Institution: University College London		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: Changing international practice for metastatic prostate cancer by improving survival and patient outcomes		
Period when the underpinning research was undertaken: Between 2005 and 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Mahesh Parmar Matthew Sydes Jayne Tierney Claire Vale Sarah Burdett Larysa Rydzewska	Prof. Medical Statistics and Epidemiology Prof. Clinical Trials & Methodology Prof. of Evidence Synthesis Principle Research Fellow Senior Research Fellow Research Fellow	All staff part of MRC Clinical Trials Unit transfer to UCL in August 2013 and have worked at UCL until the present.
Period when the claimed impact occurred: Between 2015 and present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Prostate cancer is one of the most common cancers worldwide, with more than one million men diagnosed in 2018. Until recently, men with metastatic prostate cancer have had a bleak prognosis, with standard treatment (hormone therapy) unchanged for 40 years. UCL research published between 2015 and 2019 reliably demonstrated that three new treatments given in addition to standard therapy improve the survival of prostate cancer patients. This UCL research shows that if men are given, alongside standard treatment, either (i) docetaxel chemotherapy; (ii) a new type of hormone treatment, abiraterone; or (iii) radiotherapy to the prostate, they can live substantially longer and will have a lower risk of their prostate cancer returning. Docetaxel treatment led to an overall survival benefit of 15 months. By 2019 it was estimated 36% of patients were being treated using this approach; with 2,500 per year in the UK receiving treatment with docetaxel, an extrapolated gain of 31,250 extra life years was expected. By employing a new and efficient clinical trial design, the group delivered findings that would have taken decades using the traditional trials approach. Paired with a new prospectively planned and timelier approach to systematic reviews and meta-analyses, these important improvements have been rapidly validated and adopted into national and international clinical guidelines.

2. Underpinning research

The MRC Clinical Trials Unit at UCL (a University unit from 2013) developed both (a) the multi-arm multi-stage (MAMS) platform design for clinical trials and (b) the Framework for Adaptive Meta-analysis (FAME) approach for systematic reviews and meta-analyses.

In a MAMS trial, multiple treatments of interest are tested simultaneously (multi-arm) and interim analyses are used to move focus away from treatments which turn out to be less promising as the trial progresses (multi-stage). If other new treatments look worthy of testing while the trial is underway, these are incorporated for testing rather than waiting or setting up competing trials (platform). Using the FAME approach, meta-analysts work closely with trials teams to prospectively plan meta-analysis, and access detailed trial results before they are published, to produce more timely and thorough analyses. The UCL-led STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy) trial from Parmar, Sydes and wider colleagues **[R1]** and STOPCAP systematic review and meta-analysis from Parmar, Tierney and wider colleagues **[R2]** are, respectively, the first full MAMS platform and FAME studies to be carried out. From 2005, STAMPEDE recruited >12,000 patients to report on more than 10 comparisons in 20 years – an unprecedented number. STOPCAP worked closely with STAMPEDE and other academic and industry trial groups internationally to ensure rapid and reliable synthesis of all relevant trials. Both are led from, and coordinated by, UCL and have, so

far, delivered three separate findings that have changed international prostate cancer treatment practice:

1. Docetaxel chemotherapy (2016)
Before the STAMPEDE trial, chemotherapy with docetaxel had been tested only in very late-stage prostate cancer where it had shown a small survival advantage . STAMPEDE recruited to its 'docetaxel comparison' arms of the study 1,086 men earlier in their disease pathway, those newly diagnosed with metastatic cancer. Results, reported in *The Lancet*, showed clear evidence that adding docetaxel to standard hormone therapy resulted in a 24% relative improvement in survival (hazard ratio 0.76) with median survival improved by 10 months from 45 months to 60 months **[R1]**. STOPCAP combined STAMPEDE data with two smaller trials to show that 49 in 100 men allocated chemotherapy were alive four years later compared with 40 in 100 men allocated standard care **[R2]**. Results from both studies were presented in 2015 and published in 2016 **[R1]**, **[R2]**. Subsequent long-term findings from STAMPEDE, published in 2019, corroborate these results.

