Institution: University of Bristol		
Unit of Assessment: 2) Public Health, Health Services and Primary Care		
Title of case study: Evidence-based treatments for clinically localised prostate cancer: policy, practice, and health impacts of the ProtecT randomised treatment trial		
Period when the underpinning research was undertaken: 2000 - 2016		
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:**
Jenny Donovan	Professor of Social Medicine (PI)	1990 - date
J. Athene Lane	Professor in Trials Research (coordinator)	1996 - date
Chris Metcalfe	Professor of Medical Statistics	2004 - date
Tim Peters	Professor of Primary Care Health Services Research	1992 - date
Sian Noble	Senior Lecturer in Health Economics	2000 - date
Jane Blazeby	Professor of Surgery (quality of life)	1993 - date
Richard Martin	Professor of Clinical Epidemiology	1999 - date
Julia Wade	Lecturer in Qualitative Health Science	2005 - date
Period when the claimed impact occurred: 1st August 2013 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

In 2016, the ProtecT (Prostate testing for cancer and Treatment) trial published the first and only robust randomised evidence about clinical and patient-reported outcomes following surgery, radiotherapy, and active monitoring treatments for clinically localised prostate cancer. These results have provided men and clinicians with comparative information showing similar risks of mortality and different risks of metastases, disease progression, and harms to sexual, urinary, and bowel function and quality of life caused by treatments, at a median of 10 years' follow-up. ProtecT trial evidence has changed health policy and clinical practice through updated guidelines and optimised treatment. ProtecT continues to improve patient health and care by enabling informed and evidence-based treatment decision-making.

2. Underpinning research

Prostate cancer is a common disease in older men and over 11,000 die from it each year in the UK. Around 25,000 men each year are diagnosed with clinically localised disease (confined within the prostate gland), often after having a blood test for PSA (Prostate Specific Antigen). Many of these cancers remain small and slow growing during a man's lifetime, but some become aggressive and life-threatening. Curative radical surgery or radiotherapy can be given, but they can cause damaging side-effects to sexual, urinary and bowel function. Some clinicians wanted to develop programmes of monitoring/surveillance to avoid or delay radical treatment and its effects until/unless needed. Randomised trials to evaluate these very different treatment approaches were urgently needed.

ProtecT, funded by NIHR, is the first and only randomised trial aiming to compare active monitoring, radical surgery, and radical radiotherapy in men diagnosed with localised prostate cancer. From 2001 to 2009, over 111,000 men attended a ProtecT study appointment in general practices around nine UK cities and 82,429 men received a PSA-test. After imaging and prostate biopsies, 2,664 men were diagnosed with localised prostate cancer and, of these, 1,643 (62%) agreed to be randomised between surgery, radiotherapy, and active-monitoring in the ProtecT trial [1]. The primary outcome was defined as prostate cancer mortality at a median of 10-years' follow-up, data were collected on a wide range of clinical secondary outcomes [2], and men completed validated urinary/sexual/bowel function and quality-of-life patient-reported outcome measures (PROMs) each year [3].

Key findings related to impact

ProtecT outcomes were published in 2016 [4, 5], finding very low levels of prostate cancer mortality (<1%) at a median of 10 years' follow-up, and no evidence of a difference between surgery, radiotherapy, and active-monitoring. There were also no differences between the groups in all-cause mortality, but there was a higher rate of metastases (cancer spread) in the active-monitoring group (6%) compared with 3% in each of the surgery and radiotherapy groups [4]. Sexual, urinary and bowel problems were quantified by PROMs, with the highest rates of incontinence and impotence in the surgery group, and a high rate of impotence and some bowel symptoms in the radiotherapy group [5]. In the active-monitoring group, there was an expected gradual decline in sexual and urinary function with age, but serious functional problems were avoided unless men changed to a radical treatment during follow-up [5]. The ProtecT results thus provided robust evidence about the comparative risks of harms to sexual, urinary and bowel function caused by radical treatments, balanced against the small increased risk of progression and metastases from active monitoring [4, 5].

