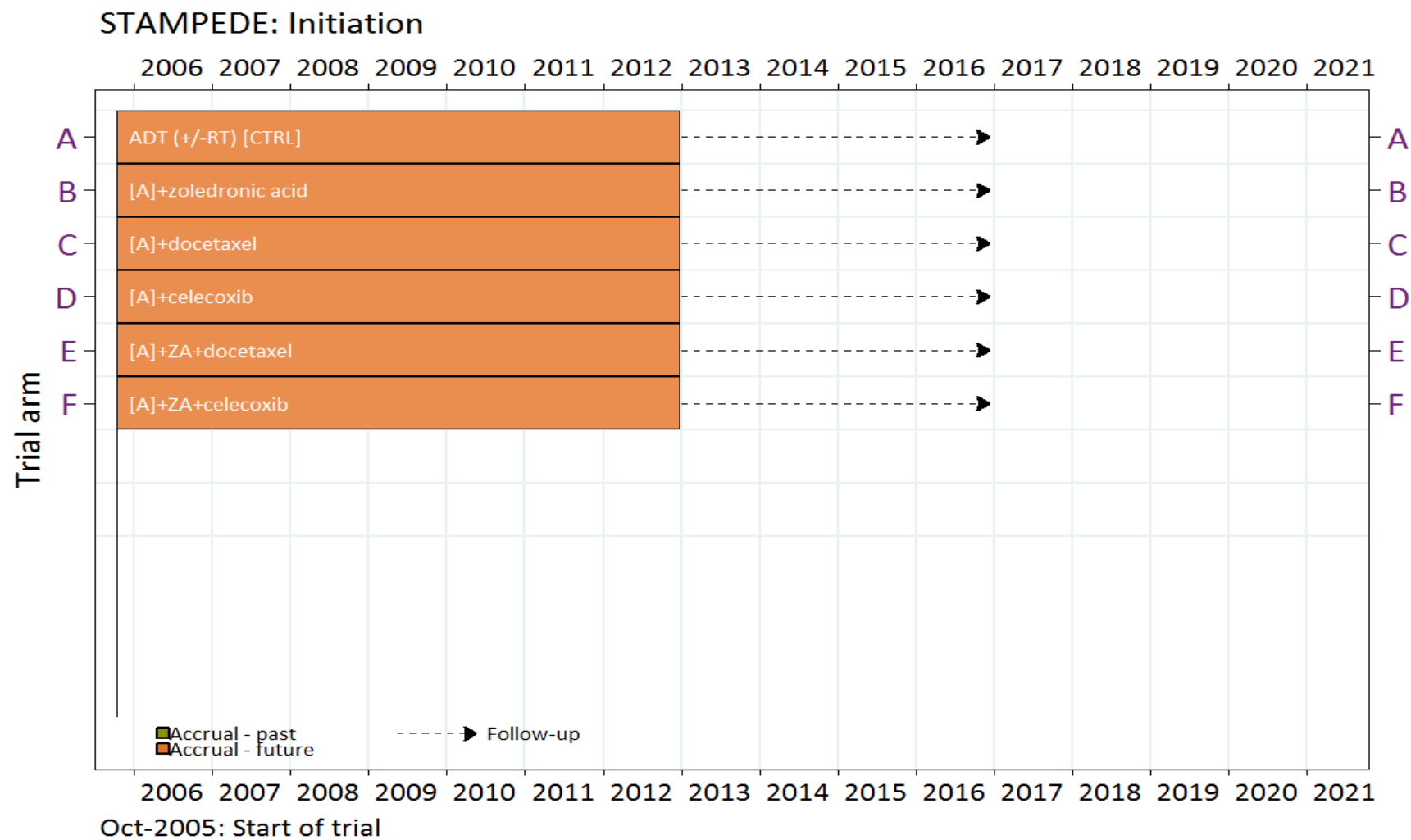
ND James, MD Mason, NW Clarke, D Dearnaley, M Sydes, MKB Parmar
The STAMPEDE investigators 2002-2004

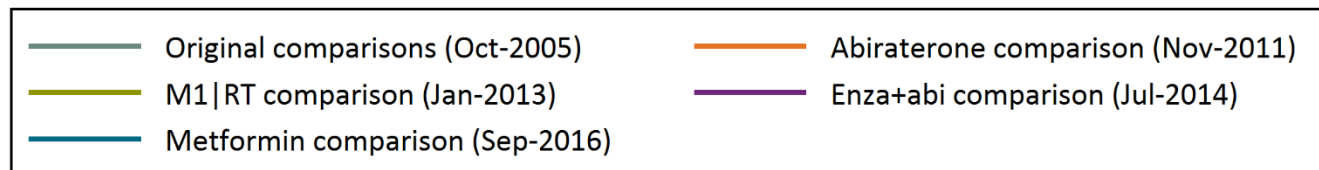
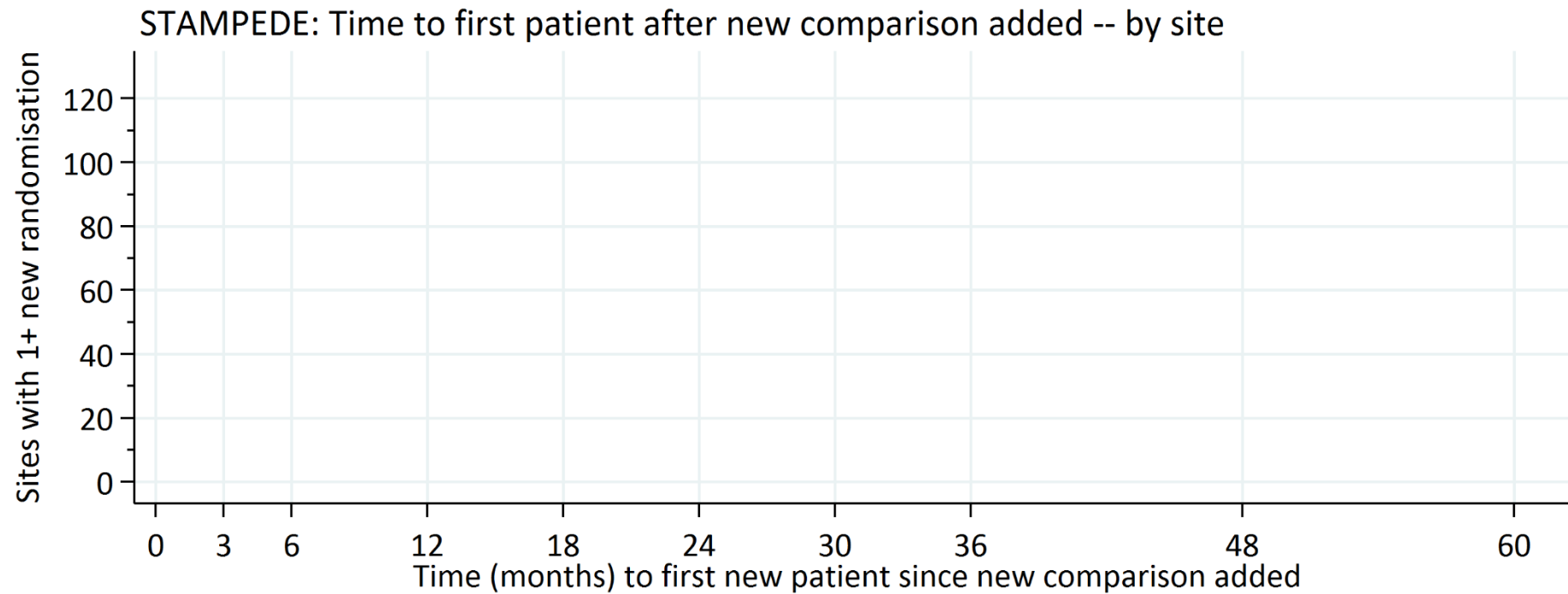


The Multi-Arm Multi-Stage Trial Design: A New Way to Conduct Large-Scale Randomised Trials



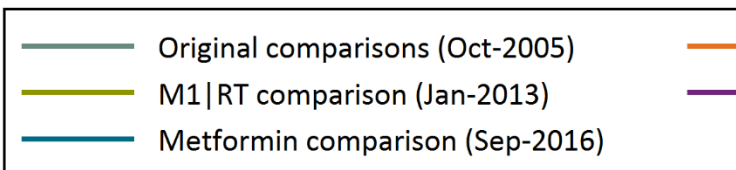
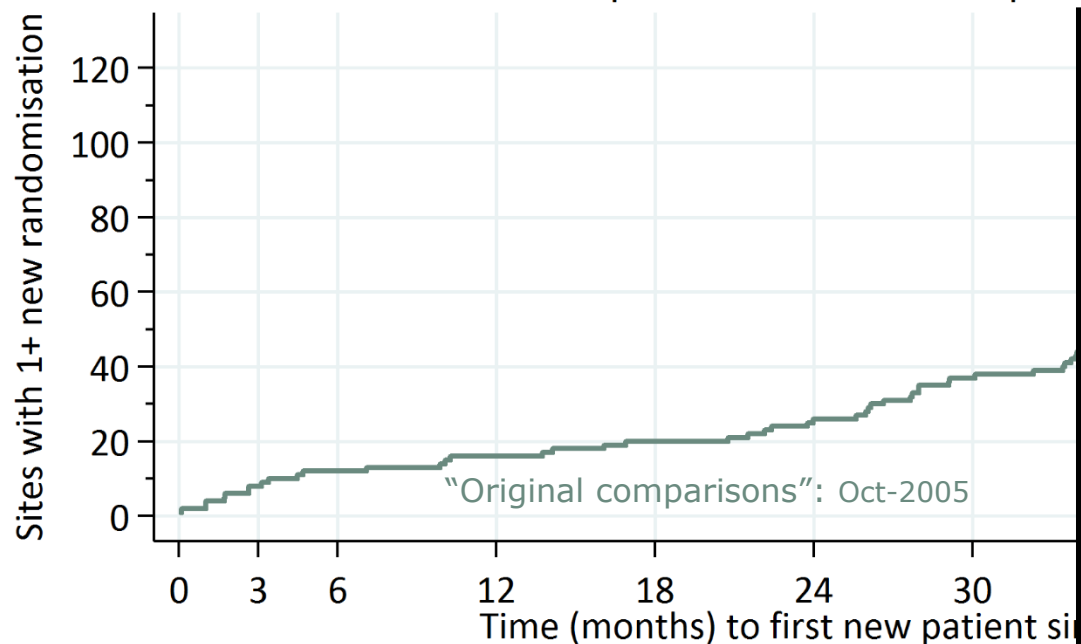
Testing Multiple Agents





The trial started with one 6-arm randomisation
The has been amended 4 times to introduce new arms
centres activated in total
Original comparison capped on graph at 5yr
--- Graph drawn 12-Apr-2017

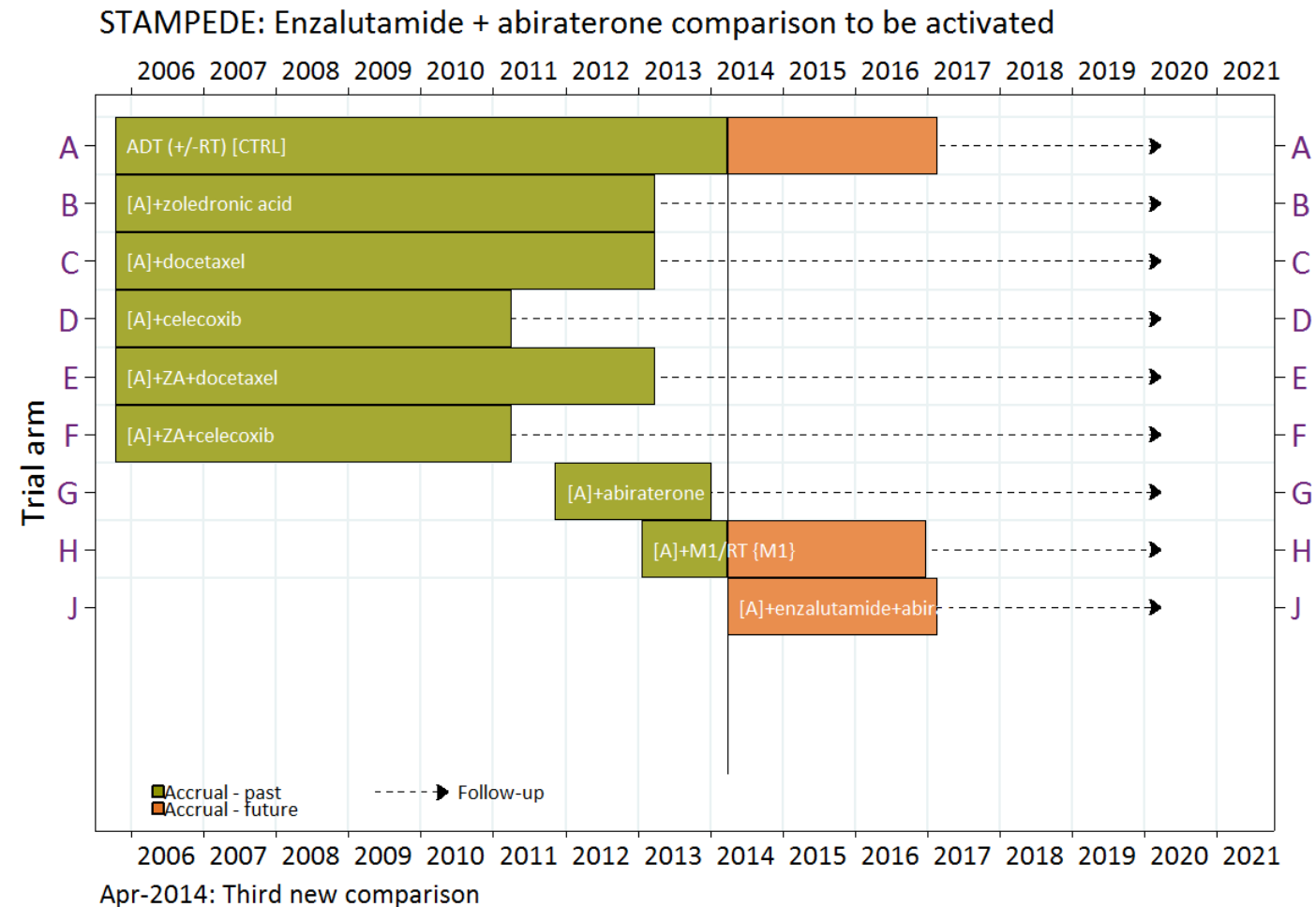
STAMPEDE: Time to first patient after new comparison added -- by site

