Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: Reducing harm from biopsy in men with suspected prostate cancer		
Period when the underpinning research was undertaken: 2000–2012		
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:**
Derek Rosario	Senior Clinical Lecturer	2005–2017
Freddie Hamdy	Professor of Urology	1999–2008
	Honorary Staff	2008–2012
James Catto	Senior Clinical Lecturer/Professor of Urology	2007–present
Period when the claimed impact occurred: August 2013-2020		
Is this case study continued from a case study submitted in 2014? N		

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

Prostate cancer is the most common malignancy in men, and its diagnosis requires biopsy. Sheffield conducted the Prostate Biopsy Effects (ProBe) study to understand the harms of transrectal ultrasound-guided (TRUS) prostate biopsy, and found that there were wide variations in biopsy protocols, that 12% of men needed medication and 1.4% were hospitalised after biopsy. 20% stated a further biopsy would be problematic. Our research has guided UK and US screening policies to recommend against prostate-specific antigen (PSA) testing amongst asymptomatic men. These recommendations have contributed to significant reductions in unnecessary PSA testing in the USA, resulting in fewer men exposed to harm from biopsy, fewer diagnoses of indolent cancers, and biopsy cost savings of $1.6 billion.

2. Underpinning research (indicative maximum 500 words)

Transrectal ultrasound-guided (TRUS) prostate biopsy, after detection of elevated PSA, is key to the diagnosis of prostate cancer. However, most men with elevated PSA do not have cancer and so may have TRUS biopsy unnecessarily. Freddie Hamdy (1999-2012), Derek Rosario (2005-2017) and James Catto (2007-current) worked to determine the harms and accuracy of TRUS biopsy in diagnosing prostate cancer and to improve the care of men with elevated PSA.

To understand the effectiveness of different types of prostate cancer screening and treatment, Hamdy co-led the ProtecT RCT (2001-2009), which compared the clinical outcomes of surgery, radiotherapy and monitoring for prostate cancer [R1, R2]. Community-based PSA testing across nine UK cities (>110,000 men screened) was conducted and evaluated the accuracy of prostate biopsy for determining cancer burden in men [R3]. The results showed that prostate biopsy was an inaccurate tool for mapping cancer burden and that a change was needed.

As part of the ProtecT study, to determine the harms of TRUS biopsy, Rosario, Catto and Hamdy conducted a multi-institutional prospective evaluation (the Prostate Biopsy Effects (ProBe) study) of men undergoing biopsy, which was funded by the NHS Prostate Cancer Risk

Management Group. Between 2006 and 2008, 1,147 men were recruited from 8 UK centres and asked to self-report their perceptions of TRUS biopsy.

The key findings [R4, R5] were that:

- a wide variety of biopsy regimens were used across the UK,
- 12% of men visited a healthcare provider after biopsy (commonly for infective symptoms),
- 1.4% were hospitalised after biopsy,
- anxiety about biopsy was common in men.

In addition, approximately 20% of men stated that having another biopsy would be a moderate or major problem. A systemic review including the ProBe data revealed frequent adverse events from biopsy [R6] and cautioned against the widespread testing of asymptomatic men with raised PSA.

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

University of Sheffield researchers in **bold**

R1. Donovan, J.L., Little, P., Mills, N., Smith, M., Brindle, L., Jacoby, A., Peters, T., Frankel, S., Neal, D., **Hamdy, F.C.** (2002). Quality improvement report; Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study Commentary: presenting unbiased information to patients can be difficult. *BMJ, 325*(7376), 766-770. https://doi.org/10.1136/bmj.325.7367.766

R2. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, **Holding P**, Davis M, Peters TJ, Turner E, Martin RM, Oxley J, Robinson M, Staffurth J, Bollina P, **Catto J,** Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, **Rosario D**, Rowe E, Neal DE for the ProtecT study group. (2016). 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *New England Journal of Medicine,* 375(15), 1415–1424. https://doi.org/10.1056/nejmoa1606220. Cited 1,049 times.

