Institution: University of Birmingham		
Unit of Assessment: UoA 1, Clinical Medicine		
Title of case study: Improving outcomes for patients with advanced prostate cancer: practice-changing evidence for new treatments		
Period when the underpinning research was undertaken: 2004–December 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:**
Prof Nicholas James	Professor of Clinical Oncology	1994–2013 2015–2019
Prof Lucinda Billingham	Professor of Biostatistics	1994–present
Miss Sarah Pirrie	Senior Biostatistician	2000–present
Dr Lazaros Andronis	Health Economist	2006–2017
Dr Prashant Patel	Clinical Senior Lecturer	2010–present
Period when the claimed impact occurred: 1 August 2013–31 December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Through 2 clinical trials in locally advanced and metastatic prostate cancer (LAMPC), we have transformed the therapeutic approaches in the management of this disease which previously had extremely poor prognosis. Specifically:

1. **Outcomes for patients with LAMPC have improved**; most importantly life expectancy has increased by 1.6 years, 3-year survival rate has increased and skeletal-related complications have decreased;
2. **Global guidelines for the treatment of LAMPC have changed**; and
3. **Clinical care practices have changed including new standards of care and new cost-effective treatment options**.

2. Underpinning research

Prostate cancer is the most common cancer in men in the UK, where it accounts for 25% of newly diagnosed cancers, and is the second most common cause of cancer death. The disease is also a major problem worldwide, being the second most common cancer in men and the sixth leading cause of cancer death, with 1.28 million new cases diagnosed in 2018. This number is expected to rise to 2.3 million by 2040 with annual deaths expected to increase from 359,000 to 740,000. Around 50% of patients are predicted to suffer locally advanced or metastatic prostate cancer (LAMPC), of which less than half are expected to survive beyond 5 years. Professor James at the University of Birmingham (UoB) has been at the forefront of developing clinical trials to evaluate new therapeutic options in LAMPC which can present either at first diagnosis or at disease progression. Often the tumour becomes insensitive to the hormone (androgen) deprivation therapy (ADT) given as standard of care (hormone refractory prostate cancer (HRPC)). Beginning in 2005, James led the **TRAPEZE** and **STAMPEDE** trials to test alternative treatment options for **metastatic HRPC** and **LAMPC presenting before ADT** respectively.

TRAPEZE trial generating evidence for new second-line therapies in metastatic HRPC

James and Billingham, at the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham, initiated, designed and conducted the large, multicentre, randomised, phase 3 **TRAPEZE trial** (Taxane, RAdioisotoPE, ZolEdronic acid) in **metastatic HRPC** comparing treatment with **docetaxel** alone as standard of care against 3 experimental treatment arms that included the addition of either the bisphosphonate zoledronic acid (**ZA**) or the radioisotope strontium-89 (**S89**) or both. The trial began in 2005, randomised 757 patients and was published in 2016 [R1]. Its key finding (KF) was:

- **KF1:** ZA can be safely and effectively combined with docetaxel for treatment of HRPC and significantly improves patient quality of life by increasing the time before a skeletal-related event (SRE) (i.e., a pathologic fracture, spinal cord compression, necessity for radiation to bone (for pain or impending fracture) or surgery to bone) from 11.2 to 13.6 months and reducing the number of severe SREs by over half (52%) [R1].

TRAPEZE also showed that ZA combined with docetaxel to treat HRPC is cost-effective [R2].