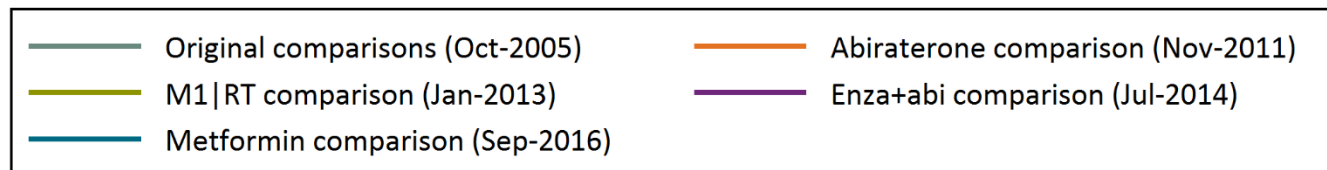
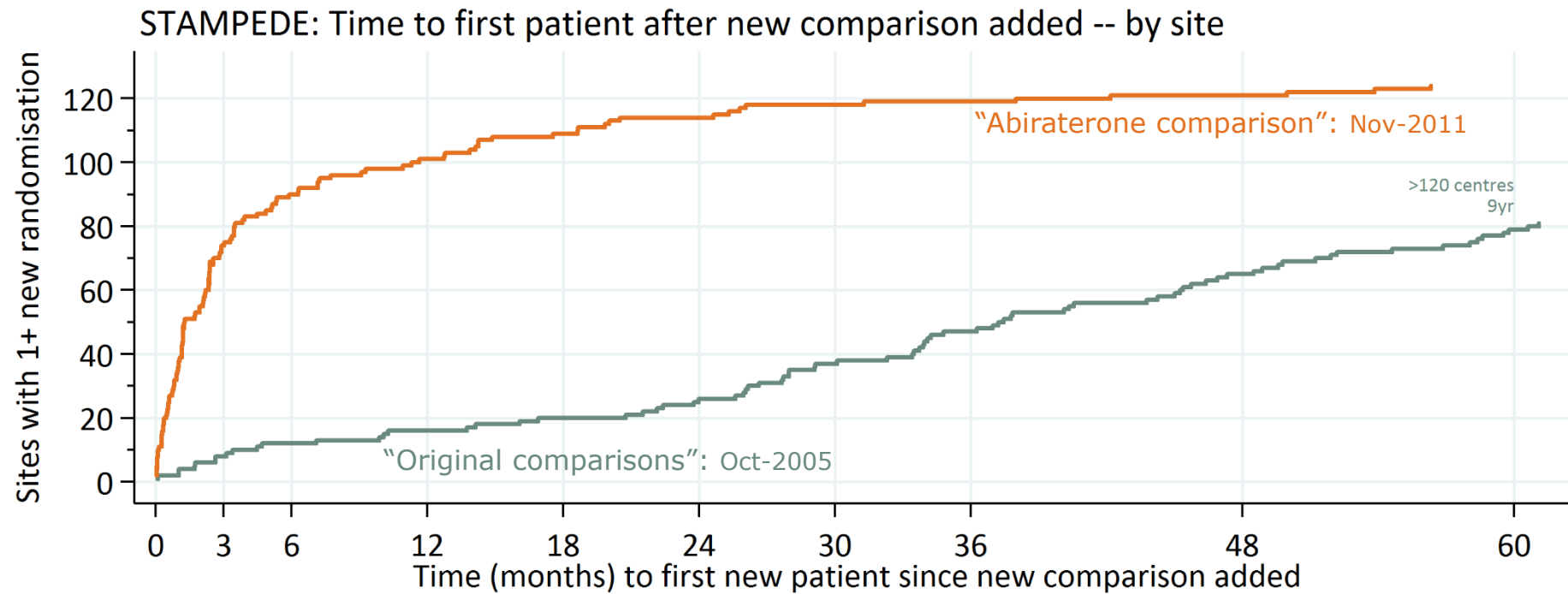


The trial started with one 6-arm randomisation
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 Original comparison capped on graph at 5yr
 --- Graph drawn 12-Apr-2017

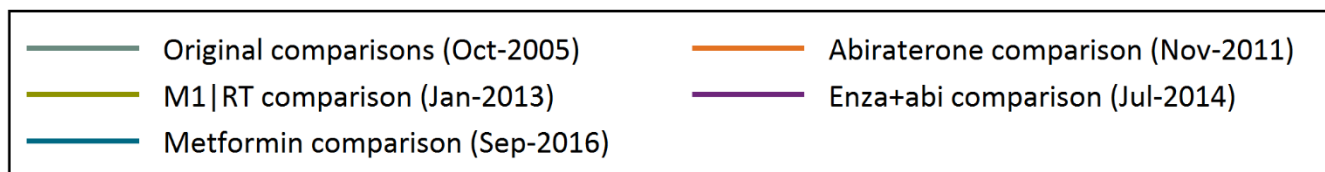
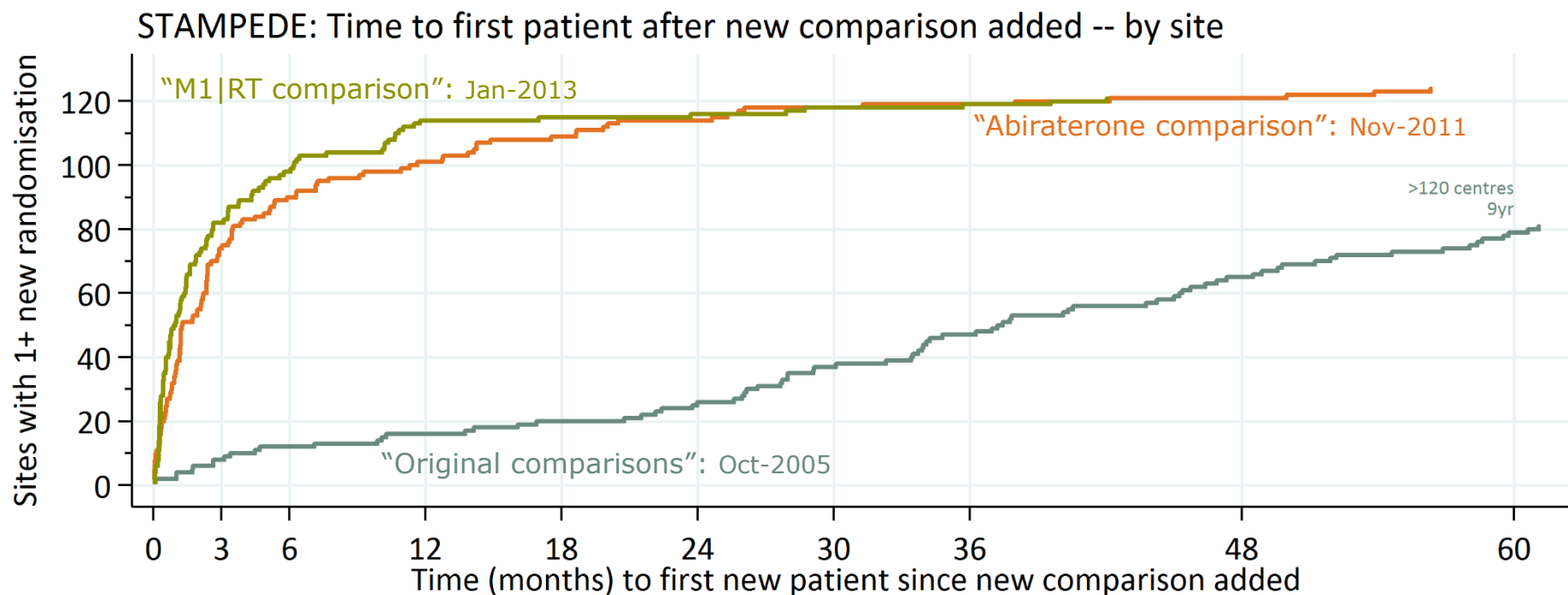


Dropping/Adding Arms and Shortening the Duration of Set-up and Recruitment

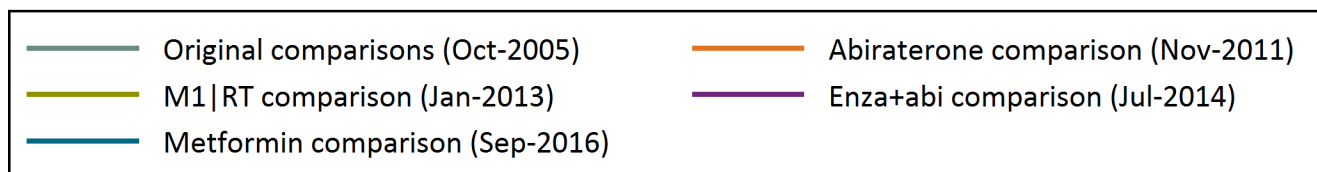
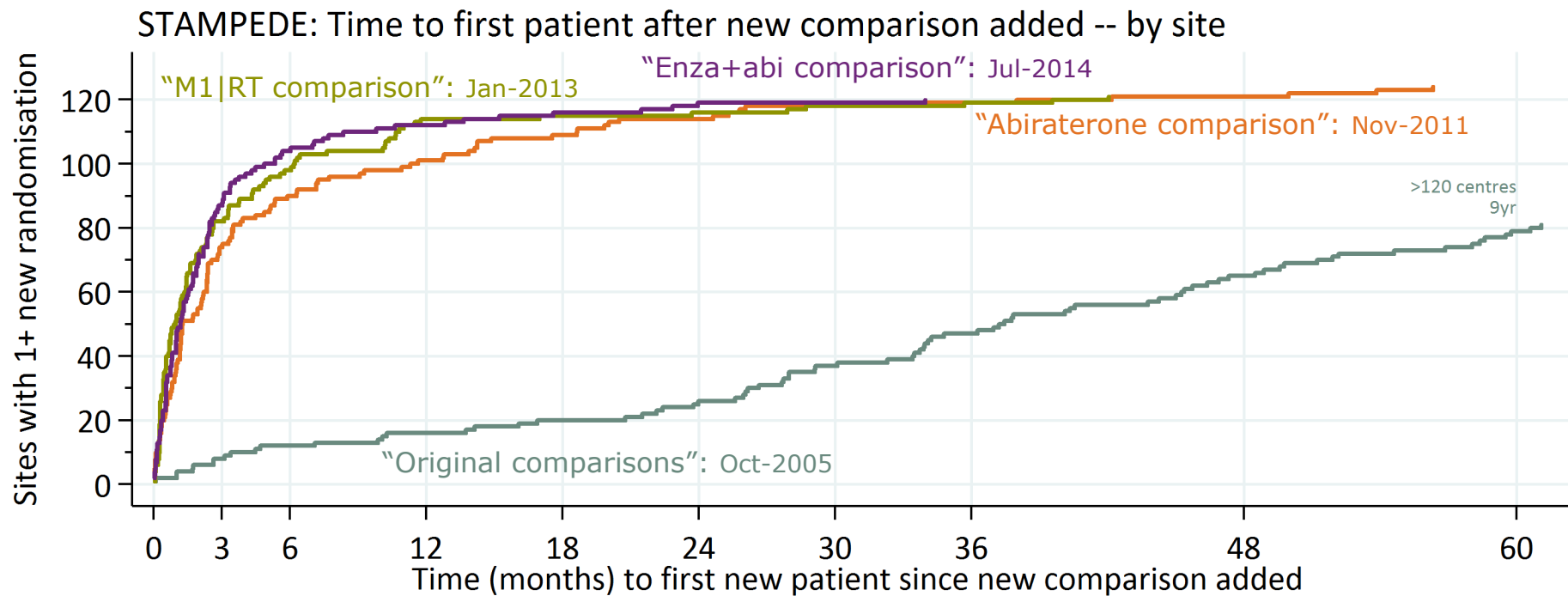