2. Abiraterone hormone therapy (2017)
Abiraterone, a CYP17A1 inhibitor, is a novel approach to hormone therapy first developed by Cancer Research UK, and had previously shown better survival outcomes in men with late-stage prostate cancer. At faster rates than expected, STAMPEDE recruited 1,917 patients earlier in the prostate cancer pathway to the study's 'abiraterone comparison', including 1,002 patients with disease which had already spread elsewhere (metastasised). Results, reported in the *New England Journal of Medicine*, showed that abiraterone treatment led to a relative increase in survival of 39% (hazard ratio 0.61), and survival at three years improved from 61 men in 100, to 73 men in 100 **[R3]**. Results were published simultaneously with a smaller, parallel trial in metastatic patients carried out by Janssen Pharmaceuticals Inc. STOPCAP rapidly combined these two sets of results to show abiraterone improved survival at three years from 55 men in 100, to 69 men in 100. Uniquely, STOPCAP quickly demonstrated consistency of benefits of abiraterone treatment, balanced with tolerable side-effects **[R4]**.

3. Radiotherapy (2018)
Radiotherapy is normally used in cases where disease is confined to the prostate. STAMPEDE's 'M1|RT comparison' tested prostate radiotherapy in 2,061 patients whose disease had already spread. Data published by the UCL team in *The Lancet* showed that radiotherapy improved survival by a relative 32% in men with less spread of the cancer (hazard ratio 0.68) with an improvement in the men's survival three years later from 73 men in 100 to 81 men in 100 **[R5]**. However, it did not help those men whose disease had spread to a greater degree **[R5]**. STOPCAP rapidly combined STAMPEDE data with data from a similar, smaller, Dutch trial, HORRAD. This showed radiotherapy improved survival at three years from 70 men in 100 to 77 men in 100, in those men with less spread of the cancer **[R6]**. A major strength of this meta-analysis was the consistency of the findings in those men with less spread and in those with greater spread **[R6]**.

Methodological innovation and design
At least 20 other trials are now following the MAMS platform design (e.g. ACTT and SOLIDARITY for COVID-19) and the MRC Clinical Trials Unit at UCL advise on independent oversight committees (e.g. PRINCIPLE for COVID-19). Additional contributors from the MRC Clinical Trials Unit at UCL include Annabelle South, Claire Amos, Ruth Langley, Adrian Cook, Chris Brawley, Melissa Spears, Nafisah Atako, Clare Gilson, Mary Rauchenberger, David Fisher; in collaboration with clinical staff across the UK and Switzerland (including clinical leads for trial comparisons: Nick James (ICR), Noel Clarke (Manchester), Malcolm Mason (Cardiff), Chris Parker (ICR), Gert Attard (UCL). Patient and Public Involvement representatives include Robin Millman, David Matheson, David Hoe-Richardson, Jim Stansfeld and John Dwyer.

3. References to the research

[R1] STAMPEDE investigators (47 authors including UCL's **Sydes, M.R., Spears, M.R., and Parmar, M.K.**). (2016). 'Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial'. *Lancet*. **387**(10024), 1163 – 1177. DOI: https://doi.org/10.1016/S0140-6736(15)01037-5

[R2] STOPCAP Steering Group: **Vale, C.L.**, **Burdett, S.**, **Rydzewska, L.H.**, Albiges, L., Clarke, N.W., **Fisher, D.**, Fizazi, K., Gravis, G., James, N.D., Mason, M.D., **Parmar, M.K.**, Sweeney, C.J., **Sydes, M.R.**, Tombal, B., **Tierney, J.F.** (2016). 'Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data'. *Lancet Oncology*. **17** (2), 243 – 256. DOI: https://doi.org/10.1016/S1470-2045(15)00489-1

[R3] STAMPEDE Investigators (47 authors, including UCL's **Spears MR**, Clarke NW, **Amos, C.L.**, **Gilson C., Parmar M.K.B.**, **Sydes M.R.)** (2017). 'Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy'. *New England Journal of Medicine*. **377**, 338-351. DOI: http://doi.org/doi:10.1056/NEJMoa1702900

[R4] Rydzewska, L.H.M., **Burdett, S.**, **Vale, C.L.**, Clarke, N.W., Fizazi, K., Kheoh, T., Mason, M.D., Miladinovic, B., James, N.D., Parmar, M.K.B., Spears, M.R., Sweeney, C.J., **Sydes, M.R.**, Tran, N., **Tierney, J.F.**, for the STOPCAP Abiraterone Collaborators. (2017). 'Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis'. *Eur J Cancer*. **84**, 88-101. http://doi.org/ 10.101 /6/j.ejca.2017.07.003

[R5] STAMPEDE investigators including UCL's **Brawley C.D.**, **Amos C.L.**, **Gannon M. R.**, **Parmar, M.K.B.**, **Sydes, M.R.** (2018). 'Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial'. *Lancet*. **392** (10162), 2353-2366. DOI: http://doi.org/10.1016/S0140-6736(18)32486-3