Clinically localised prostate cancers are usually categorised into two groups indicating whether they are at a lower or higher risk of cancer progression and spread. Policy and practice has increasingly tried to optimise treatment and reduce harms caused by 'over-treatment' (radical treatment not needed by men with low-risk cancer), and 'under-treatment' (radical treatment not given when needed for intermediate/high-risk cancer). As 66% of ProtecT participants had low-risk and 34% intermediate/high-risk disease [6], the study's results have addressed both issues.

Key researchers

The ProtecT study is a collaboration between the Universities of Bristol, Oxford, and Cambridge. Co-Principal Investigators are Donovan (Bristol), Hamdy (Oxford), Neal (Cambridge/Oxford). Oxford/Cambridge researchers contributed clinical expertise. University of Bristol researchers contributed trial design/conduct and methodological expertise (Lane - trial coordination, Metcalfe/Peters - statistics, Noble - health economics, Blazeby - quality of life, Martin - epidemiology, and Wade - qualitative research).

3. References to the research

[1] **Donovan** JL, **Young** GJ, **Walsh** EI, **Metcalfe** C, **Lane** JA, **Martin** RM and 26 members of the ProtecT study group. A prospective cohort and extended comprehensive-cohort design provided insights about the generalizability of a pragmatic trial: the ProtecT prostate cancer trial. *Journal of Clinical Epidemiology,* 2018, 96: 35-46. DOI:10.1016/j.jclinepi.2017.12.019

[2] **Lane** JA, **Donovan** JL, **Davis** M, **Walsh** E, **Dedman** D, **Down** L, **Turner** EL, Mason MD, **Metcalfe** C, **Peters** TJ, **Martin** RM, Neal DE, Hamdy FC & ProtecT study group. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. *Lancet Oncology,* 2014; 15, 10: 1109-18. DOI:10.1016/S1470-2045(14)70361-4

[3] **Lane** JA, **Metcalfe** C, **Young** G, **Peters** TJ, **Blazeby** J, **Avery** K, **Dedman** DJ, **Down** L, Mason MD, Neal DE, Hamdy FC. & **Donovan** JL. Patient-reported outcomes in the ProtecT randomised trial of clinically localised prostate cancer treatments: study design and baseline urinary, bowel and sexual function and quality of life. BJUI *Urological Oncology,* 2016; 118: 869-879. DOI:10.1111/bju.13582

[4] Hamdy FC, **Donovan** JL, **Lane** A, Mason M, **Metcalfe** C, Holding P, **Davis** M, **Peters** TJ, **Turner** EL, **Martin** RM and 26 members of the ProtecT study group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *New England Journal of Medicine*. 2016; 375, 15: 1415-1424. DOI:10.1056/NEJMoa1606220

[5] **Donovan** JL, Hamdy FC, **Lane** A, Mason M, **Metcalfe** C, **Walsh** E, **Blazeby** J, **Peters** TJ, and 26 members of the ProtecT study group. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *New England Journal of Medicine,* 2016; 375, 15: 1425-1437. DOI:10.1056/NEJMoa1606221

[6] Bryant RJ, Oxley J, **Young** GJ, **Lane** JA, **Metcalfe** C, **Davis** M, **Turner** EL, **Martin** RM, and 14 members of the ProtecT study group and **Donovan** JL, Hamdy FC. The ProtecT trial: analysis of the patient cohort, baseline risk stratification and disease progression. BJUI 2020, 125: 506-514. DOI:10.1111/bju.14987

Grant: Hamdy FC, **Donovan** JL, Neal DE (co-PIs), **Peters** TJ, **Martin** RM, **Lane** JA, **Metcalfe** C, et al. The ProtecT trial: a multi-centre randomised controlled trial of treatments for localised prostate cancer. NIHR HTA Programme (Ref: 96/20/06 & 96/20/99) 1/5/2001-30/6/2021. Sponsor: Oxford University. Value: GBP39.4 million.