The trial started with one 6-arm randomisation
The has been amended 4 times to introduce new arms
centres activated in total
Original comparison capped on graph at 5yr
--- Graph drawn 12-Apr-2017

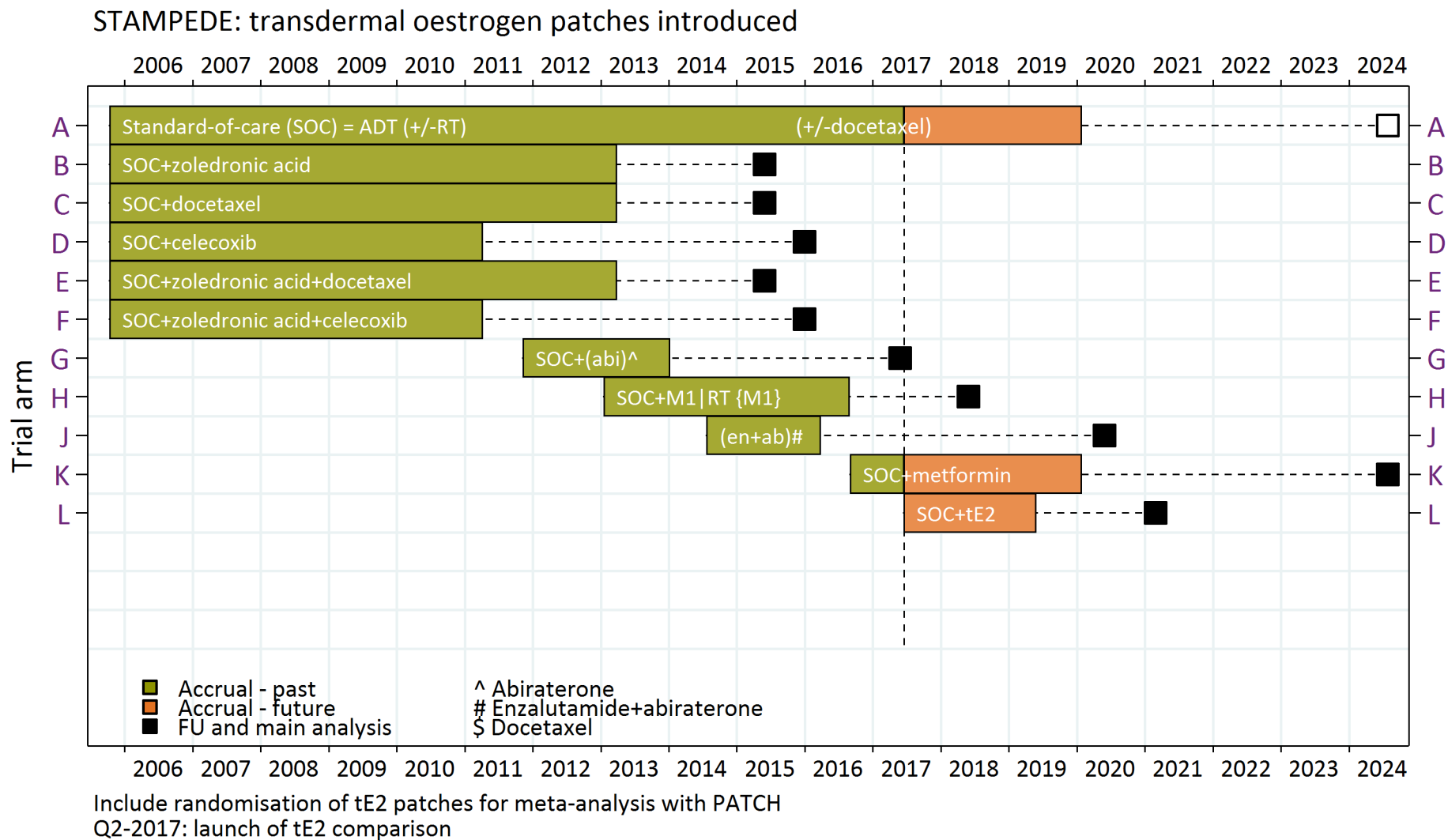


The trial started with one 6-arm randomisation
 The has been amended 4 times to introduce new arms
 centres activated in total
 Original comparison capped on graph at 5yr
 --- Graph drawn 12-Apr-2017



The trial started with one 6-arm randomisation
 The has been amended 4 times to introduce new arms
 centres activated in total
 Original comparison capped on graph at 5yr
 --- Graph drawn 04-Jul-2017

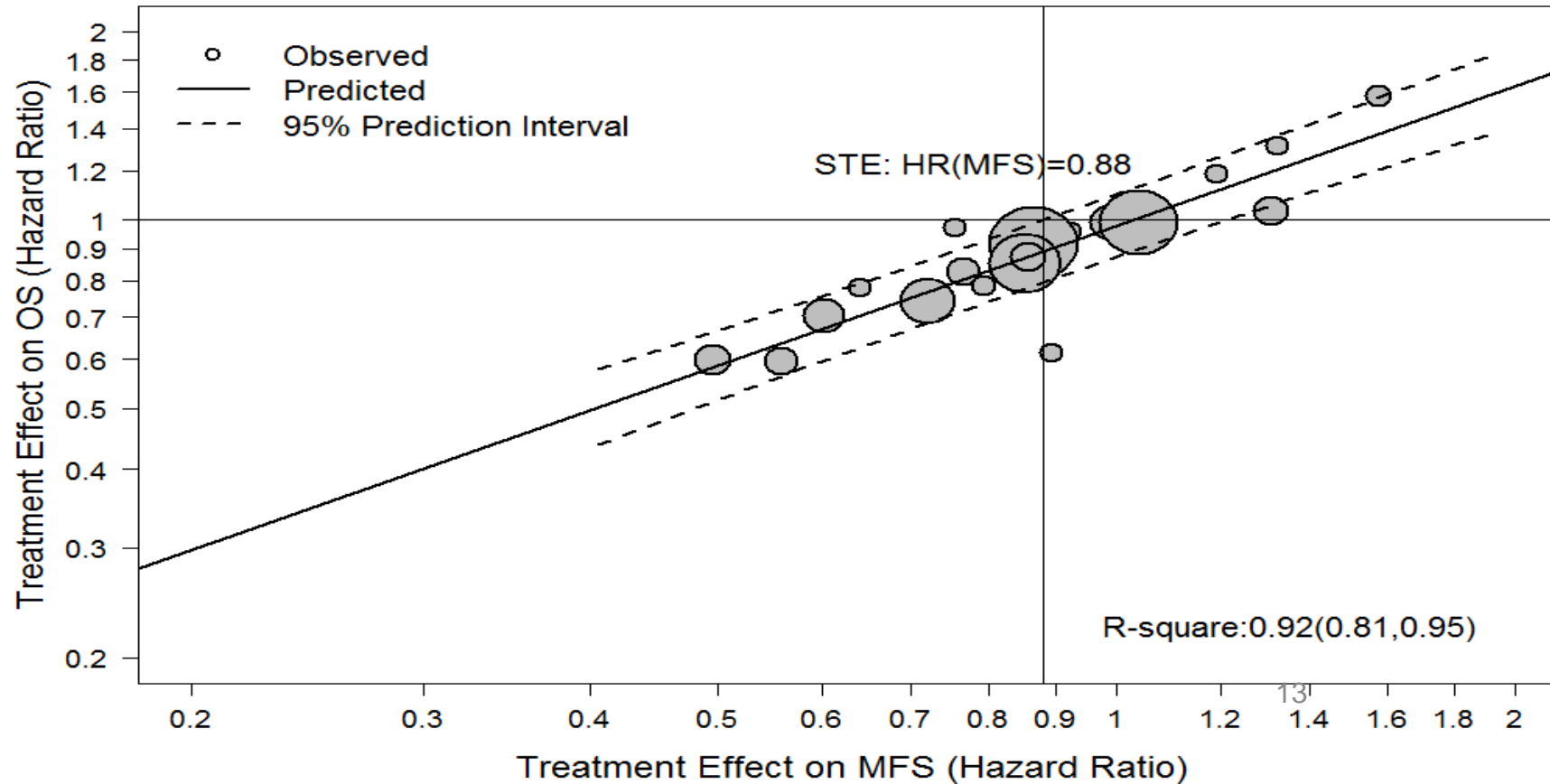
Changing the Standard of Care Control Arm



Adapting the Protocol: Meta-Analysis and the Rationale for 5y MFS

MFS as Surrogate for OS- Surrogacy Threshold Effect

(C)



Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

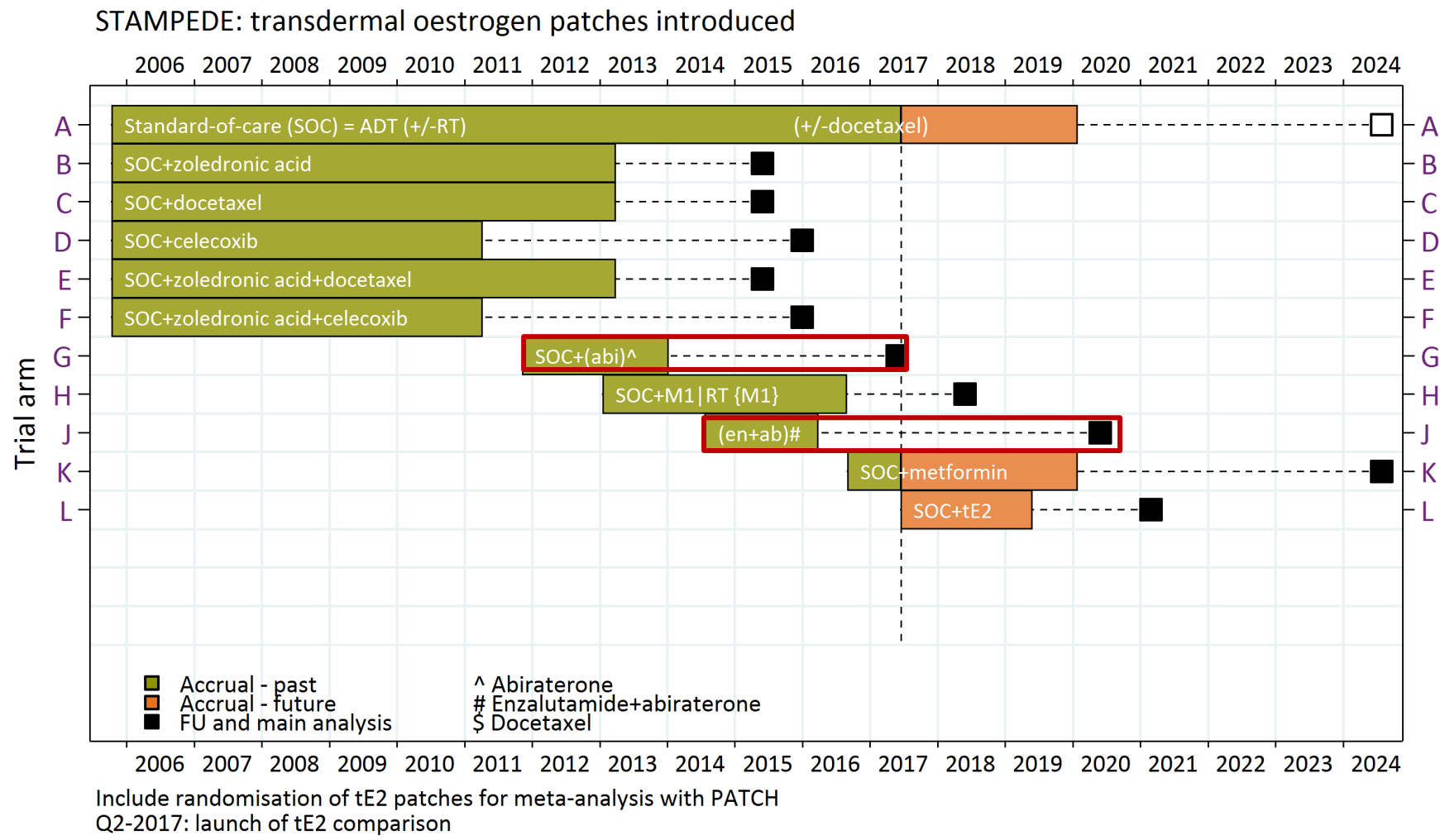
Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher Sweeney, on behalf of the ICECaP Working Group