[R6] Burdett S., Boeve L.M., **Ingleby F.C.**, **Fisher D.J.**, **Rydzewska L.H.**, **Vale C.L.**, van Andel G., Clarke N.W., Hulshof M.C., James N.D., Parker C.C., **Parmar M.K.**, Sweeney C.J., **Sydes M.R.**, Tombal B., Verhagen P.C., **Tierney J.F.** for the STOPCAP Meta-analyis Radiotherapy Collaborators. (2019). 'Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis'. *European Urology*. **76**, (1), 115-124. DOI: http://doi.org/10.1016/j.eururo.2019.02.003

4. Details of the impact

Docetaxel chemotherapy improves survival

NHS England's Clinical Commissioning Policy statement, commissioning docetaxel for men with metastatic, hormone-sensitive prostate cancer, was published in early 2016 **[S1]**, just four weeks after STAMPEDE and STOPCAP's results were published. This recognised that when *"men who are diagnosed with metastatic prostate cancer are given docetaxel at the same time as ADT* [androgen deprivation therapy] *they have an improved overall survival benefit of up to 15 months longer, when compared to current practice"* The four-week turnaround was uncommonly fast, since the process usually takes months, if not years, signalling the strength of evidence provided by STAMPEDE and STOPCAP. The statement continues: *"NHS England has reviewed the evidence and concluded that it is sufficient to enable docetaxel to be routinely funded for the treatment of newly-diagnosed hormone naïve metastatic prostate cancer, where treatment with docetaxel is started within 12 weeks of commencing treatment with ADT."* Subsequently, STAMPEDE and STOPCAP papers **[R1]**, **[R2]** have been globally cited in at least 20 international, national and regional key clinical care guidelines **[S2]**. These include the widely influential US National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and the European

Association of Urology (EAU)-led consortium, all recommending the use of upfront docetaxel alongside hormone therapy for the treatment of metastatic prostate cancer.

Whilst the patent for docetaxel, held by manufacturer Sanofi-Aventis, expired around the time of STAMPEDE's results, the company commissioned and submitted a report on STAMPEDE's results to successfully extend its license in 2019 across Europe, Russia, Pakistan and Colombia. Sanofi's statement confirms: *"*[STAMPEDE] *data, along with … contributions of Eastern Cooperative Oncology Group [USA] … and Unicancer [France], supported Sanofi's submission of the registration dossier to EMA. In December 2019, Taxotere in combination with androgen deprivation therapy (with or without prednisone or prednisone), was officially approved for the treatment of men with mHSPC* [metastatic hormone-sensitive prostate cancer]*"* **[S3]**. The EMA license, in particular, will further encourage uptake in countries where it is difficult to use drugs for indications beyond those for which they are explicitly licensed. For example, licensing applications were ongoing in Brazil in 2020.

The National Prostate Cancer Audit of England and Wales introduced the proportion of metastatic patients receiving docetaxel treatment as a performance indicator in 2019. The proportion rose from 27% in the 2019 report (April 2017 to March 2018 diagnoses) to 36% in the 2020 report (April 2018 to March 2019 diagnoses), although the authors note that the proportion *"seems quite low"* **[S4]**. Currently, approximately 7,000 people are diagnosed with metastatic prostate cancer in the UK each year. Assuming docetaxel rates are similar across the UK and the clinical benefit is consistent, approximately 2,500 of those people should receive primary docetaxel. This can be extrapolated to a gain of 31,250 extra life-years over the next decade in the UK, assuming the proportion of men treated with docetaxel remains the same. The proportion of people treated with up-front docetaxel on the findings of STAMPEDE and STOPCAP is likely to further increase.

New health economic data from STAMPEDE in 2018 showed that adding docetaxel was cost-effective in the long run in both metastatic and non-metastatic patients **[S5]**. The model, based on STAMPEDE trial data, projected that docetaxel would be cost-effective in both metastatic prostate cancer (incremental cost-effectiveness ratio GBP5,514 per quality-adjusted life-year (QALY) compared with standard of care) and nonmetastatic prostate cancer (higher QALYs, lower costs versus standard of care). Docetaxel remained cost-effective in non-metastatic prostate cancer when the assumption of no survival advantage was modelled **[S6]**. NICE Guideline 'NG131: Prostate cancer: diagnosis and management' was published in 2019, extending docetaxel as a treatment option to men with high-risk non-metastatic disease **[R1]**. This recommendation, based on data from the only UK trial considered (STAMPEDE), advised that the option of docetaxel chemotherapy should be discussed with people who have newly diagnosed non-metastatic prostate cancer, who are starting long-term ADT **[S7]**. Further, there was worldwide consensus among 60 key opinion leaders at the Advanced Prostate Cancer Consensus Conference (2017) in St Gallen, that docetaxel should be used as standard care in metastatic, hormone-sensitive, prostate cancer **[S8]**. This was corroborated at the following conference in 2019 **[S8]**, giving a global consensus on treatment pathways with the aim of helping clinicians across the world discuss innovative new therapies with patients.