R3. **Catto JWF,** Robinson M, Albertsen PC, **Goepel JR**, **Abbod MF, Linkens DA**, Davis M, **Rosario DJ**, Warren AY, Varma M, Griffiths DF, Grigor KM, Mayer NJ, Oxley JD, Deshmukh NS, Lane JA, Metcalfe C, Donovan JL, Neal DE and Hamdy FC on behalf of the ProtecT study group. (2011). Suitability of PSA-detected localised prostate cancers for focal therapy: experience from the ProtecT study. *British Journal of Cancer, 105*(7), 931–937. https://doi.org/10.1038/bjc.2011.314. Cited 23 times.

R4. **Rosario DJ,** Lane JA, Metcalfe C, Donovan JL, Doble A, **Goodwin L**, Davis M, **Catto JW,** Avery K, Neal DE, Hamdy FC. (2012). Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. *BMJ, 344*, d7894. https://doi.org/10.1136/bmj.d7894. Cited 234 times.

R5. Wade J, **Rosario DJ,** Macefield RC, Avery KN, Salter CE, **Goodwin M**L, Blazeby JM, Lane JA, Metcalfe C, Neal DE, Hamdy FC**,** Donovan JL. (2013). Psychological Impact of Prostate Biopsy: Physical Symptoms, Anxiety, and Depression. *Journal of Clinical Oncology, 31*(33), 4235–4241. https://doi.org/10.1200/jco.2012.45.4801. Cited 66 times.

R6. Loeb S, Vellekoop A, Ahmed HU, **Catto J,** Emberton M, Nam R, **Rosario DJ,** Scattoni V, Lotan Y. (2013). Systematic Review of Complications of Prostate Biopsy. *European Urology, 64*(6), 876–892. https://doi.org/10.1016/j.eururo.2013.05.049. Cited 522 times.

Grants

G1. Donovan JL, Hamdy FC, Neal DE (PIs) et al. The ProtecT study: a multi-centre RCT of treatments for localised prostate cancer, NHS/NIHR HTA Programme:01/05/01- 31/5/08 (£20M).

G2. Neal DE, Maitland Nj, Donovan J, Hamdy FC, Clarke NW. MRC G0100444 Northern (& Bristol) Prostate Cancer Collaborative- Sheffield component: 01/09/01-31/08/06 (£559,072)

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

Impact on PSA screening policy and guidance in the UK and USA:

Sheffield research findings informed the UK National Screening Committee's position on PSA screening [S1] and were cited as the key reference regarding the harms of TRUS biopsy in the NICE guidelines in both 2014 and 2019 [S2]. In addition, our findings on the harms of TRUS biopsy [R3] were used by School of Health and Related Research, University of Sheffield [S1], to create a model of PSA testing that was commissioned by the National Screening Committee. Based on the evidence, both the National Screening Committee and NICE concluded that the harms of TRUS biopsy (from over-treatment, inaccurate diagnosis and biopsy) outweighed the benefits. As a result, in 2015 the NHS Prostate Cancer Risk Management Group recommended against PSA screening [S1], and the National Screening Committee and the NHS continue to take this position in 2020.

In the USA, a combination of opportunistic PSA testing and private healthcare has made overdiagnosis and overtreatment for prostate cancer prevalent. By defining the harms of biopsy, our research informed the 2012 guidelines, and the 2018 revision of the guidance of the U.S. Preventive Services Task Force (USPSTF), newly advocating a discontinuation of PSA testing among asymptomatic men ("*Appendix 2: Information related to the harms of biopsy is derived from the work of Rosario and colleagues (ref 6)"*) [S3].