JOURNAL OF CLINICAL ONCOLOGY

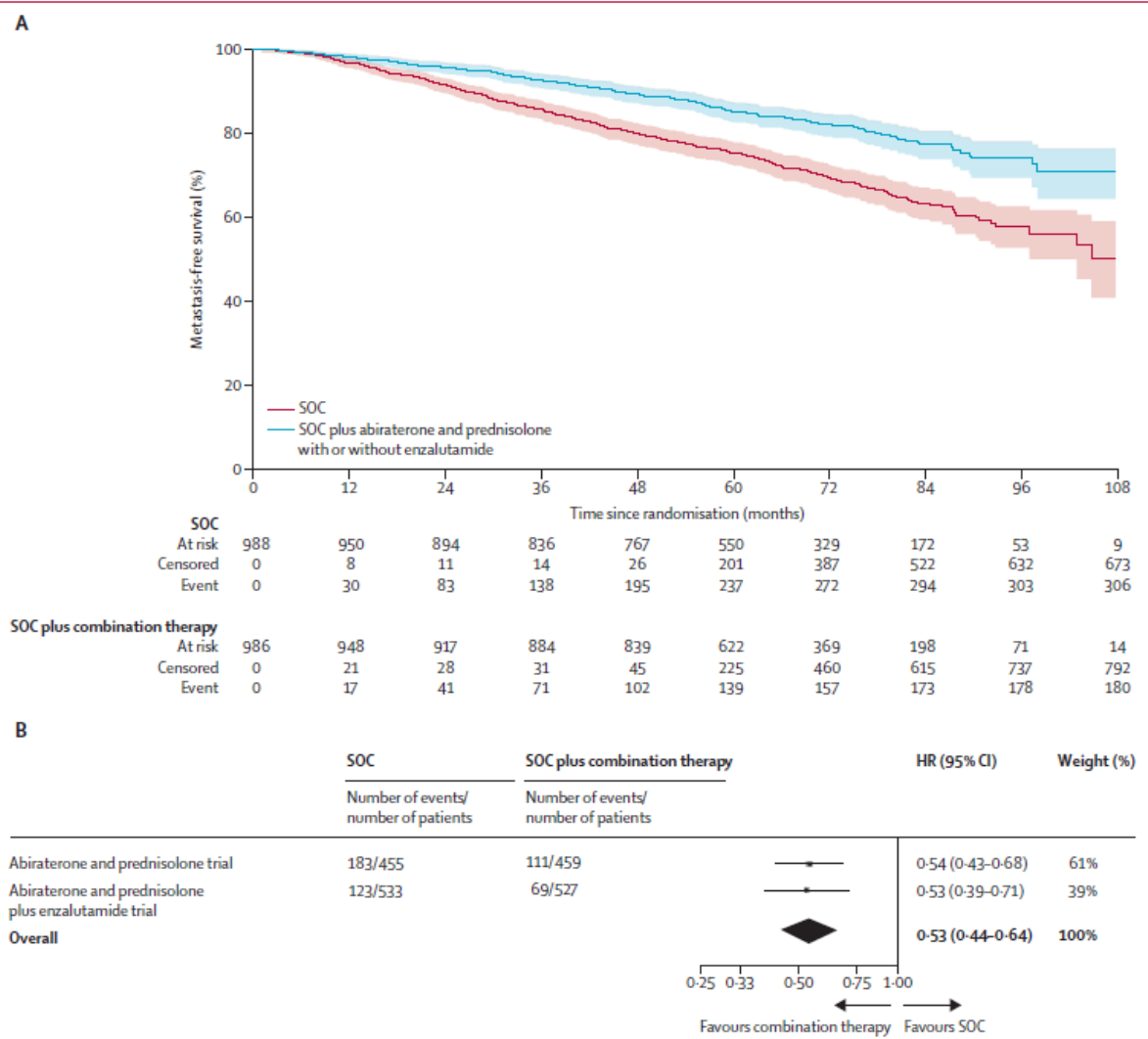
ORIGINAL REPORT

ICECaP Collaboration JCO 2017

Adapting the Protocol in Long-Term Studies: Primary Radiotherapy + ADT + Abiraterone ± Enzalutamide in Stampede



Adapting the Protocol in Long-Term Studies: Primary Radiotherapy + ADT + Abiraterone ± Enzalutamide in Stampede



Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker, Silke Gillissen, Adrian Cook, Chris Brawley, Claire L Amos, Nafisah Atako, Cheryl Pugh, Michelle Buckner, Simon Chowdhury, Zafar Malik, J Martin Russell, Clare Gilson, Hannah Rush, Jo Bowen, Anna Lydon, Ian Pedley, Joe M O'Sullivan, Alison Birtle, Joanna Gale, Narayanan Srihari, Carys Thomas, Jacob Tanguay, John Wagstaff, Prantik Das, Emma Gray, Mymoona Alzoueb, Orni Parikh, Angus Robinson, Isabel Syndikus, James Wylie, Anjali Zarkar, George Thalmann, Johann S de Bono, David P Dearnaley*, Malcolm D Mason*, Duncan Gilbert, Ruth E Langley, Robin Millman, David Matheson, Matthew R Sydes†, Louise C Brown†, Mahesh K B Parmar†, Nicholas D James†, on behalf of the Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators‡

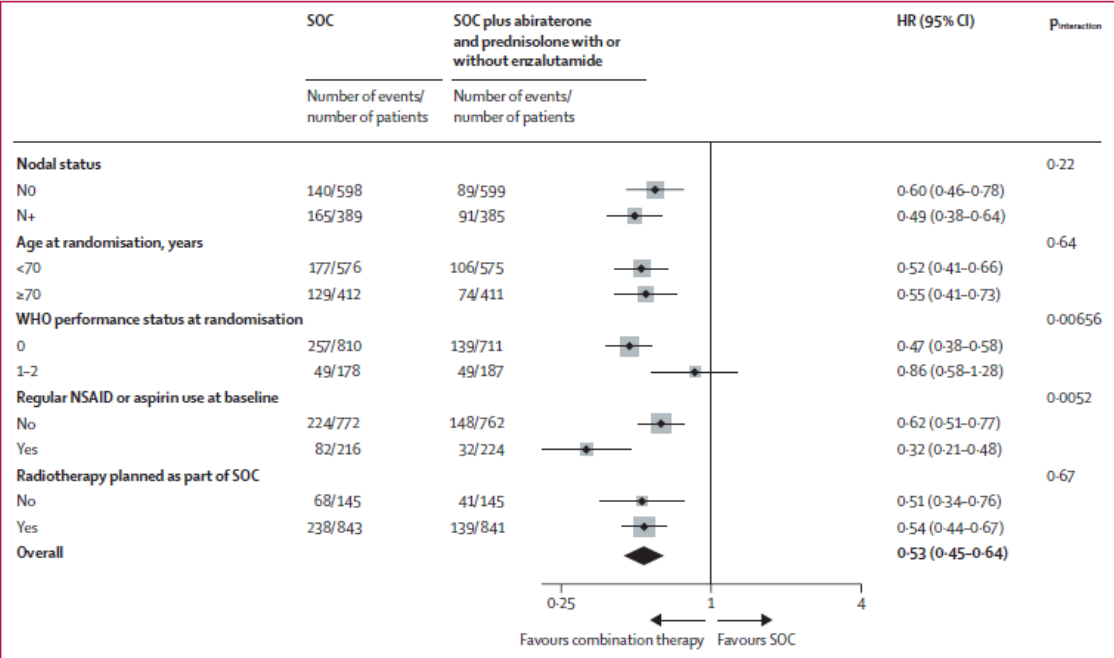
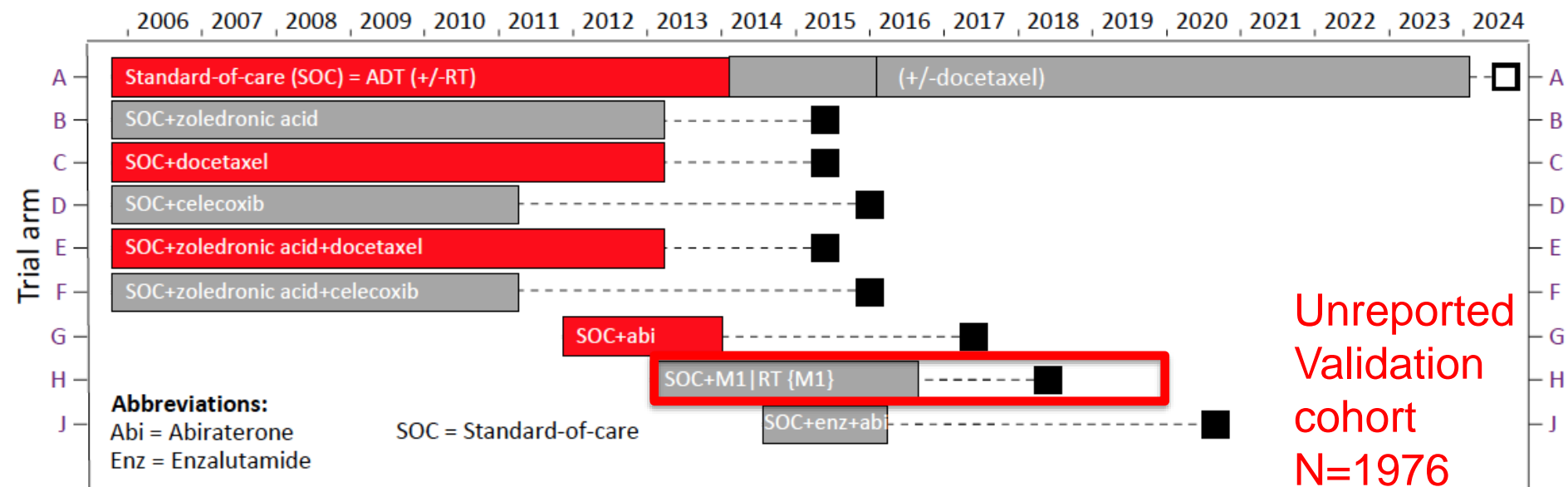


Figure 3: Forest plots of treatment effect on metastasis-free survival for baseline randomisation stratification factors (except recruiting centre and type of androgen-deprivation therapy)

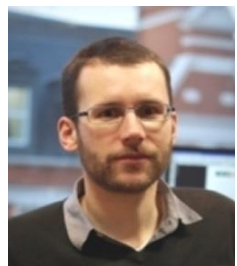


Published Online
December 23, 2021
[https://doi.org/10.1016/S0140-6736\(21\)02437-5](https://doi.org/10.1016/S0140-6736(21)02437-5)

Translational Science: The STRATOSPHERE consortium and the BIG Group



“..I give my authority for my remaining samples to be used for additional research analyses by ethics approved protocols. I understand this is a gift.”



STAMPEDE Translational Research: The Stratosphere and BIG Projects

Informatics

MRCCTU / Stampede TMG

Central Stampede Data Repository

The Biomedical Research Group (BRG): UCL London

Tumour and ctDNA collection

PI: Gert Attard (Stampede TMG)

Germ line DNA collection

>3000 blocks collected

ctDNA from Arm J Abiraterone + Enzalutamide



Movember

The Biomedical Imaging Group (BIG):

GU Cancer Research Group Christie / Manchester Cancer Institute

Image bank

PI: Noel Clarke (Stampede TMG)

>24,000 Scans Centralised

Categorised and Quantified for Tumour Burden / Distribution (Bone / Node/ Visceral)

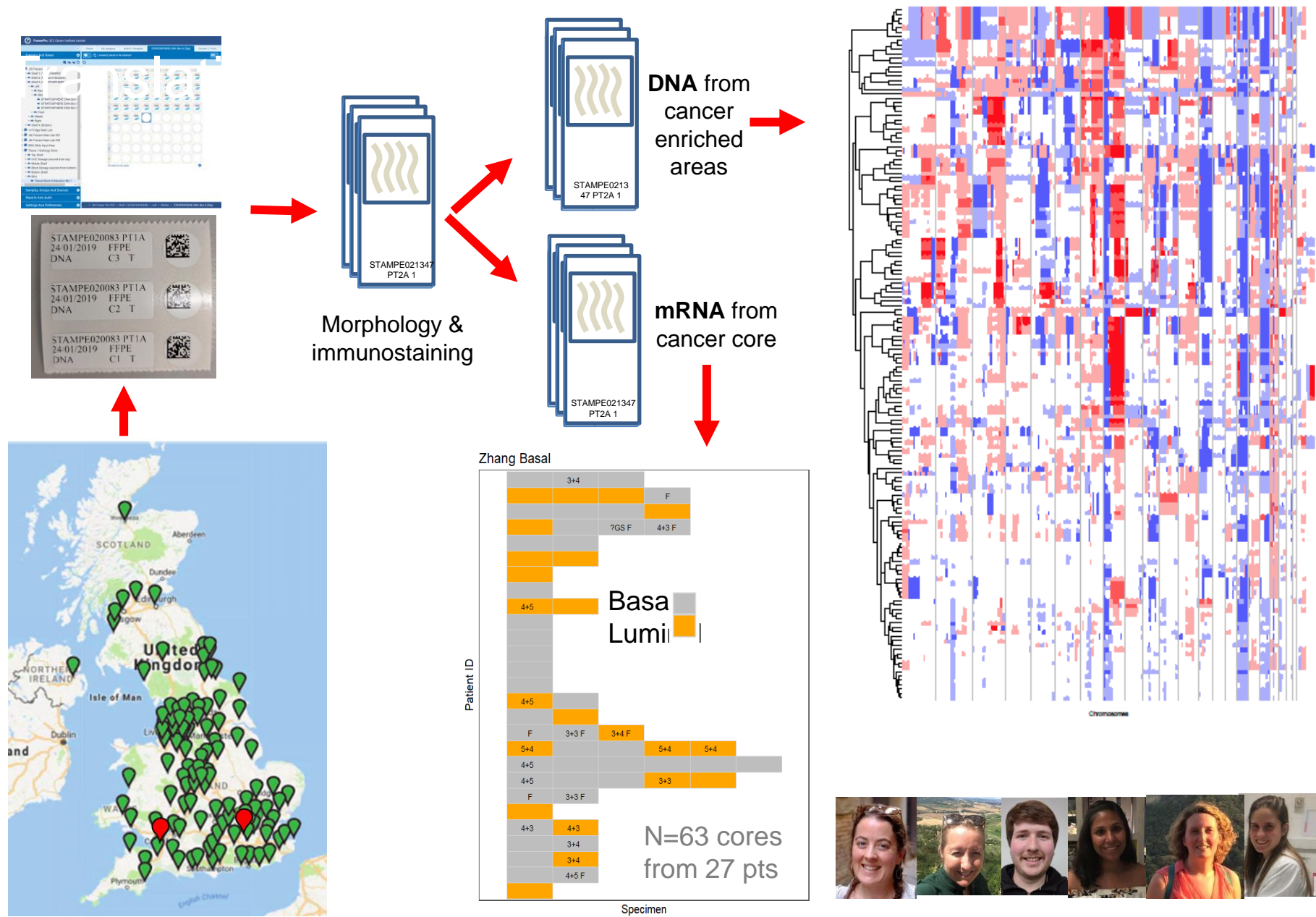
Correlated with Treatment Outcome linked to Genomic Data

