Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: ProtecT study: Enabling men to make better prostate cancer screening and treatment choices		
Period when the underpinning research was undertaken: October 2008 – Dec 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:**
Freddie Charles Hamdy	Nuffield Professor of Surgery, Professor of Urology	October 2008 - present
David Neal	Professor of Surgical Oncology	August 2015 - Sept 2019
Doug Altman	Professor of Statistics in Medicine	1995 - June 2018
Peter Holding	Lead Study Nurse	2009 - present
Period when the claimed impact occurred: 2016 - November 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research led by the University of Oxford has changed the way that men with prostate cancer are diagnosed are treated. Two large, linked, multi-centre randomised clinical trials assessed the effectiveness of screening and treatment for prostate cancer. These studies demonstrated that a prostate cancer screening programme using a single PSA (prostate-specific antigen) blood test offers no survival benefits, but causes over-detection of indolent cancers and potential harm due to over-treatment.

The combined outcomes of the ProtecT (**Pro**state **te**sting for **c**ancer and **T**reatment) and CAP (**C**lustered r**A**ndomised trial of PSA testing for **P**rostate Cancer) trials have led to major changes in policy and guidelines globally, including NICE, US and European guidelines all recommending more active monitoring to reduce harmful non-beneficial interventions. As a result of these studies, and changes to the guidelines, men are able to make informed choices about whether to undertake PSA testing in the first place, to understand the potential significant harms and assess the risk/benefit of treatment. This has, for example, resulted in over-treatment falling from 12% in 2016 to 4% in 2018 in the UK.

The research has also provided evidence necessary to prevent the implementation of a non-beneficial PSA screening programme, which in the UK has avoided 10,000,000 more PSA tests and 1,400,000 biopsies, delivered an estimated cost saving to the NHS of GBP1,000,000,000 per year and prevented the resulting physical and mental harms to men.

2. Underpinning research

The ProtecT trial is a large-scale, collaborative RCT, spanning twenty years, beginning in 1999 as a feasibility study; the main trial started in 2002 and will end March 2022, to enable extended 15-year follow-up. The trial was designed to test the treatment effectiveness and cost effectiveness of active monitoring, surgery or radiotherapy in clinically localised prostate cancer detected through screening, with a primary endpoint of prostate cancer specific mortality at 10 years. Hamdy led the trial as Chief Principal Investigator (University of Sheffield until 2008, then University of Oxford from 2008 - present), together with Co-Principal Investigators J Donovan (University of Bristol) and D Neal (University of Cambridge, then University of Oxford from 2015 - 2019).

Hamdy moved to the University of Oxford in October 2008, bringing the role of Chief Principal Investigator with him to Oxford; the underpinning research for the impact claimed began at this

point and focuses on the follow-up phase of the study. The full RCT completed recruitment in January 2009, with 111,000 men recruited, and 82,429 tested. The 10-year median follow-up milestone was reached in November 2015, when the data were unblinded. During the subsequent 6 month period the statistical analysis was conducted in collaboration with colleagues at the University of Bristol, and interpretation of the results and determination of findings was led by Hamdy at Oxford. This research led to two papers describing primary and secondary endpoints [1, 2]. The research showed that cancer deaths occurred at very low rates (approximately 1%), irrespective of the treatment allocated; all-cause mortality was also low at approximately 10% with no differences between the arms; radical treatments reduced disease progression and metastases by approximately 50% compared with active monitoring; and surgery and radiotherapy were equivalent in oncological outcomes, but had different side-effect profiles [1, 2].

Further statistical analysis demonstrated that although surgery and radical treatment reduced metastasis and progression compared with active monitoring (AM), there were negative impacts on sexual, urinary, and bowel functioning. In addition, radical treatments may be associated with lower prostate cancer mortality than AM, although the numbers of such deaths were low irrespective of treatment. More than 95 out of every 100 men with low or intermediate risk localised prostate cancer do not die of prostate cancer within 10 years, irrespective of whether treatment is by means of monitoring, surgery, or radiotherapy. The research showed that there was a trade-off between the side effects on sexual function and urinary continence, which are better after active monitoring, against the risks of spreading of prostate cancer [3].

The cohort study of men undergoing prostate biopsy in the ProtecT study showed that 1.3% required hospital admission and 10.4% consultation with a doctor because of post-biopsy symptoms including pain, fever, and blood in urine, faeces and ejaculate [4].

In the ProtecT study, GP practices from 9 UK centres were randomised to either the ProtecT intervention (which consisted of an invitation to PSA testing in men aged 50 - 69 years) or routine NHS practice (where PSA testing is very low in the UK). This created a natural control arm with the practices which were not randomised to ProtecT. This allowed ProtecT to become the intervention arm of the CAP study of prostate cancer screening, with Hamdy as a joint PI, the largest randomised controlled trial of screening for prostate cancer worldwide, using a single PSA test, with 415,357 participants. After a median follow up of 10 years, there was no significant difference in prostate cancer mortality between the group of men invited to screening and the control group, but an increase in the number of low-risk prostate cancers detected. The research also showed that in addition to the 2,965 men diagnosed through ProtecT, the diagnostic pathway missed the diagnosis of 1,433 cases, of whom 188 men died of prostate cancer. This confirmed that the worldwide conventional diagnostic pathway of PSA testing followed by biopsies was inadequate and missed too many lethal cancers [5].