STAMPEDE trial generating evidence for new drugs to treat LAMPC

James, as Chief Investigator, in collaboration with the MRC Clinical Trials Unit (MRCCTU) at University College London, devised the **STAMPEDE trial** (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy), which launched in October 2005 as an international trial and is ongoing. The trial represents a novel and paradigm-changing approach to trial design [R3]. It is a multi-arm multi-stage (MAMS) phase II/III platform clinical trial originally including a single control arm of androgen deprivation therapy (**ADT**) alone as standard of care **and** 5 experimental treatment arms that involved the addition of **docetaxel**, **ZA** and **celecoxib** alone or in combination. The options with or without **radiotherapy** were also assessed. The model was subsequently expanded to include a further 6 experimental treatment arms, one of these being **abiraterone** in 2011 and another, a more focussed study into radiotherapy in metastatic disease, in 2012. Results from the trial so far have concluded that celecoxib and ZA are not effective drugs in this disease setting [R4] but the study made the following significant findings:

- **KF2:** Prostate radiotherapy significantly increases 3-year overall survival for patients with low metastatic burden prostate cancer by 8% (from 73% to 81%) [R5].
- **KF3:** Addition of docetaxel to ADT significantly increases median overall survival time for patients with LAMPC by 10 months (from 71 to 81 months), increases mean time to first skeletal-related event by 6.6 months (from 61.4 to 68.0 months) and is cost-effective [R4].
- **KF4:** Addition of Abiraterone to ADT significantly increases 3-year overall survival for patients with LAMPC by 7% (from 76% to 83%) and increases rate of 3 years without symptomatic skeletal complications by 10% (from 78% to 88%) [R6].

3. References to the research

R1: Clinical outcomes and survival following treatment of metastatic castrate-refractory prostate cancer with docetaxel alone or with strontium-89, zoledronic acid or both. **James ND**, **Pirrie SJ**, Pope AM, Barton D, **Andronis L**, Gorantis I, Collins S, Daunton A, McLaren D, O'Sullivan J, Parker C, Porfiri E, Staffurth J, Stanley A, Wylie J, Beesley S, Birtle A, Brown J, Chakraborti P, Hussain S, Russell M, **Billingham LJ**. JAMA Oncology 2016; 2(4): 493-499. doi:10.1001/jamaoncol.2015.5570

R2: Cost-effectiveness of zoledronic acid and strontium-89 as bone protecting treatments in addition to chemotherapy in patients with metastatic castrate-refractory prostate cancer: results from the TRAPEZE trial (ISRCTN 12808747). **Andronis L**, Gorantis I, **Pirrie S**, Pope A, Barton D, Collins S, Daunton A, McLaren D, O'Sullivan JM, Parker C, Porfiri E, Staffurth J, Stanley A, Wylie J, Beesley S, Birtle A, Brown JE, Chakraborti P, Hussain SA, Russell JM, **Billingham LJ**, **James ND**. BJU International 2017; 119:522-529. doi: 10.1111/bju.13549

R3: 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 Sydes MR, Parmar MKB, Mason MD, Clarke NW, Amos C, Anderson J, de Bono J, Dearnaley DP, Dwyer J, Green C, Jovic G, Ritchie AWS, Russell JM, Sanders K, Thalmann G, **James ND**.Trials 2012, 13: 168. doi: 10.1186/1745-6215-13-168

R4: 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. **James ND**, Sydes MR, Clarke NW, et al; for the **STAMPEDE investigators**. Lancet 2016; 387(10024):1163-77. doi: 10.1016/S0140-6736(15)01037-5. Epub 2015 Dec 21

R5: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Parker CC, **James ND**, Brawley CD, et al; for the **STAMPEDE investigators**. Lancet. 2018 Dec 1;392(10162):2353-2366. doi: 10.1016/S0140-6736(18)32486-3. Epub 2018 Oct 21.

R6: Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. **James ND**, de Bono JS, Spears MR, et al; **STAMPEDE Investigators**. N Engl J Med. 2017 Jul 27;377(4):338-351. doi: 10.1056/NEJMoa1702900. Epub 2017 Jun 3.