Fracture and Sarcopenia Assessment

Linkage to National Databases and Audits



Stampede Tumour Tissue Acquisition: The BRG Programme



RESEARCH

Open Access

Accumulation of copy number alterations and clinical progression across advanced prostate cancer

Emily Grist^{1†}, Stefanie Friedrich^{1†}, Christopher Brawley², Larissa Mendes¹, Marina Parry¹, Adnan Ali³, Aine Haran⁴, Alex Hoyle⁴, Claire Gilson², Sharanpreet Lall¹, Leila Zakka¹, Carla Bautista¹, Alex Landless¹, Karolina Nowakowska¹, Anna Wingate¹, Daniel Wetterskog¹, A. M. Mahedi Hasan¹, Nafisah B. Akato², Malissa Richmond², Sofeya Ishaq², Nik Matthews^{5,6†}, Anis A. Hamid⁷, Christopher J. Sweeney⁷, Matthew R. Sydes², Daniel M. Berney⁸, Stefano Lise¹, STAMPEDE investigators, Mahesh K. B. Parmar², Noel W. Clarke³, Nicholas D. James⁹, Paolo Cremaschi^{1†}, Louise C. Brown^{2†} and Gerhardt Attard^{1†*}

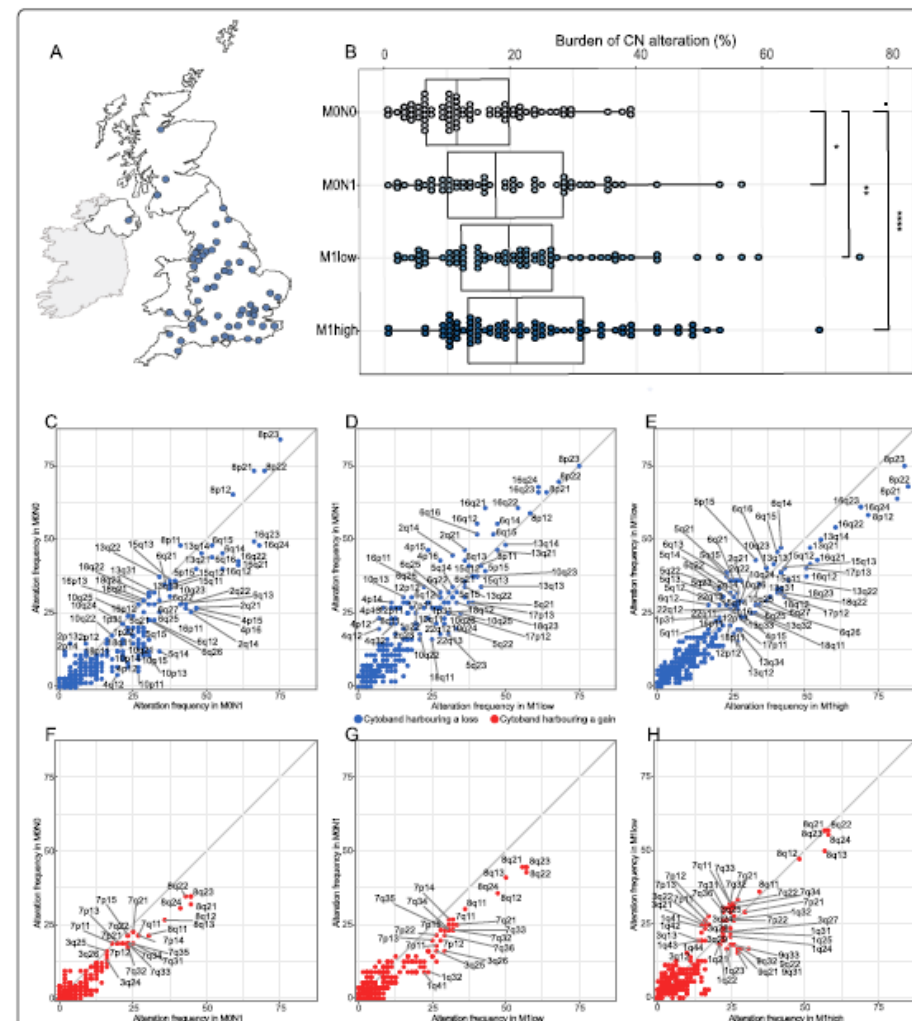
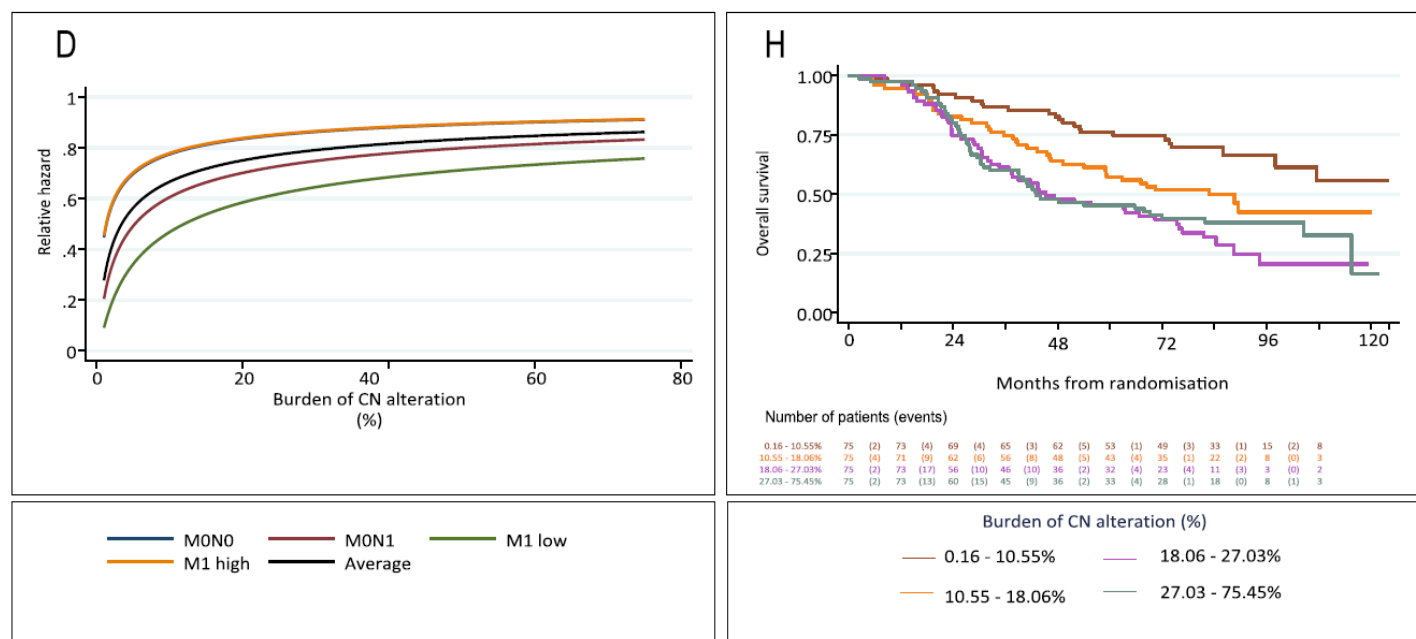
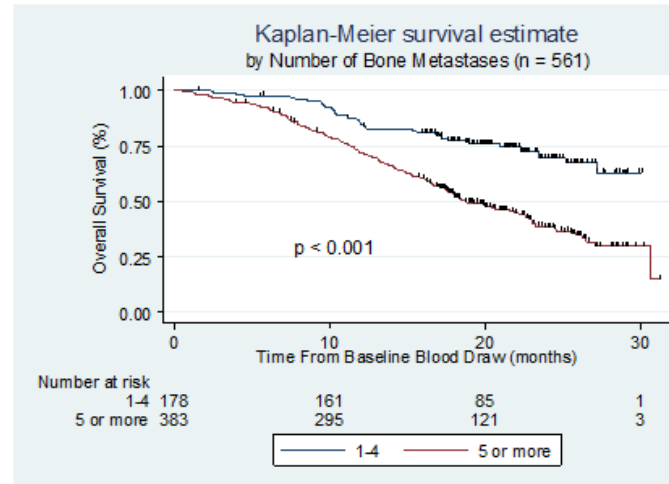


Fig. 1 CN-300 cohort and association of the burden of copy number alteration with metastatic states. **A** Map demonstrating all UK STAMPEDE trial sites recruiting patients included in the CN-300 cohort. **B** Distribution of burden of copy number (CN) alteration (%) in tumour-enriched region of index core split by metastatic states ($N=284$; 16 metastatic patients with unknown designation for low versus high volume were excluded). **C-E** Alteration frequency (%) of patients with at least one segment of loss mapped to denoted cytobands in **C** M0N1 versus M0N0; **D** M1 low versus M0N1; **E** M1 high versus M1 low. **F-H** Alteration frequency (%) of patients with at least one segment of gain mapped to denoted cytobands in **F** M0N1 versus M0N0; **G** M1 low versus M0N1; and **H** M1 high versus M1 low

The BIG Group

Challenging Existing Dogma: Understanding “Low” and “High” Burden: Stampede’s BIG Idea

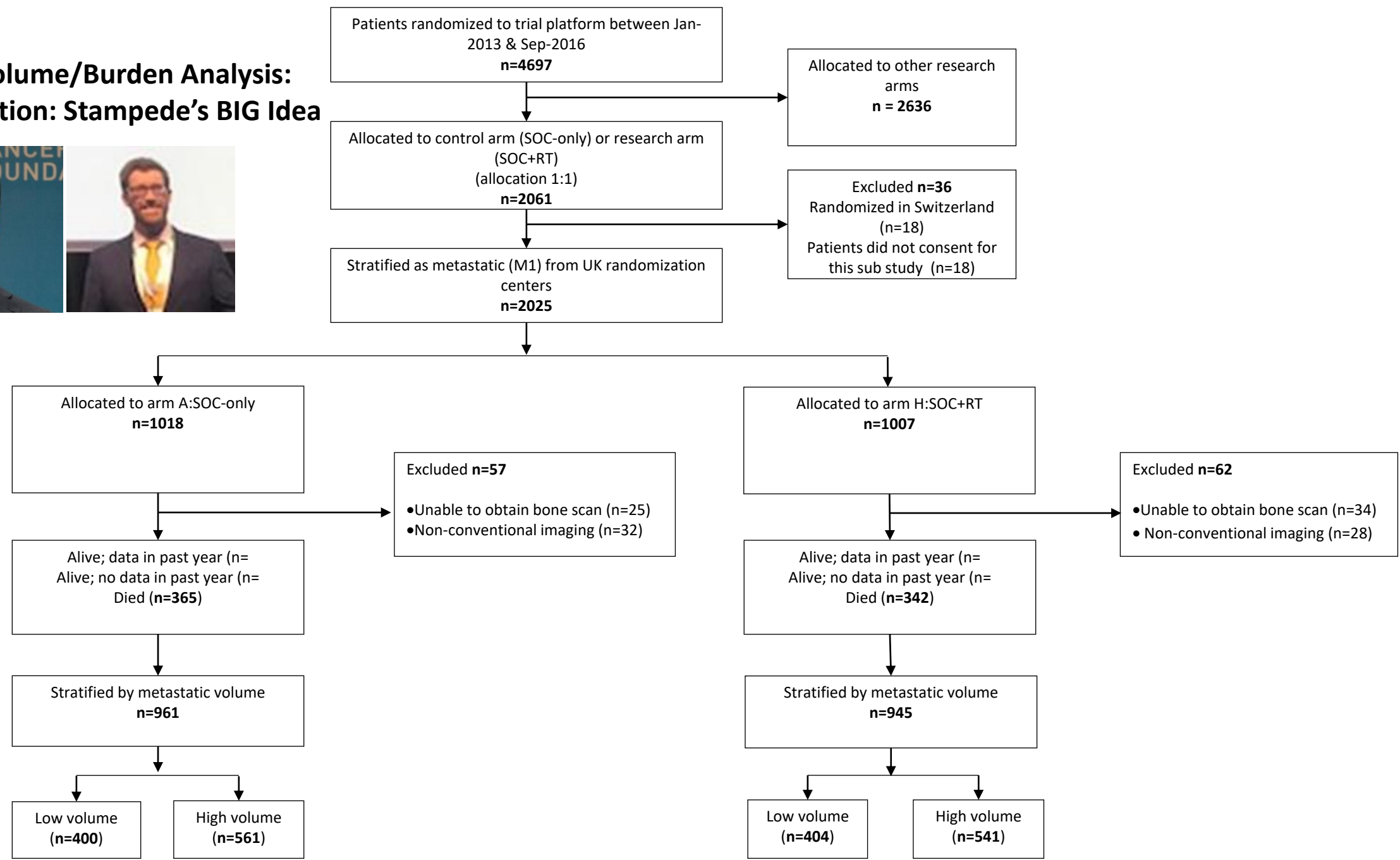


Kaplan-Meier progression free survival estimates for patients dichotomised into 1-4 and ≥ 5 bone metastases groups

