Institution: Cardiff University

Unit of Assessment: Clinical Medicine (1)

Title of case study: Establishing new worldwide standards of care for prostate cancer patients

Period when the underpinning research was undertaken: 2000-2020

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:
Mason, Malcolm	Clinical Professor	01/04/1998 - present
Kynaston, Howard	Clinical Professor	01/05/2011 - present
Staffurth, John	Clinical Professor	02/02/2004 - present

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Prostate cancer is the most common male cancer in the UK. Historically, some patients received unnecessary treatment that impaired quality of life, while for others, treatment was ineffective. Cardiff researchers played leading roles in four major clinical trials, which improved the treatment of prostate cancer. Tailoring treatment decisions with each stage of the disease, they advocated four clinical recommendations, which influenced the way oncologists routinely employ monitoring criteria, surgery, radiotherapy and hormone therapy. These trials define the standard of care for prostate cancer and underpin the international guidelines endorsed by NICE, the European Association of Urology, and the National Comprehensive Cancer Network in the UK, Europe and North America.

2. Underpinning research (indicative maximum 500 words)

Prostate cancer affects one in eight men in the UK. It progresses from the earliest stages, confined to the prostate gland ('localised disease'), spreads beyond the prostate to surrounding tissues ('locally advanced disease'), or spreads to other organs, especially bone ('metastatic disease'). Approaches to treatment are limited with many of these leading to severe side effects which reduced patients' quality of life. Cardiff researchers led elements of four randomised clinical trials that investigated the effectiveness of new approaches to treatment of the four different stages of prostate cancer.

2.1 ProtecT: Localised prostate cancer trial: Prostate Testing for Cancer and Treatment

ProtecT was the largest global clinical trial for the treatment of localised prostate cancer. Kynaston was the Principal Investigator and lead of the Cardiff ProtecT centre (one of nine in the UK) and Mason designed and led the radiotherapy arm of the trial. Staffurth and Mason also performed and published the radiotherapy quality assurance. Findings indicated that aggressive intervention was not always more beneficial than monitoring for localised disease. Where treatment was deemed necessary, radiotherapy had the same effectiveness as surgery, giving patients and clinicians objective evidence to offer a preference with no risk of loss of efficacy. Results also showed that the risk of dying from prostate cancer is very low (around 1%) at ten years, irrespective of the treatment (surgery, radiotherapy, or active monitoring). The risks of disease progression are higher with active monitoring, but with the benefit of being free from treatment side-effects. **[3.1,3.2]**.

2.2 CHHIP: Localised prostate cancer trial: Conventional versus hypofractionated high dose intensity modulated radiotherapy for prostate cancer

CHHIP was a randomised clinical trial which compared standard radiotherapy treatment to hypofractionation (a treatment schedule whereby the total dose of radiation is divided into large doses given over a shorter period of time). Cardiff researchers led on quality assurance across 71 sites, ensuring the validity of the trial and verifying standards of accuracy in

radiotherapy dosing. The findings demonstrated that a shorter course of radiotherapy, with fewer treatments offset by higher dose radiotherapy, was as effective as the standard schedule of treatment **[3.3]**.

2.3 MRC PR07: Locally advanced prostate cancer trial - hormone therapy plus radical radiotherapy versus hormone therapy alone in non-metastatic prostate cancer

This clinical trial was outlined in a REF14 case study which detailed how routine approaches to prostate cancer treatment did not discriminate between locally advanced (spread into adjacent tissue) and metastatic disease, with hormone therapy being the recommended intervention for both. Mason was Co-PI on this study which showed that over a seven-year period, deaths were 9% for patients receiving radiotherapy and standard hormone therapy, compared to 19% for patients receiving the standard hormone therapy only **[3.4]**. This demonstrated that adding radiotherapy to standard hormone therapy more than halved the risk of dying for patients with locally advanced prostate cancer and allowed for a more specific approach to treatment **[3.4, 3.5]**.