4. Details of the impact

1. Improved outcomes for patients with LAMPC

Survival and quality of life of sufferers have been transformed. In particular, for UK men diagnosed with metastatic prostate cancer, analysis of Hospital Episode Statistics (HES) data [S1] shows:

- **Life expectancy has increased by 1.6 years**: median 50% survival is now 39 months compared to 20 months before the trial results were published [S1i];
- **3-year survival has increased** from 34% to 52% such that *c.*700 more of the *c.*3800 men diagnosed each year can now expect to live for at least 3 years [S1i];
- **Skeletal related complications within 1 year of treatment have decreased by over 23%** such that *c.*200 more of the *c.*3800 men diagnosed each year can now expect to live without suffering the physical challenges of SREs in the first year of treatment [S1ii].

Patients have been made aware of the new improved treatment options indicated by our research through their promotion by the websites and literature of the major cancer charities (e.g. Prostate Cancer UK and Cancer Research UK), the Institute of Cancer Research and the STAMPEDE trial [S2]. As a result, patients are better able to discuss their treatment options with their doctor and are reassured that further options exist if their first or current treatment does not work for them. In addition, through these sites patients have access to the discussions around the licencing of the medications and are informed how they might access those options which are off-label or that are not standard of care. Furthermore, the united campaigning by patients and charities speeded uptake of treatments into guidelines [S2].

2. <u>Clinical guidelines have changed worldwide for the treatment of LAMPC</u>

All major guideline bodies in oncology and urology in the **UK** (National Institute for Health and Care Excellence (NICE) (2019) [S3i–ii]), **Europe** (European Society of Medical Oncologists (ESMO) (2020) [S3iii] and European Association of Urology (EAU) (2020) [S3iv]), **America** (American Urological Association (AUA) (2020) [S3v] and American Society of Clinical Oncology (ASCO) (2018) [S3vi]) and **Scotland** (Scottish Medicines Consortium (SMC) (2020) [S3vii]) have **changed their guidance** on the use of **docetaxel, ZA, ADT, radiotherapy and abiraterone** to treat LAMPC as a result of the 4 new combination therapies our trial findings had indicated:

1. Docetaxel alone changed to docetaxel + ZA [KF1];
2. ADT alone changed to ADT + radiotherapy [KF2];
3. ADT alone changed to ADT + docetaxel [KF3];
4. ADT alone changed to ADT + abiraterone + steroids [KF4].

The 51 member countries of the EAU and 43 member countries of the ESMO, which include non-EU countries, also endorse their guidelines as national guidance. In the UK, 85% of Oncologists and Urologists consider the EU as well as NICE guidelines in their practice [S4].

Specifically:

- **UK (NICE**) recommends considering giving "**ZA as well as docetaxel** to people with metastatic HRPC to prevent or reduce skeletal-related events" [S3i–ii; KF1].
- **European** [S3(iii, iv)] and **American** [S3(v)] guidelines recommend that for patients with low-volume metastatic disease, **radiotherapy of the prostate should be considered** [KF2].
- **UK (NICE)** [S3i], **European** [S3iii, iv] **and American** [S3v, vi] guidelines recommend clinicians **offer ADT standard therapy combined with docetaxel** to men presenting with metastases at first presentation provided they are fit enough [KF3]. **NICE** also extended this recommendation to high-risk, non-metastatic (locally advanced) prostate cancer patients in line with KF3 [S3i].
- **European** [S3iii, iv] **and American** [S3v, vi] **guidelines** recommend **upfront abiraterone acetate with prednisone combined with ADT** as an alternative standard of care therapy to docetaxel combined with ADT for men presenting with metastases at first presentation provided they are fit enough [KF4]. **Scottish** guidelines also changed in 2020 to extend their recommendation of **abiraterone** with prednisone or prednisolone together with ADT to all newly diagnosed high-risk metastatic hormone-sensitive prostate cancer patients, not only those with contraindication to the standard of care therapy, docetaxel [S3vii; KF4]. This guidance came in response to pressure from the Health Improvement Scotland Medicines Team (HIS) which considered it unethical not to offer abiraterone to all patients diagnosed with high-risk metastatic hormone-sensitive prostate cancer [S3viii] given the robust evidence (including KF4) in support of its off-label use as a first-line treatment for

prostate cancer, and the regular requests made by clinicians to give it through the unlicensed medicines process. A similar decision by NICE is expected in 2021.