Tait C et al British Journal of Urology International 2014



Docetaxel Volume/Burden Analysis:
Cohort selection: Stampede's BIG Idea



Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer

A Secondary Analysis of a Randomized Clinical Trial

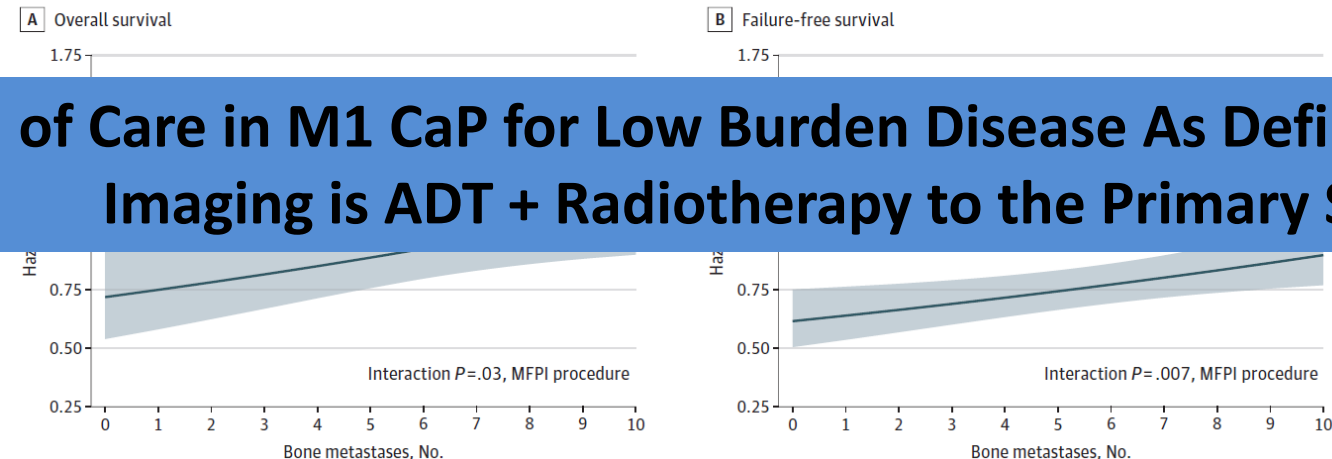
Adnan Ali, MBBS; Alex Hoyle, MBBS, MRCS, MD; Áine M. Haran, MRCS; Christopher D. Brawley, MSc; Adrian Cook, MSc; Claire Amos, PhD; Joanna Calvert, MSc; Hassan Douis, PhD; Malcolm D. Mason, MD; David Dearnaley, MA, MD; Gerhardt Attard, MD, PhD; Silke Gilleksen, MD; Mahesh K. B. Parmar, DPhil; Christopher C. Parker, MD; Matthew R. Sydes, MSc; Nicholas D. James, MBBS, PhD; Noel W. Clarke, MBBS, ChM

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gilleksen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar*, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†

JAMA Oncol. doi:10.1001/jamaoncol.2020.7857
Published online February 18, 2021.

Figure 2. Treatment Effect Plots for Bone Metastasis Count



Estimated treatment effect (solid line) with pointwise 95% CI (shaded area) is shown for overall survival (A) and failure-free survival (B). The horizontal gray line at hazard ratio 1.00 denotes equivalence of treatment effects, with values

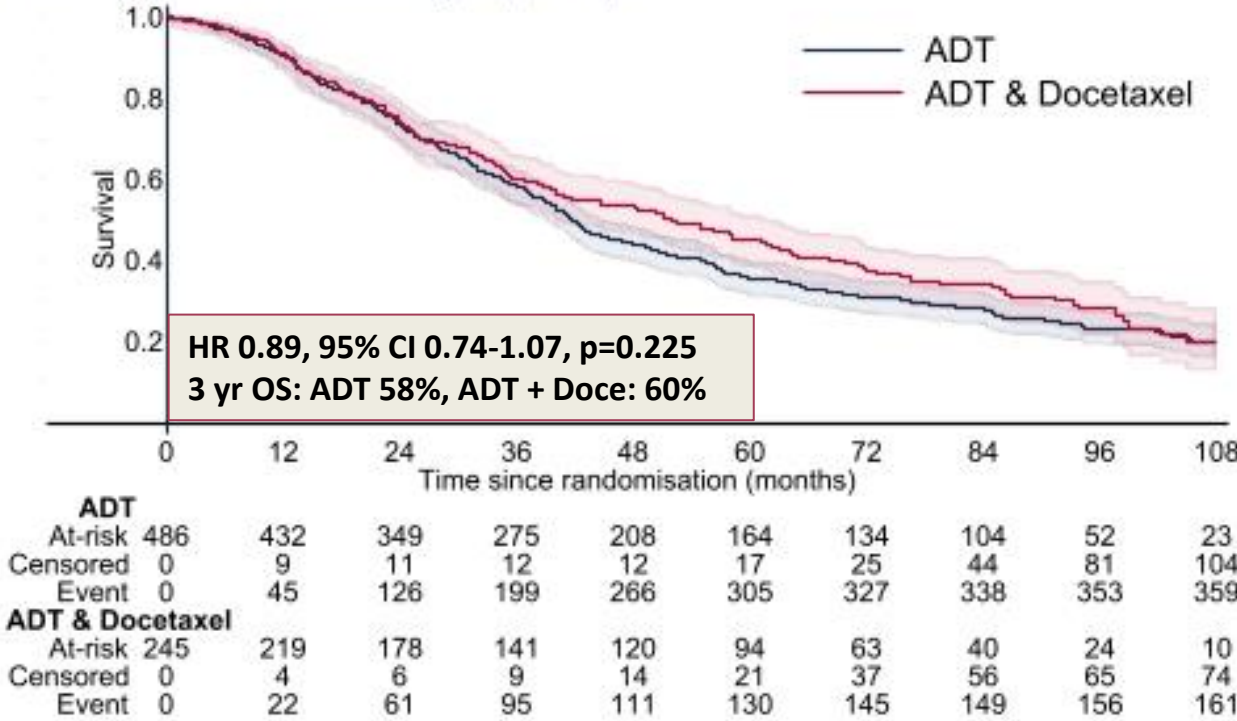
below 1.00 favoring prostate radiotherapy. MFPI indicates multivariable fractional polynomial interaction.

The Standard of Care in M1 CaP for Low Burden Disease As Defined by Conventional Imaging is ADT + Radiotherapy to the Primary Site