Impact on patients, physicians, and healthcare providers due to reductions in PSA testing rates and the avoidance of biopsy

Our research was used to justify the NHS and USPSTF recommendations against PSA testing. This contributed to PSA-based prostate cancer screening not being introduced in the UK and a significant reduction in PSA testing rates in the USA. In the USA, PSA testing dropped by 8%, which led to the detection of 28% fewer new prostate cancers in 2013 and the reduction in PSA testing rates has since been maintained [S4]. Most of the detected cancers (57%) were of low or intermediate risk and unlikely to be clinically important. As such, these men were spared overdiagnosis and overtreatment and did not have their risk of advanced prostate cancer increased. The results of a modelling study supported this data, estimating that if non-selective PSA testing in the USA were to continue, 710,000-1.1 million men would be over-diagnosed with prostate cancer [S5].

The reduced PSA testing rates underpinned by our research have had a major economic benefit for healthcare providers in the USA. Routine PSA testing of the 38.7 million men in the USA aged 50-70 yrs would cost $1,355 million for the blood tests, and lead to the biopsy of 3,251,640

men (based on 8.4% of the cohort having PSA >4.0 ng/mL), with a TRUS biopsy cost of $585/person, for a cost of $1.9 billion [S6].

Our work [R3, R5] has had further impacts on patients through its use in the development of an informational website by Prostate Cancer UK to guide men in determining whether to undergo PSA screening or a prostate biopsy [S7]. Furthermore, biopsy-related anxiety and uncertainty has been used to encourage men to stay in active surveillance regimes or to inform abdominal aortic aneurysm screening [S7].

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

S1. Combined: confirmation of Sheffield research contribution to NHS, (https://webarchive.nationalarchives.gov.uk/20150505144744/http://www.cancerscreening.nhs.uk/prostate/pcrmp02.pdf), UK National Screening Committee Guidelines (https://legacyscreening.phe.org.uk/prostatecancer) and commissioned modelling for PSA testing (https://legacyscreening.phe.org.uk/prostatecancer).

S2. Use of Sheffield research in NICE Prostate Cancer Guidelines 2014 (https://www.nice.org.uk/guidance/cg175, p.394) and 2019 (https://www.nice.org.uk/guidance/cg175, evidence review).

S3. U.S. Preventive Services Task Force (USPSTF) 2018 Guidance Revisions: The 2018 USPSTF guidance used our data to inform their policy on PSA testing in the USA. Reference to our research in Reference 53 in Fenton, J. J., Weyrich, M. S., Durbin, S., Liu, Y., Bang, H., & Melnikow, J. (2018). Prostate-Specific Antigen–Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA, 319(18), 1914. https://doi.org/10.1001/jama.2018.3712

S4. Sustained reductions in PSA testing: Fedewa, S. A., Ward, E. M., Brawley, O., & Jemal, A. (2017). Recent Patterns of Prostate-Specific Antigen Testing for Prostate Cancer Screening in the United States. *JAMA Internal Medicine, 177*(7), 1040. https://doi.org/10.1001/jamainternmed.2017.0340; and reductions from 2013 (whole year) onwards: Drazer, M. W., Huo, D., & Eggener, S. E. (2015). National Prostate Cancer Screening Rates After the 2012 US Preventive Services Task Force Recommendation Discouraging Prostate-Specific Antigen–Based Screening. *Journal of Clinical Oncology, 33*(22), 2416–2423. https://doi.org/10.1200/jco.2015.61.6532

S5. Gulati, R., Tsodikov, A., Etzioni, R., Hunter-Merrill, R. A., Gore, J. L., Mariotto, A. B., & Cooperberg, M. R. (2014). Expected population impacts of discontinued prostate-specific antigen screening. Cancer, 120(22), 3519–3526. https://doi.org/10.1002/cncr.28932

S6. Evidence of economic impact in the USA and cost of biopsy in the NHS in England.

S7. Patient and practitioner information on PSA testing (https://prostatecanceruk.org/prostate-information/prostate-tests/psa-test) and prostate biopsy (https://prostatecanceruk.org/prostate-information/prostate-tests/prostate-biopsy) on Prostate Cancer UK website and the BMJ (https://bmjopen.bmj.com/content/7/12/e017565.abstract).