- During the COVID-19 pandemic, the **British Association of Urological Surgeons** released urgent new guidance on the combinations of drugs to use for the treatment of patients with metastatic prostate cancer, advising clinicians to consider giving abiraterone plus steroids with ADT instead of docetaxel with ADT for patients with newly diagnosed metastatic disease, who are intolerant of enzalutamide [S3ix; KF4]. This advice was given due to concern that immunosuppressive chemotherapy (docetaxel) would increase the risk of poor prognosis from infection with COVID-19.

As testified by a member of the European Urology Guideline panel, the ability of STAMPEDE to "inform all major guidelines in prostate cancer after a thorough review process" is a result of its "landmark trial design (MAMS)" through which it "addressed several questions in an efficient manner" [S5i]. In just 13 years, STAMPEDE has tested 8 treatments in LAMPC and involved *c.*10,000 patients. The Senior Policy officer of Prostate Cancer UK has further identified that "The unique multi-stage, multi-arm approach of STAMPEDE has enabled meta-analyses to be carried out to [...] fast-track treatments to men." He says that "we now wait with anticipation for results from subsequent arms of the trial, with complete belief that they will drive improvements in the treatment and care of men with metastatic prostate cancer" [S5ii]. STAMPEDE was awarded the International David Sackett Trial of the Year award by the Society for Clinical Trials in 2017, which is awarded to studies which demonstrate "methodological excellence, intellectual soundness and believed ability to provide substantial, beneficial change in healthcare" [S6].

3. Care practices for men with LAMPC have changed

Clinical practitioners have changed the treatments they give to men with advanced prostate cancer in line with the findings of the STAMPEDE and TRAPEZE trials [KF1–KF4]. Specifically,

- **In January 2016, Docetaxel with ADT became standard of care in the UK** for all men newly diagnosed with metastatic prostate cancer immediately following publication of R4. As a result, use of docetaxel increased 2.4 fold from 14% of patients diagnosed in April–June 2015 to 34% of patients diagnosed in July–September 2016 as demonstrated in HES data [S1iii]. This change in clinical practice to use docetaxel off-label in these patients (i.e, beyond the drug's licenced purpose), and before changes to NICE guidelines, was actioned by release of an NHS policy statement (January 2016) that was issued following an evidence review by NHS England of 3 major trials (including R4) that found that ADT + docetaxel therapy would provide "an overall survival benefit of up to 15 months for patients when compared to current practice" [S7] — a change which Prostate cancer UK has called an "unparalleled survival benefit from a readily available generic treatment" [S5ii].
- **Abiraterone was adopted rapidly into practice** following publication of R6 in 2017 evidenced by a **40% ($1 billion) rise in Johnson and Johnson's sales** of Zytiga® (abiraterone) in the following year [S8]. Although this change was partly informed by the results of a second trial (LATTITUDE) that also confirmed first-line abiraterone plus ADT for high-risk hormone-sensitive metastatic prostate cancer patients and was published at the same time as STAMPEDE, only STAMPEDE confirmed abiraterone for locally advanced non-metastatic patients and was therefore foundational to this change.

The impact of our research on care practices for LAMPC patients in the UK is further attested to by a survey of Urologists and Oncologists involved with the care of these patients [S4], which found all participants were aware of the STAMPEDE trial and because of it:

- 92% give radiotherapy to patients with low metastatic burden disease [R5; KF2];
- 94% give docetaxel to patients with LAMPC who are starting first-line ADT [R4; KF3];
- 60% give abiraterone to patients with LAMPC who are starting first-line ADT [R6; KF4];

All participants believed the STAMPEDE trial has had global impact in the management of prostate cancer.