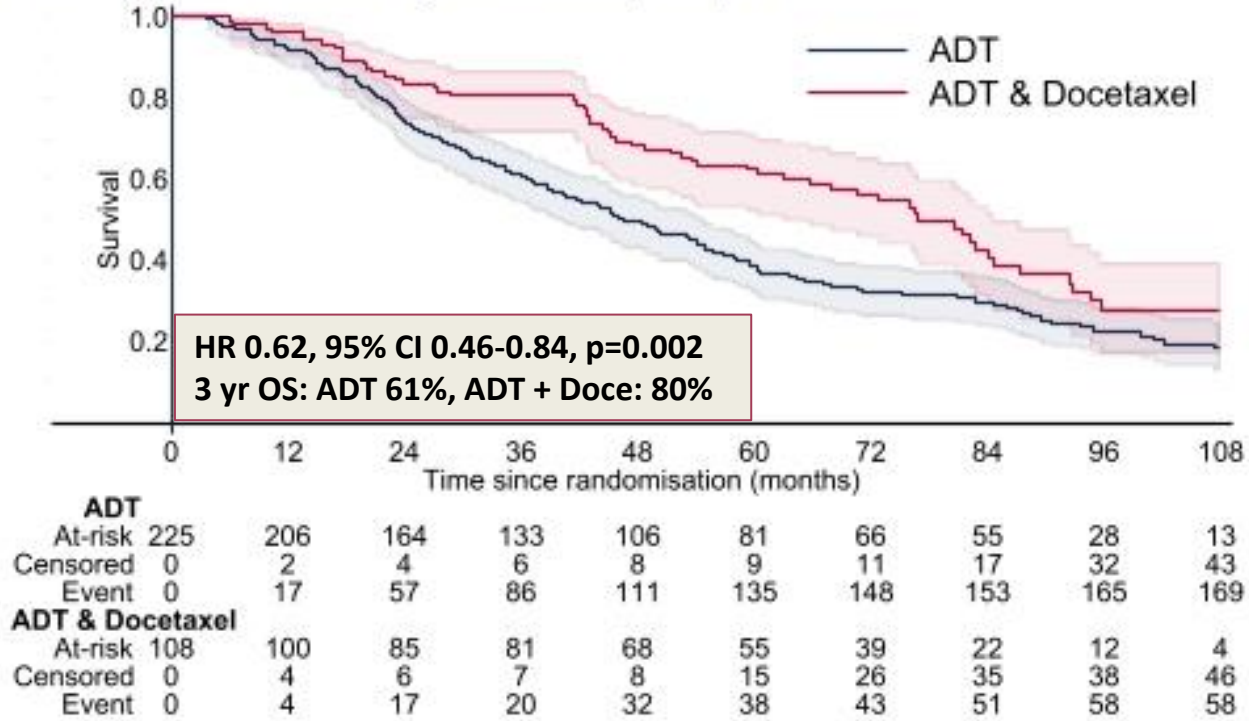


Nodal Burden and Differential Treatment Response: ADT/Docetaxel

Overall Survival: Nodal subgroup 731 pts



Overall Survival: Bone only metastases, 333 pts

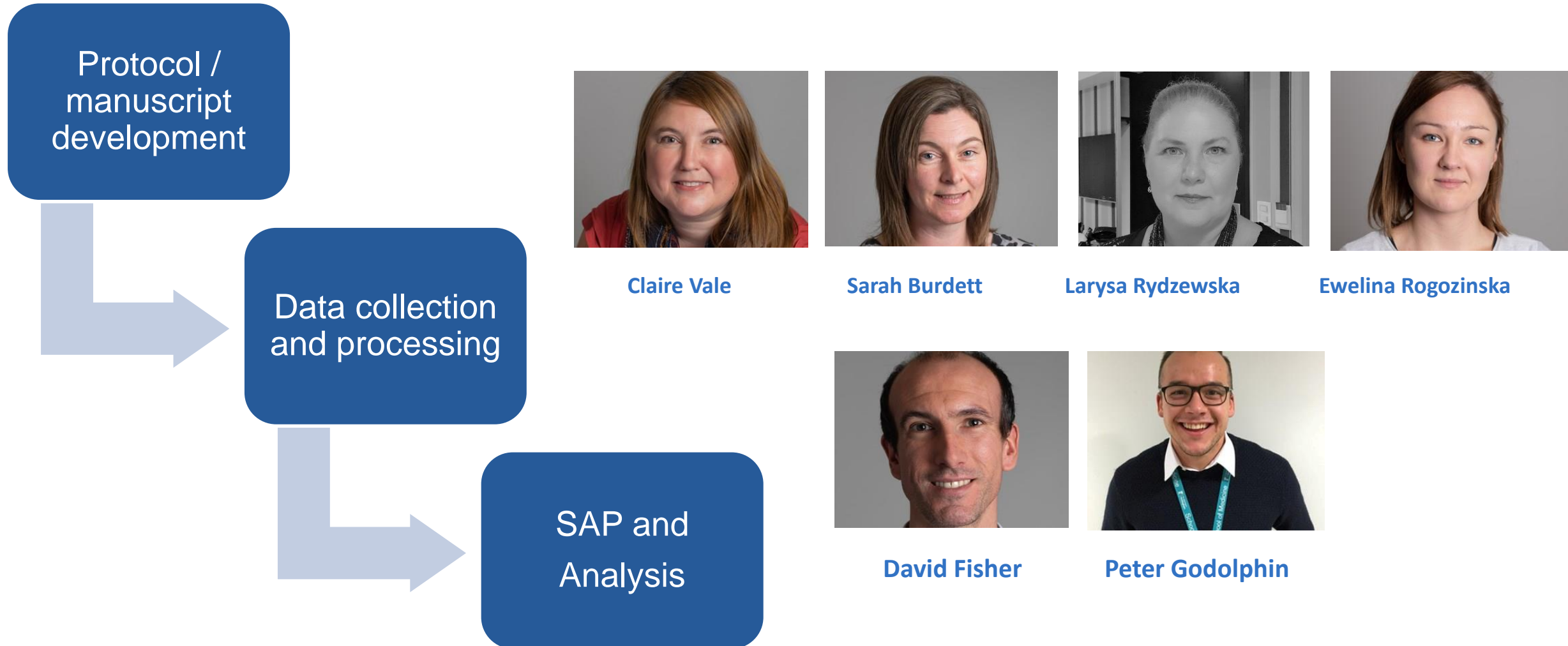


Interaction HR 1.43 95% CI 1.01-2.03 p= 0.046

Haran A et al ESMO 2022: Paper in Submission



Harnessing the Power of Meta-Analysis: The StopCaP MRC CTU team



Outcomes Following Treatment of Synchronous or Metachronous M1 Prostate Cancer

Figure 2: Effect of docetaxel on PFS by disease volume at randomisation

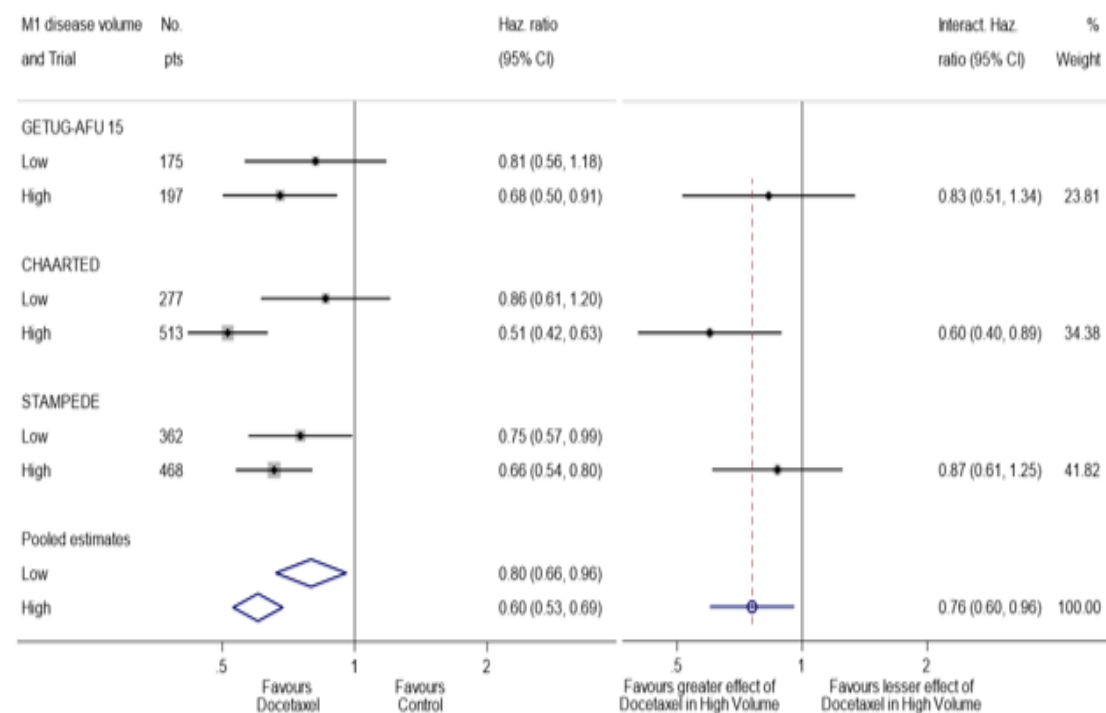
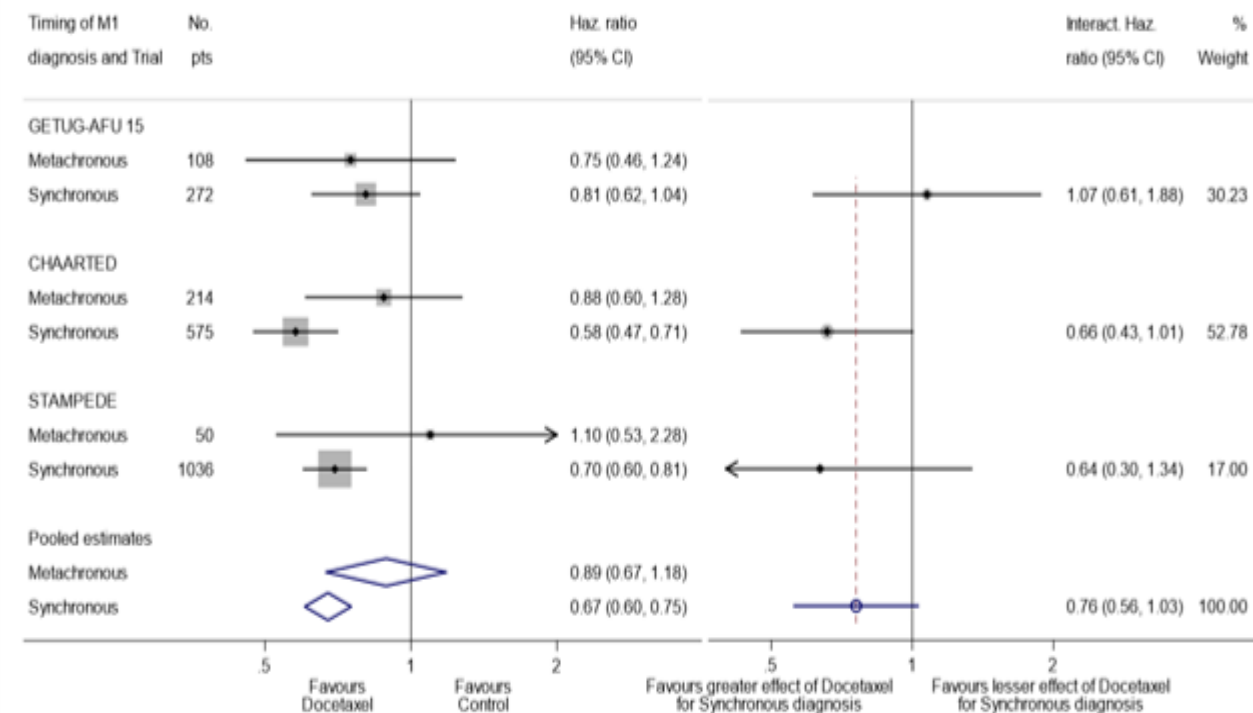


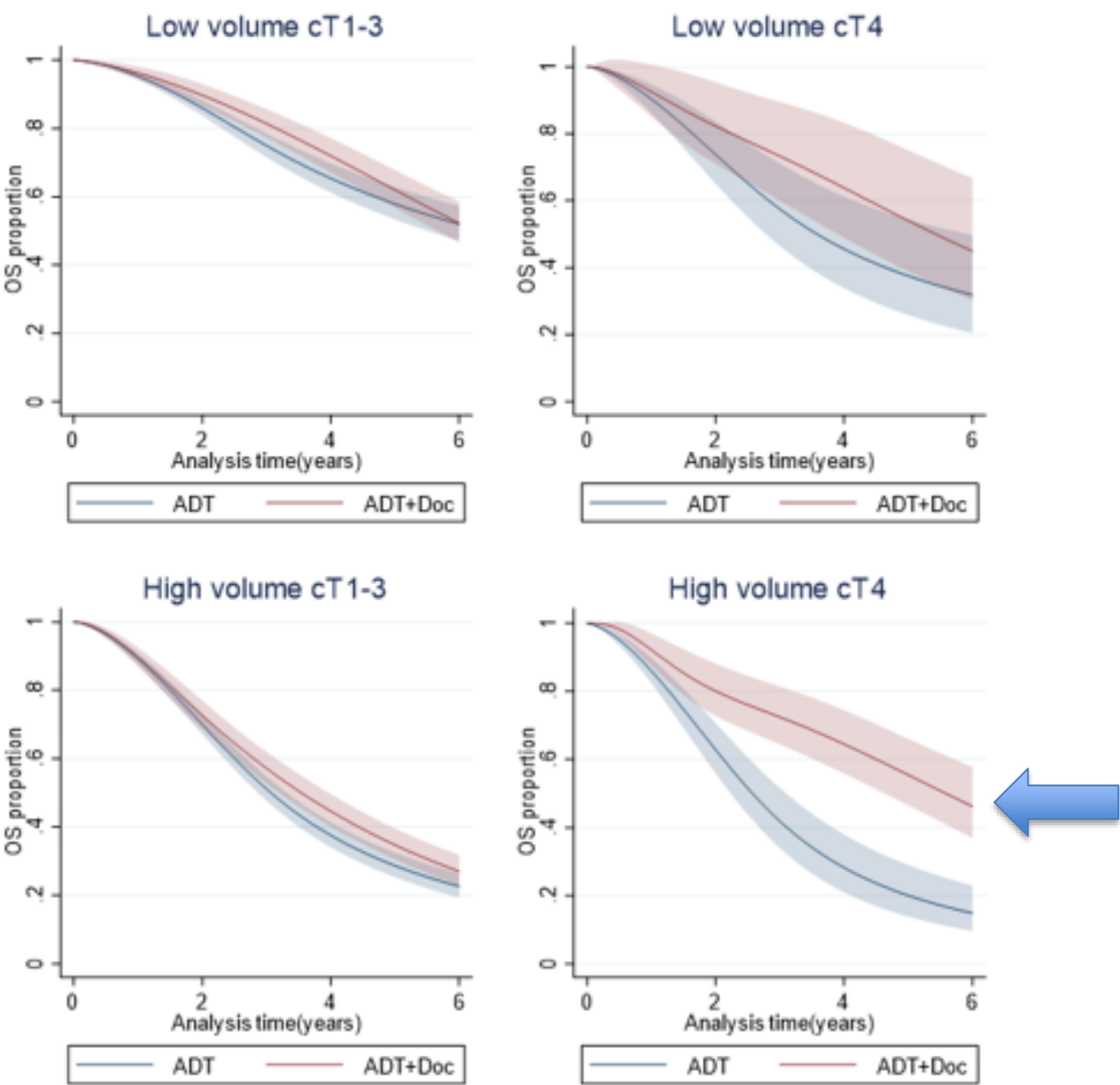
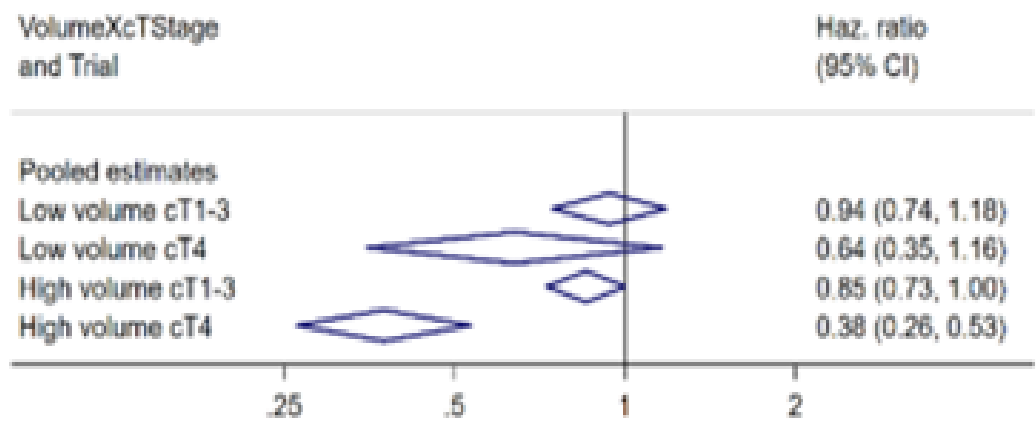
Figure 3: Effect of docetaxel on PFS by timing of metastatic disease diagnosis