4. Details of the impact

The ProtecT trial outcome papers published in 2016 [4, 5], provided the first (and only) clear and robust comparative evidence about the risks and benefits of the three major treatments for localised prostate cancer. ProtecT had the following impacts: (a) changed health policy to influence clinical practice, (b) changed clinical practice to avoid harm and optimise treatment, and (c) continues to improve health and care by enabling informed evidence-based treatment decisions:

(a) Changed health policy to influence clinical practice

Publication of the ProtecT outcomes led to UK NICE launching an exceptional review "to determine the clinical and cost-effectiveness of treatments for localised prostate cancer", directly referring to ProtecT as "the only UK-based study, making it directly applicable to current practice in the NHS" [A p.11]. An updated guideline: NG131 Prostate cancer: diagnosis and treatment was issued in 2019 [B] with changes to three major recommendations based on ProtecT evidence:

1. **Treatment of low-risk prostate cancer**
   2019-NG131 new recommendation was to "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" [B p.13].
   (Changed from 2014-CG175: "offer active surveillance… as an option to men with low-risk localised prostate cancer") [C].
2. **Treatment of intermediate-risk prostate cancer**
   2019-NG131 new recommendation was to "offer radical prostatectomy or radiotherapy and consider active surveillance for people with intermediate-risk localised prostate cancer" [B p.19].
   (Changed from 2014-CG175: "consider active surveillance for men with intermediate-risk localised prostate cancer") [C].
3. **Informing evidence-based treatment decision-making**
   2019-NG131 new recommendation advising clinicians and patients to use Table 3, comprising "factors to consider … using evidence from a large UK trial (ProtecT) … to discuss the benefits and harms of each treatment option" when deciding on treatment for low- and intermediate-risk prostate cancer [B].
   (*No such Table was included in 2014-CG175)* [C].

Major international clinical guidelines rapidly incorporated ProtecT results, e.g.:

- American Urological Association/American Society for Radiation/Society of Urologic Oncology, 2017, citing ProtecT evidence for treatment of localised prostate cancer [Di].
- European Association of Urology/European Society for Radiation Oncology/ European Society of Urogenital Radiology/International Society of Geriatric Oncology, 2017, citing ProtecT "level 1 data to help patients navigate the choice between active monitoring and treatment, and balance the risks and benefits" [Dii p.8].

- US Preventive Services Task Force recommendation of “individual decision by men” for prostate cancer screening, referring to evidence of “overdiagnosis, overtreatment, and treatment complications” from ProtecT, [Diii p.1902].

(b) Changed clinical practice and avoided harm by reducing over-treatment

Before ProtecT, studies in the UK and USA showed that over 90% of men diagnosed with localised prostate cancer received radical treatment, usually surgery. As ProtecT recruited successfully (2001-9), there was growing awareness of the need to reduce the level of radical treatment. NICE guidelines in 2008 and 2014 relied on expert opinion (including from ProtecT investigators) to “offer” active surveillance as an option, particularly for men with low-risk disease. Further, in 2014, the National Prostate Cancer Audit (NPCA) was established to assess the quality of services in England and Wales. NPCA set a major benchmark – to “reduce over-treatment of men with low-risk prostate cancer” – by auditing the percentage of men with low-risk prostate cancer receiving radical treatment. NPCA estimated 28% of men were over-treated in 2014 [Ei]. In 2016, it was 12%, and NPCA authors commented, “the proportion of men with low-risk disease being potentially ‘over-treated’ is an area of concern, especially given the recent publication of the ProtecT study,” [Ei p.47-8]. In the years after the publication of ProtecT, over-treatment reduced further to 8% in 2017, and to 4% in 2018 and 4% again in 2019 [Eii].

In addition, NPCA reported serious concern that over-treatment varied so widely (from 0% to 94%) across the 51 hospital-clusters in England [Ei]. Following ProtecT study publication, geographical variation in over-treatment largely disappeared (0% to 16%), with no concerning outliers [Eii, Figure 2].

(c) Continues to improve patient health and care through informed evidence-based treatment decision-making

Men newly diagnosed with clinically localised prostate cancer, their families, and the clinicians involved in prostate cancer care (urologists, oncologists, nurses, and general practitioners) can now consider the comparative benefits and harms of the main treatment modalities based on robust evidence from the ProtecT study to inform treatment decision-making. They can balance the clear risks of treatment harms and benefits in the context of similar very low levels of mortality risk, based on ProtecT trial evidence [4, 5]. This affects the decision-making of over 23,000 men diagnosed each year with low- or intermediate-risk prostate cancer in England alone [Eii]. Guidelines across the UK [B], Europe and the USA [D] encourage consideration of the ProtecT evidence in decision-making indicating wide reach and impact.