Key Research Team
In the ProtecT Study: University of Oxford (trial sponsor since 2008): F Hamdy, Chief Principal Investigator, funding from NIHR, conduct oversight, study design, data interpretation. J Donovan, (co-PI University of Bristol Trials Unit responsible for co-ordination and QoL study). D Neal (co-PI Cambridge, University of Oxford from 2015).
CAP: University of Bristol (trial sponsor): F Hamdy (joint PI) with R Martin (joint PI, University of Bristol), D Neal (joint PI), J Donovan (joint PI, University of Bristol).

3. References to the research

Oxford authors in **bold**

1. **Hamdy FC**, Donovan JL, Lane JA, **Neal DE** et. al. (23 authors including **Holding P**) for the ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med.* 2016 Oct 13;375(15):1415-1424. *[Quoted by NEJM Editor as most 'notable article' for 2016; 903 WoS citations to date; accessed 06/07/2020]* DOI:10.1056/nejmoa1606220

2. Donovan JL, **Hamdy FC***, Lane JA, **Neal DE**, et. al. (34 authors) for the ProtecT Study Group. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med.* 2016 Oct 13;375(15):1425-1437. *[*joint first author; 392 WoS citations accessed 06/07/2020]* DOI: 10.1056/nejmoa1606221
3. **Neal DE**, Metcalfe C, Donovan JL, Lane JA, **Hamdy FC**, et. al (25 authors including **Dutton SJ, Bryant R, Holding P** and **Altman DG**), for the ProtecT Study Group. Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. *European Urology* (2020) 77(3):20– 33 DOI: 10.1016/j.eururo.2019.10.030
4. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, Davis M, Catto J, Avery K, Neal D, **Hamdy FC**. Short-term outcomes of prostate biopsy in men tested for cancer by prostate-specific antigen: evaluation within ProtecT study. *BMJ* 2012 Jan 9;344:d7894. doi: 10.1136/bmj.d7894
5. Martin RM, et. al. (25 authors including **Holding P**, **Neal DE,** and **Hamdy FC**) for the CAP Trial Group. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. *JAMA* 2018 Mar 6;319(9):883-895. *[104 WoS citations accessed 06072020]* DOI: 10.1001/jama.2018.0154

Peer-reviewed funding includes to The ProtecT trial: Department of Health and NIHR Health Technology Assessment Programme ref 96/20/99, to the University of Oxford, totalling GBP39,722,444. The CAP trial: Cancer Research UK (GBP215,641 component to the University of Oxford), ref RJ5197 A11235.

4. Details of the impact

Screening and management of PSA-detected prostate cancer has been a controversial healthcare topic globally. Cancer Research UK estimates that there are approximately 48,500 new cases of prostate cancer each year in the UK, and the American Cancer Society estimates that there are approximately 191,930 new cases each year in the US.
Opportunistic PSA testing in asymptomatic men has led to early detection and drives subsequent radical treatments that were intended to improve quantity and quality of life of these men, but are associated with a risk of significant adverse side-effects. Prior to the initiation of the ProtecT trial, studies in the UK (British Association of Urological Surgeons) and US (Department of Veterans Affairs) showed that over 90% of men diagnosed with localised prostate cancer received radical treatment, mostly in the form of radical prostatectomy.

The Oxford research [1 – 5] provided a powerful evidence base for the effectiveness of screening and treatments, highlighting how the harms of screening and treatment can outweigh the benefits. This has informed practice changes globally, reflected in global NICE, US and European guidelines recommending more active monitoring to reduce harmful non-beneficial interventions allowing clinicians and individuals to benefit by making better decisions about care.

Changes to global clinical guidance and policy

The NICE guideline on Prostate cancer: diagnosis and management published in May 2019 [Ai] describes and references the ProtecT trial in detail and appends a presentation given by Hamdy and Donovan (Oct 2018), which cites [1, 2 and 5] to the evidence considered by NICE [Aii]. The research informed the NICE guidelines as follows:

- Citing [2], NICE recommends active surveillance be offered as an option to people with low-risk localised prostate cancer: "*Based on the evidence from the ProtecT trial (Donovan et al., 2016), the choice of active surveillance, prostatectomy or radiotherapy appears to be a trade-off between the benefits offered by prostatectomy and radiotherapy against their potential risk of side effects…….. Based on this evidence, the committee decided that all three treatment options may be suitable for different people and therefore agreed to keep the existing recommendation to offer active surveillance as an option to people with low-risk localised prostate cancer*" [Aii]

- Based on [2], NICE kept the recommendation that the progression to radical treatment should be based on the man's personal preferences. Side-effect profiles extracted from and referring to ProtecT analysis are listed in the guidance [Ai].