Leading international clinicians in uro-oncology, including a member of the European Urology Guidelines Committee [S5i] and the lead clinician of the Urology Tumour Collaborative [S5iii], have testified to the **major influence of our research on care practices for LAMPC worldwide** describing TRAPEZE and STAMPEDE as "game changers in prostate cancer management" [S5i]

with STAMPEDE being "one of the most important and influential uro-oncology trials of all time" [S5iii]. They confirm that "it is now a norm in clinics world-wide [to use] ZA in combination with docetaxel" [S5iii; KF1] and acknowledge that "moving to a new 'standard of care' has been provided by STAMPEDE" such that clinicians "are now confident in treating patients with locally advanced high risk prostate cancer with docetaxel as first-line therapy" [S5iii; KF3]. This is in contrast to the early 2000s when clinicians would use chemotherapy (docetaxel) only as a "last-ditch therapy" in metastatic HRPC [S5iii]. They also identify that the "STAMPEDE trial demonstrated that prostate cancer is one of the only malignancies where radiotherapy to the primary in presence of low burden metastatic disease improves outcomes" [S5iii; KF2] and say "combining abiraterone to hormone therapy in locally advanced disease" [S5i; KF4], "including the recent addition [of this therapy] in hormone sensitive high risk non-metastatic prostate cancer, has also changed practice" [S5iii; KF4].

Considerable **health economic benefits** have also come from these changes to clinical practice in prostate cancer care. HES data suggest that through the changes to treatment informed largely by our trials, SREs in the first year of diagnosis have been reduced by *c.*200 per year [S1ii, S4]. SREs are a particularly significant burden on healthcare spending: for example, in the UK, unit costs of surgical procedures to address skeletal-related problems range £3,888 (pathological fractures with complications) to £9,573 (decompression for spinal cord compression) [S9i] and a study in the US found that SREs increase average treatment costs for men over age 66 years with metastatic prostate cancer by *c.*US$30,000 [S9ii].

5. Sources to corroborate the impact

S1i: HES data report on overall survival of metastatic prostate cancer patients
S1ii: HES data report on skeletal-related events in metastatic prostate cancer
S1iii: HES data report on use of upfront chemotherapy in metastatic prostate cancer
S2: Compilation of URLs identifying patient-facing information on the trials developed by organisations to inform patients and the public
S3i: NICE 2019 guideline (NG131) on prostate cancer diagnosis and management
S3ii: NICE 2019 evidence review for bisphosphonates
S3iii: ESMO 2020 guidelines on prostate cancer
S3iv: Joint EAU/EANM/ESTRO/ESUR/SIOG 2020 guidelines on Prostate Cancer
S3v: Joint AUA/ASTRO/SUO 2020 guidelines on advanced prostate cancer
S3vi: Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline 2018
S3vii: Scottish medicines consortium guideline 2020 for use of abiraterone acetate (Zytiga®) within NHS Scotland (SMC2215)
S3viii: Letter from Health Improvement Scotland Medicines Team (HIS) to the Scottish Medicines Consortium requesting approval of abiraterone within NHS Scotland
S3ix: British Association of Urological Surgeons COVID-19 strategy for the Interim Management of Prostate Cancer
S4: Survey to assess changes to clinician practice informed by the STAMPEDE trial
S5i: Testimonial from panel member of the European Urology Guidelines
S5ii: Testimonial from Senior Policy Officer for Prostate Cancer UK
S5iii: Testimonial from lead clinician of the Urology Tumour Collaborative
S6: David Sackett Trial of the Year award by the Society for Clinical Trials in 2017
S7: NHS England Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy to treat hormone naive metastatic prostate cancer B15/PS/a
S8: Johnson and Johnson's Zytiga® sales report.
S9i: Unit costs of surgical procedures to address skeletal-related problems taken from the National Schedule of Reference Costs 2011–2012 as given in the TRAPEZE HTA report.
S9ii: Study of health utilisation costs of SREs in men over 66 years of age in the US.