Abiraterone changing international policy and practice for patient benefits

Whilst in the UK docetaxel is more readily available to patients through the NHS and administered similarly to other intravenous chemotherapy drugs, abiraterone is not yet NICE-approved for men with hormone-sensitive disease. However, as a tablet-based treatment that would allow patients to control their medication at home, there has been wide enthusiasm for access to abiraterone based on STAMPEDE and STOPCAP papers **[R3]**, **[R4]** for patients with advanced prostate cancer. Results are cited in at least 10 key international and national care and clinical guidance documents for metastatic prostate cancer **[S2]**, including: the NCCN, ASCO, ESMO, Canadian Urological Association (CUA) and EAU. For example, the EAU Oncology guidelines state: *"Based on these data, upfront abiraterone acetate plus prednisone combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug"* **[S2]**. To set standards, the

STAMPEDE team adapted the protocol to allow abiraterone as an amended standard-of-care in ongoing comparisons where abiraterone was available.

Janssen submitted for and obtained a license for use only in patients with 'high volume' metastatic disease. Despite this, the international clinical community widely encourages use for patients with newly diagnosed metastatic prostate cancer **[S2]**. Whilst not yet recommended, during COVID-19 NICE have allowed treatment using abiraterone as an alternative to docetaxel because docetaxel causes transient immune suppression and requires more frequent hospital visits.

Radiotherapy improves survival in metastatic disease

In 2018, findings from **[R5]** and **[R6]** indicated that radiotherapy can help some men to live longer with metastatic prostate cancer. By the end of 2020, this had already been cited in eight major international guidelines and clinical care documents, encouraging radiotherapy for low metastatic burden prostate cancer **[S2]**. These include the US NCCN and the ESMO. The EAU Oncology Guidelines for Prostate Cancer, published in 2020, refer to STOPCAP, saying: *"the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients. However, there was a clear difference in the effect of metastatic burden on survival, with an absolute improvement of 7% in three-year survival in men who had four or fewer bone metastases."* **[S9]**. The Association used this to justify its recommendation to offer radiotherapy to men with 'low volume' metastatic disease. The radiotherapy schedule used is simple to plan and cheap to deliver, so it has potential be used in middle income countries (LMICs) as much as higher income countries. Prostate Cancer UK stated: *"The breadth of STAMPEDE and its applicability to everyday practice in the NHS mean that Prostate Cancer UK has been able to use this robust evidence to influence for access to life extending treatments for men that previously had few options available to them."* **[S10]**. A leading oncologist and research at Canadian Cancer Trials Group said: *"Thanks to these data, there'll be men dancing at their daughter's weddings who wouldn't otherwise have been there."*

5. Sources to corroborate the impact

[S1] NHS England 2016 Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer.
[S2] Table of national and international clinical guidelines citing STAMPEDE and STOPCAP
[S3] Sanofi corroborative testimony
[S4] National Prostate Cancer Audit Annual Report 2020 (Pdf; Published January 2021)
[S5] Woods BS, Sideris E, Sydes MR, Gannon MR, Parmar MKB et al. (2018). 'Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-adjusted Survival, and Cost-effectiveness'. *Eur Urol Oncol*.**1**(6), 449-58.DOI: https://doi.org/10.1016/j.euo.2018.06.004
[S6] NICE Prostate cancer: diagnosis and management (B) 'Evidence review for docetaxel in people with hormone sensitive prostate cancer'.
[S7] Gillessen S, Attard G, Beer TM, Beltran H, Bossi A, Bristow R et al. (2017). 'Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017'. *Eur Urol*. doi:10.1016/j.eururo.2017.06.002
[S8] Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A et al. (2020). 'Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019'. *Eur Urol.* **77**(4), 508-47. DOI: doi:10.1016/j.eururo.2020.01.012
[S9] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M et al. (2017). 'EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent'. *Eur Urol.* **71**(4), 618-629. doi:10.1016/j.eururo.2016.08.003.
[S10] Corroborative testimony from Senior Policy Officer, Prostate Cancer UK