ProtecT evidence also directly reached men through over 400 media stories (review of 33 published within 30 days [Fi]), popular prostate cancer charity websites (such as Cancer Research UK [Fii] and Prostate Cancer UK [Fiii]), and the high social media presence of the study [Fiv] (paper [4] ranked 5th for social media impact in 2017 (63rd in 2020)).

ProtecT evidence reached clinicians and service providers through high citation papers (1,500 [4] and 700 [5], with paper [4] being listed as one of the NEJM’s 12 notable articles of 2016 [Gi] and Altmetric’s 22nd most impactful paper globally that year [Gii]); and through editorials in key specialist clinical journals [H] as well as updated guidelines [B, D].

Summary: ProtecT outcomes published in 2016 changed clinical practice and health policy, and the evidence continues to improve patient health and care by optimising treatment and enabling informed evidence-based treatment decision-making.

5. Sources to corroborate the impact

[A] NICE (2019). NICE Guideline [NG131]: [G] Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer

[B] NICE (2019). NICE Guideline [NG131]: Prostate cancer: diagnosis and management
See Table 3 and pp.13-19 for references to ProtecT

[C] NICE (2014). CG175 Prostate cancer diagnosis and treatment

[D] i) American Urological Association, American Society for Radiation, Society of Urologic Oncology (2017). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline
ProtecT references [4 (50), 5 (41) (and 52)] - these cited as providing evidence for guideline recommendations numbers 4, 7, 9, 16, 19, 29, 33.

ii) EAU-ESTRO-ESUR-SIOG (European Association of Urology-European Society for Radiation Oncology-European Society of Urogenital Radiology-International Society of Geriatric Oncology) prostate cancer guidelines panel. Prostate cancer and the 'John West' effect. European Urology 2017; 72: 7-9. DOI:10.1016/j.eururo.2017.02.006
ProtecT references [4, 5] cited (p.8).

iii) US Preventive Services Task Force. Screening for prostate cancer. JAMA. 2018; 319 (18): 1901-1913. DOI:10.1001/jama.2018.3710 *ProtecT references [4, 5] cited (p.1902).*

[E] National Prostate Cancer Audit (NPCA) for England and Wales:

i) Annual Report 2016 and

ii) Annual Report 2019

[F] Media:

i) Westerman et al. Media reporting of ProtecT: a disconnect in information dissemination? Prostate cancer and prostatic diseases 2017: 1-6. DOI:10.1038/pcan.2017.27

ii) CRUK (2016). A trial comparing treatment approaches for prostate cancer (ProtecT)

iii) Prostate Cancer UK (2016). Long-term study shows active surveillance offers same 10-year survival rate as radiotherapy or surgery

iv) ProtecT paper [4] ranked 5th for social media impact in 2017 (63rd in 2020) https://www.nejm.org/doi/metrics/10.1056/NEJMoa1606220

[G] Citations:

i) New England Journal of Medicine (NEJM) (2017). Notable Articles of 2016 *ProtecT paper [4] listed in 12 "most notable" 2016 NEJM papers*

ii) Altmetric (2016). Article #22 of 100 ProtecT paper [4] listed 22nd in Top 100 Articles of 2016 by Altmetric

[H] Editorials (small selection):

i) Albertsen P. Who Should Consider Active Surveillance? *J Urology,* 2016, 196:1604-5. DOI:10.1016/j.juro.2016.09.068

ii) Spratt DE. To ProtecT our patients with prostate cancer. *JAMA Oncology,* 2017, 3:1461-2. DOI:10.1001/jamaoncol.2017.0274

iii) Wang et al. 'ProtecTion' from over-treatment: does an RCT finally answer the question in localized prostate cancer? *BJU International,* 2017, 119:513–514. DOI:10.1111/bju.13734

iv) Cooperberg MR. What early ProtecT results have confirmed about risk-stratified prostate cancer management. *European Urology,* 2017; 71:389-90. DOI:10.1016/j.eururo.2016.10.017

v) Sharma V, Karnes TJ. To serve and ProtecT: has the pendulum swung too far towards surveillance? *European Urology,* 2020, 77:331-2. DOI:10.1016/j.eururo.2019.12.007