2.4 MRC STAMPEDE: Metastatic Prostate Cancer trial

Treatment options for more advanced cases of prostate cancer are limited and the prognosis is poor. While treatment with hormone therapy can produce some dramatic responses, these are often temporary. Cardiff was a partner in STAMPEDE, a multi-arm, multi-stage trial which investigated the addition of a range of therapeutic interventions to standard hormone therapies. Mason was one of the originators of the trial, the vice-chair of the Trial Management Group, one of three grant-holders and first author on one of the reports.

STAMPEDE tested simultaneously the effects of adding docetaxel, celecoxib, zoledronic acid or abiraterone to standard hormone therapy. The study demonstrated the benefit of these additional therapies. Median survival for the whole group (approximately 4,000 men), which included high risk localised disease, was extended from 71 months to 81 months post-diagnosis **[3.6]**.

Overall, Cardiff played a pivotal role in four clinical trials which led to a far greater understanding of possible treatment options for prostate cancer patients at each stage of the disease.

3. References to the research (indicative maximum of six references)

[3.1] Donovan JL, Hamdy FC, Lane JA, **Mason MD**, Metcalfe C, Walsh E, *et al*. (2016). Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *The New England Journal of Medicine*, 375, 1425-1437. DOI: 10.1056/NEJMoa1606221

[3.2] Hamdy FC, Donovan JL, Lane JA, **Mason MD**, Metcalfe C, Holding P, *et al*. (2016). 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *The New England Journal of Medicine*, 375(15), 1415–1424. DOI: 10.1056/NEJMoa1606220

[3.3] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, Parker C, Patterson H, Scrase C, **Staffurth J**, *et al*. (2016). Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 17(8), 1047-1060. DOI: 10.1016/S1470-2045(16)30102-4

[3.4] Warde P, **Mason MD*** (JOINT FIRST AUTHORS), Ding K, Kirkbride P, Brundage M, Cowan R, *et al*. (2011). Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*, 378(9809), 2104–2111. DOI: 10.1016/S0140-6736(11)61095-7

[3.5] Mason MD, Parulekar WR, Sydes MR, Brundage M, Kirkbride P, Gospodarowicz M, *et al*. (2015). Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *Journal of Clinical Oncology*, 33(19). DOI: 10.1200/JCO.2014.57.7510

[3.6] James ND, De Bono JS, Spears MR, Clarke NW, **Mason MD**, Dearnaley DP, *et al*. (2017). Abiraterone for prostate cancer not previously treated with hormone therapy. *The New England Journal of Medicine*, 377, 338-351. DOI: 10.1056/NEJMoa1702900

4. Details of the impact (indicative maximum 750 words)

The clinical trials outlined in Section 2 provided critical evidence for new clinical guidelines enabling more effective treatment of patients with prostate cancer, aligned to their stage of the disease.

4.1 Informing clinical guidelines for shared decision making and refined radiotherapy treatment in localised prostate cancer

Before the ProtecT study **[3.1, 3.2]**, many specialists believed that immediate treatment was superior to surveillance, meaning patients were being treated unnecessarily. Yet, side effects of surgery include 46% of patients needing to use incontinence pads six months after a prostatectomy, compared to only 4% who opted for active surveillance. ProtecT trial findings (namely that patients' risk of dying is very low; that aggressive intervention was not always necessary; and that surgery and radiotherapy are equivalent in effectiveness) changed multiple clinical guidelines focusing on clearer communication of options alongside risks to patients, as well as shared decision making. These included:

- **NICE guideline NG131:** This underwent rapid review and update in 2019 to include the recommendation (1.3.7) that clinicians should "Offer a choice between active surveillance, radical prostatectomy or radical radiotherapy to people with low-risk localised prostate cancer for whom radical treatment is suitable" **[5.1**, p.13**]**. The ProtecT trial was one of 3 studies cited in the evidence underpinning the recommendation. It was the largest in terms of participants and the only one to consider radiotherapy as an alternative treatment to surgery **[5.2**, p.7**]**.
- **European Association of Urology (EAU) prostate cancer guidelines** (6.1.1.4): This states that "…the ProtecT study has reinforced the role of deferred active treatment (i.e. either AS [Active Surveillance] or some form of initial AM [Active Monitoring]) as a feasible alternative to active curative interventions for patients with low-grade and low-stage disease" **[5.3**, p.35**]**.
- **European Association of Urology Editorial:** This emphasises the importance of the ProtecT trial, stating "we now have level 1 data to help patients navigate the choice between active monitoring [active surveillance] and treatment, and to balance the risks and benefits of each" **[5.4**, p.8**]**.

By giving patients the option for their cancer to be actively monitored, as outlined in these guidelines, patients are now able to avoid unnecessary treatment with harsh side effects that could significantly affect their quality of life.

Where radiotherapy is identified as the appropriate treatment for localised prostate cancer, the CHHIP study **[3.3]** provided the evidence for updates to guidance which recommend hypofractionation of doses. This approach meant that instead of daily treatment for six to seven weeks, a patient receives a higher daily dose for four weeks only. NICE Guideline 131 (1.3.17) recommends hypofractionated radiotherapy "unless contraindicated" **[5.1]**. The CHHIP study is referred to in the evidence review as a "key trial" **[5.5**, p.6**]**. Radiotherapy given over a shorter duration is now standard practice for localised prostate cancer, recommended by NICE, EAU, and National Comprehensive Cancer Network (NCCN) guidelines in the UK, Europe and North America.

4.2 Enhancing treatment in locally advanced prostate cancer

Prior to the MRC PR07 trial, locally advanced prostate cancer was frequently treated in the same way as metastatic disease, solely with hormone therapy. This was not based on clinical evidence. Following on from earlier recommendations cited in 2014 NICE guidelines (highlighted in the previous REF 2014 case study), PR07 findings were incorporated into NICE Guideline 131 entitled *Prostate cancer: diagnosis and management* which was published in

May 2019 with recommendation 1.3.19 stating that clinicians should: "Offer people with intermediate and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone" **[5.1** p.20**]**. This change to the NICE guideline and in clinical practice is underpinned by Cardiff research findings following the MRC PR07 trial, as detailed in section 2 **[3.4, 3.5]**.

Following these changes to guidelines, an impact analysis estimated that alterations in UK patient treatment practice resulted in between 3,730 and 5,177 extra life-years at 15 years for a group of men diagnosed in a single year (7,930 men) **[5.6]**. As noted by Amini et al (2016) "The updated study results presented by Mason *et al.* […] confirms that local control of high-risk prostate cancer categorically improves survival at long term follow up" **[5.7]**.

4.3 A change to the recommended therapy in advanced (metastatic) prostate cancer

STAMPEDE trial results **[3.6]** were translated into both the NCCN and EAU guidelines with approval for clinical use of agents, such as docetaxel and abiraterone, in this difficult to treat stage of the disease **[5.2, 5.8a, 5.9]**. As such, the worldwide standard of care is no longer conventional hormone therapy alone for patients with advanced prostate cancer. Two other randomized trials of docetaxel (GETUG 15 and CHAARTED) yielded conflicting results but the STAMPEDE trial convinced the medical community of docetaxel's benefit due to its significant size, as well as evidence of an increase in median survival when patients were given docetaxel in addition to the standard treatment. This was underpinned by a non-Cardiff meta-analysis of all three trials **[5.8b]**.

Tsao and Oh, Icahn School of Medicine at Mount Sinai, New York stated: "subsequent large randomized studies demonstrated a significant overall survival benefit with the addition of either docetaxel chemotherapy (CHAARTED, STAMPEDE) or abiraterone acetate plus prednisone (LATITUDE, STAMPEDE) to standard ADT in patients with metastatic, hormone-sensitive prostate cancer (mHSPC). On the basis of these data, a combination approach is now considered standard of care for mHSPC" **[5.10]**.