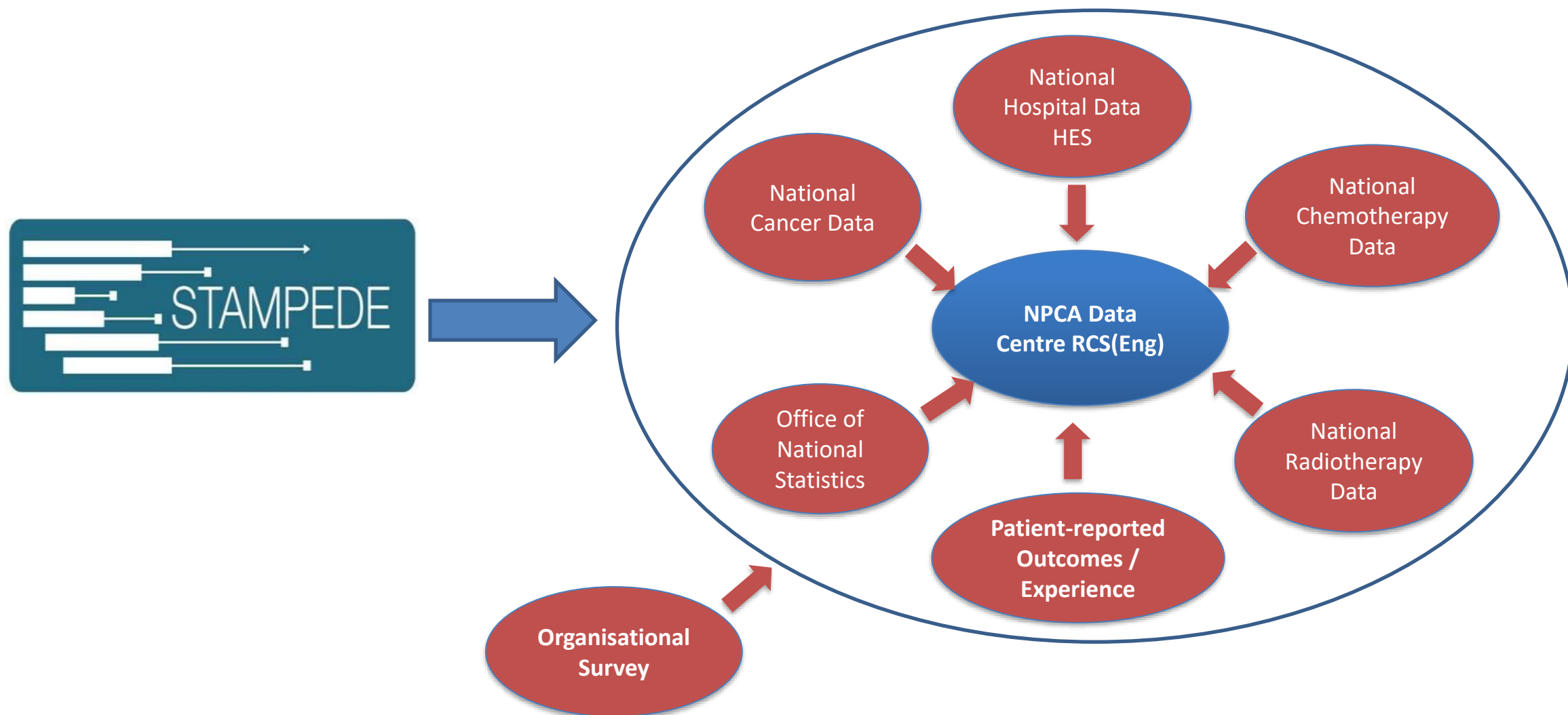
The Differential Effect of Docetaxel and Local Stage

Four-way subgroup plot for Overall survival

(b) Volume x Clinical T-stage/



Linking National Datasets to Clinical Trial Data for “Real World” Validation





ELSEVIER

Identifying skeletal-related events for prostate cancer patients collected hospital data

Matthew G. Parry^{a,b,*}, Thomas E. Cowling^a, Arunan Sujenthiran^b, Julie Nos
Brendan Berry^{a,b}, Paul Cathcart^c, Noel W. Clarke^{d,e}, Heather Payne^f, Ajay A
Jan van der Meulen^{a,1}

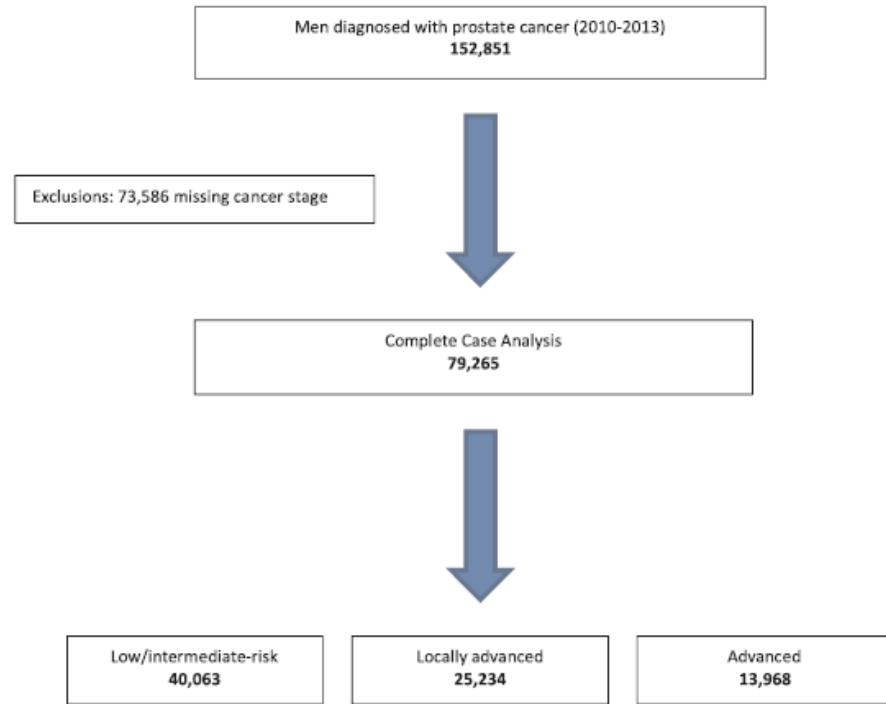
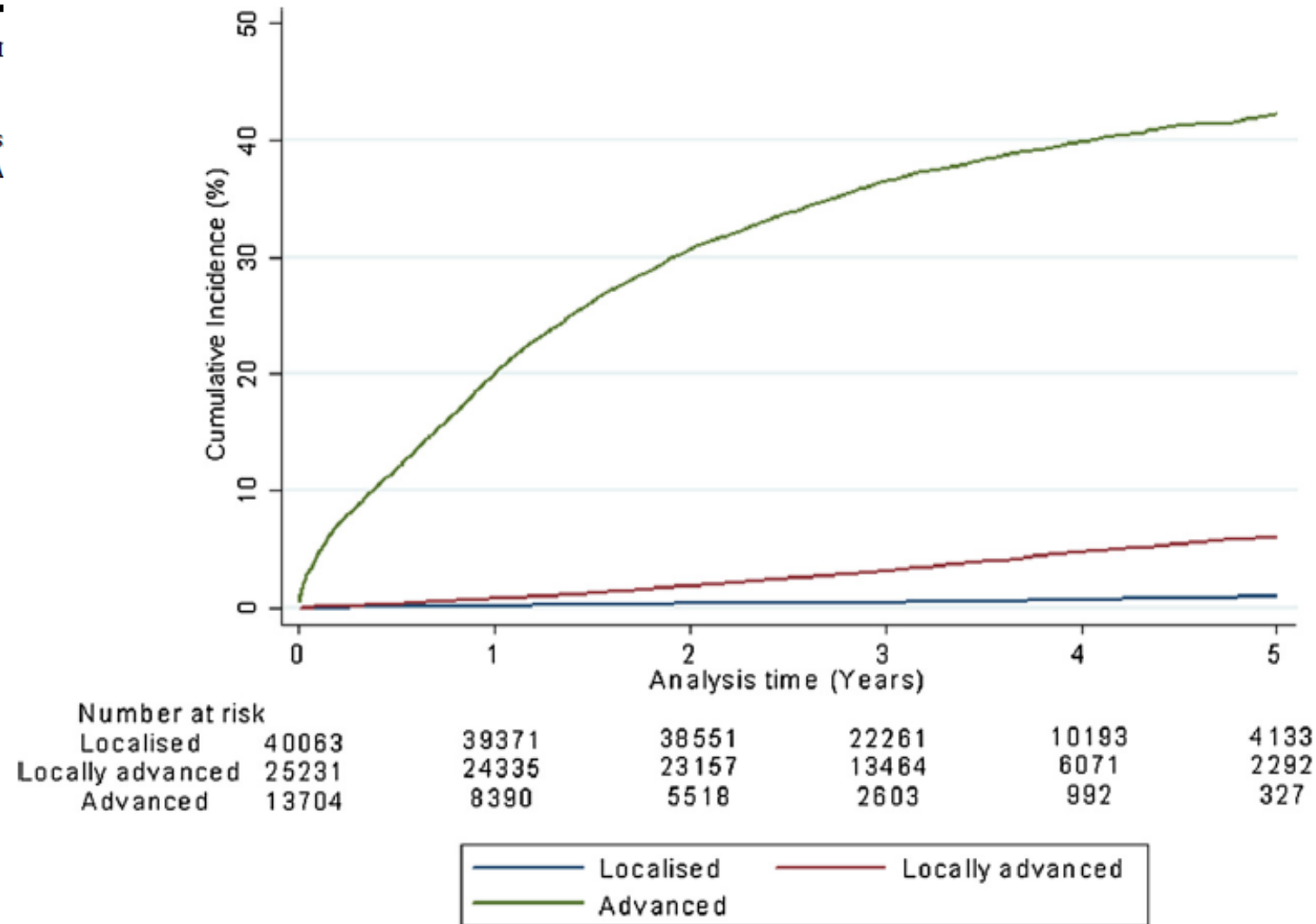
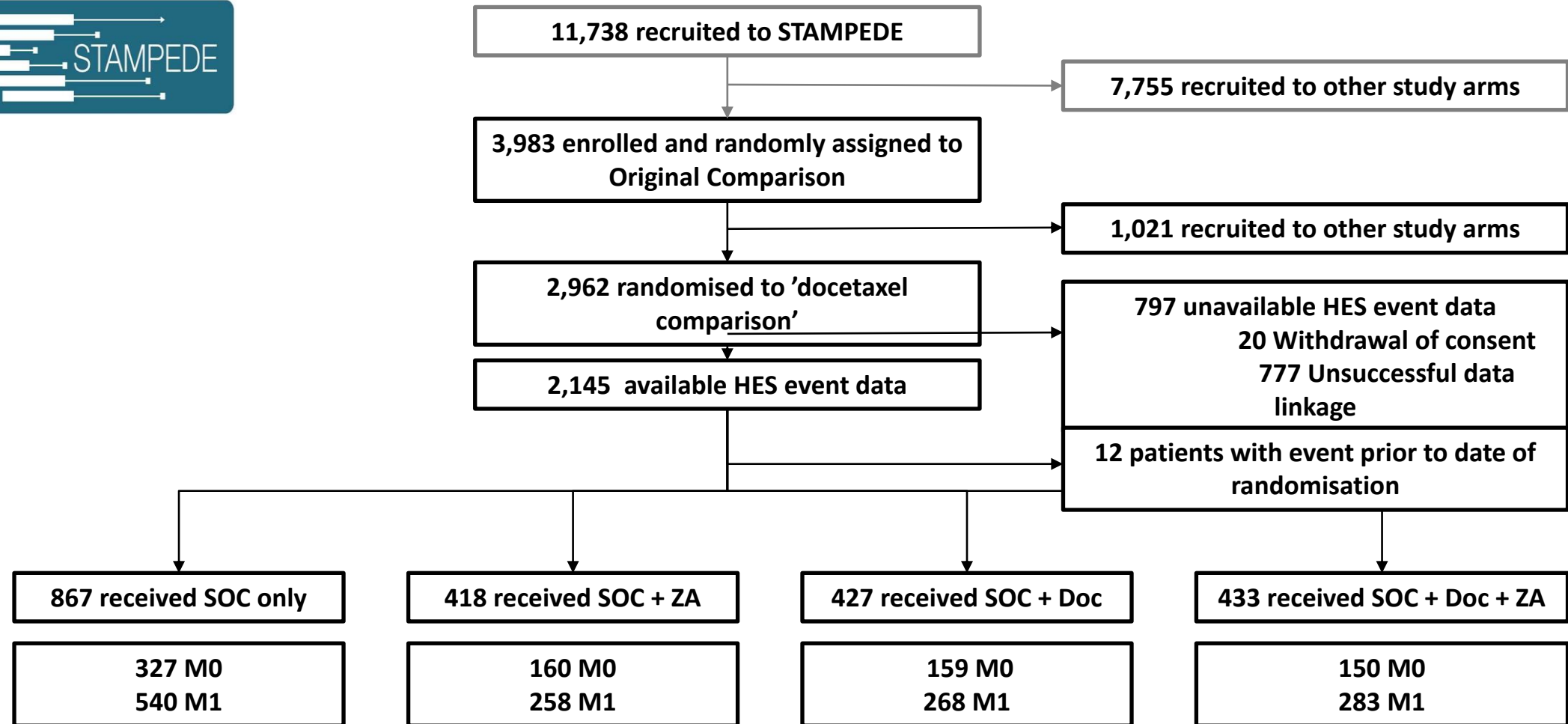
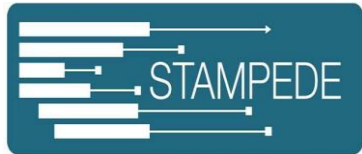


Fig. 1. Flow chart of men included in the study.

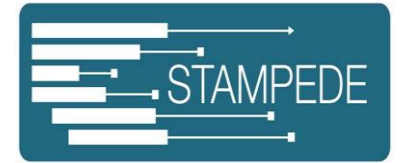


Long Term Fracture Rate M0 and M1 ± Bisphosphonate Stampede Arms A to E Data Linkage Through Hospital Episode Statistics (HES)



Stampede 2

Starting Feb 2023



Low Volume on
Standard Imaging



High Volume on
Standard Imaging



Translational:
Image and Tissue Centralisation
for Sub-Analysis (Including
PSMA PET

Stampede International
The Role of Surgery in
Oligometastatic Disease