In 2019, NICE guidelines were revised to reflect the STAMPEDE trial findings, recommending offering docetaxel to patients with mHSPC (Recommendation 1.5.6) **[5.1**, p.30.**]**, where previously it had only been recommended for hormone-insensitive metastatic prostate cancer. The implementation of these guidelines can also be seen in Scottish Government policy, where the STAMPEDE treatment recommendations were included in clinical quality performance indicators **[5.11]**. Over 87% of patients diagnosed annually (over 3,000 men per annum in Scotland) were treated according to the STAMPEDE standards between 2015 and 2018 **[5.11]**.

In summary, Cardiff's contribution to four robust clinical trials provided clear research evidence that changed clinical guidelines and practice for prostate cancer patients at all stages of the disease. These changes in clinical practice have led to better quality of life for patients and improved survival rates.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] NICE guidelines NG131: *Prostate cancer: diagnosis and management* (May 2019)

[5.2] NICE guideline NG131: *Prostate cancer: diagnosis and management – intervention comparisons*, [G] Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer (May 2019)

[5.3] European Association of Urology (EAU) prostate cancer guidelines (6.1.1.4) (March 2018)

[5.4] Editorial which describes the impact of ProtecT: EAU Prostate Cancer Guidelines Group. Prostate Cancer and the John West Effect. *European Urology*, 72 (1):7-9, 2017. DOI: 10.1016/j.eururo.2017.02.006

[5.5] NICE guideline NG131: *Prostate cancer: diagnosis and management*, [C] evidence review for radical radiotherapy (May 2019)

[5.6] South, A., et al, (2016). Estimating the impact of randomized controlled trial results on clinical practice: Results from a survey and modelling study of androgen deprivation therapy plus radiotherapy for prostate cancer. *Eur Urol Focus,* 2: 276-283. DOI: 10.1016/j.euf.2015.11.004

[5.7] Amini, A., Kavanagh, B.D., Rusthoven, C.G. (2016). Improved survival with the addition of radiotherapy to androgen deprivation: questions answered and a review of current controversies in radiotherapy for non-metastatic prostate cancer. *Annals of Translational Medicine*, 4 (1), DOI: 10.3978/j.issn.2305-5839.2015.10.13

[5.8] a. James, N.D., Sydes, M.R., Clarke, N.W., Mason, M.D., Dearnaley, D.P., Spears, M.R., et al. (2015). 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. *The Lancet*, 387(10024), 1–15. DOI: 10.1016/S0140-6736(15)01037-5 **b.** Botrel, T.E.A., Clark, O., Lima Pompeo, A.C., Horta Bretas, F.F., Said, M.V., Ferreira, U., et al. (2016). Efficacy and Safety of Combined Androgen Deprivation Therapy (ADT) and Docetaxel Compared with ADT Alone for Metastatic Hormone-Naive Prostate Cancer: A Systematic Review and MetaAnalysis. *PLoS ONE*, 11(6): e0157660. DOI:10.1371/ journal.pone.0157660

[5.9] National Comprehensive Cancer Network guidelines on prostate cancer (August 2019)

[5.10] Tsao, C.-K., and Oh, W.K. (2018). First-Line Treatment of Hormone-Sensitive Metastatic Prostate Cancer: Is There a Single Standard of Care? Editorial in *Journal of Clinical Oncology*, 36(11). DOI: 10.1200/jco.2017.77.4315

[5.11] Scottish Quality Performance Indicators Evidence Group: **a.** Scottish Cancer Taskforce National Cancer Quality Steering Group Prostate Cancer Clinical Quality Performance Indicators Engagement Document (May 2016) **b.** NHS Scotland Prostate Cancer Quality Performance Indicators (December 2019)