The US Preventive Services Task Force changed its policy for prostate cancer screening from a D ("Discourage the use of this service") recommendation in 2011, to a C recommendation ("Offer or provide this service for selected patients depending on individual Circumstances") in 2018 for men aged 55 - 69 years, largely based on outcomes from the ProtecT and CAP trials. The cited Oxford research that showed no significant improvement in all-cause or prostate cancer mortality in any of the treatment groups [1, 5] and the analysis of surgery and radical treatment vs. active monitoring [3] is cited in the policy. The "*change in recommendation grade further reflects new evidence about and increased use of active surveillance of low-risk prostate cancer, which may reduce the risk of subsequent harms from screening*." The guidelines go on to elaborate that "*the decision to be screened for prostate cancer should be an individual one*" and "*before deciding whether to be screened, men aged 55 to 69 years should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision*". [B]

The European Association of Urology prostate cancer guidelines published in 2019, refer to the ProtecT Study research [1] on describing Active Surveillance (AS) / Active Monitoring (AM) thus: "*…, the ProtecT study has reinforced the role of deferred active treatment (i.e. either AS or some form of initial AM) as a feasible alternative to active curative interventions for patients with low-grade and low-stage disease*" and that *"AS should be the default management strategy in patients with low-risk disease and a life expectancy > 10 years"* [C].

Financial savings to healthcare providers

The NHS and other healthcare providers have benefitted from costs and resources avoided by not implementing a regular PSA test-based screening platform. A UK options appraisal [D] found that annual screening would result in almost 10,000,000 more PSA tests per year and 1,400,000 biopsies and, therefore, a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments). Total additional lifetime costs for a cohort of men aged 50 of a screen-once policy at 50 were estimated as GBP50,000,000, rising to almost GBP1,000,000,000 for an annual screening policy in the UK [D]. The clinical costs of screening in the UK, without administrative costs, were estimated to be GBP600,000,000 to GBP1,700,000,000 per year [E].

In November 2020, the UK National Screening Committee (UK NSC) completed its first periodic review since 2016 and concluded that a screening programme for prostate cancer in the UK was not recommended, for reasons including the harms caused and no single better treatment for early-stage disease [H]. The evidence document included numerical data from the ProtecT trial and cited [1] and [2] as part of the 2019 NICE review for NG131 [A].

Health benefits to patients

The high-quality evidence from ProtecT enables men to make properly-informed choices about testing and, for those with clinically localised prostate cancer, to decide on the balance between the benefits and side-effect profiles of radical treatments.

The cohort study of men undergoing prostate biopsy in the ProtecT study showed that 1.3% required hospital admission and 10.4% consultation with a doctor because of post-biopsy adverse symptoms including pain, fever, and blood in urine, faeces and ejaculate [4]. Among the two-thirds of men who received a negative or inconclusive biopsy result as part of ProtecT, around 20% reported high distress persisting up to 12 weeks [F]. By contributing to the evidence base used by policy makers to decide not to put screening in place, the Oxford research has helped avoid 1,400,000 biopsies per year [D] and subsequent harms avoided e.g. an estimated 18,200 men requiring hospital admission, 145,600 men suffering post-biopsy adverse symptoms and 184,800 men suffering high distress, per year.

The National Prostate Cancer Audit (NPCA) assesses the quality of services in England and Wales, and aimed 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. In 2016, the rate of over-treatment was 12%, and NPCA authors cited [1] and 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"* [Gi]. In the 2 years after the publication of the main ProtecT study clinical outcomes, over-treatment reduced by two-thirds (from 12% to 8% in 2017 [Gii], and to 4% in 2018 [Giii]). In 2017, the NPCA noted that *"the trend seen towards a reduction in men with low-risk disease being "potentially over-treated" is encouraging"* and suggested that the results of studies such as [1] were being disseminated into national practice [Gii].

5. Sources to corroborate the impact

A. (i) NICE guideline: Prostate cancer: diagnosis and management (2019) https://www.nice.org.uk/guidance/NG131
(ii) NICE guideline: Prostate cancer: diagnosis and management Appendix G: Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer (2019) https://www.nice.org.uk/guidance/ng131/evidence/g-active-surveillance-radical-prostatectomy-or-radical-radiotherapy-in-people-with-localised-prostate-cancer-pdf-6779081780

B. US Task Force recommendations: Screening for Prostate Cancer (2018) https://jamanetwork.com/journals/jama/fullarticle/2680553

C. European Association of Urology Guidelines https://uroweb.org/guideline/prostate-cancer/

D. UK Government Guidance Prostate cancer risk management programme (PCRMP): benefits and risks of PSA testing (2016) https://www.gov.uk/government/publications/prostate-cancer-risk-management-programme-psa-test-benefits-and-risks/prostate-cancer-risk-management-programme-pcrmp-benefits-and-risks-of-psa-testing

E. J Chilcott, S Hummel and M Mildred, Option appraisal: screening for prostate cancer: Report to the UK National Screening Committee (2010); https://legacyscreening.phe.org.uk/policydb_download.php?doc=79

F. Journal article: Macefield RC, Metcalfe C, Lane JA, Donovan JL, Avery KN, Blazeby JM, Down L, Neal DE, **Hamdy FC,** Vedhara K; ProtecT Study Group. Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result. *Br J Cancer.* 2010 Apr 27;102(9):1335-40. DOI: 10.1038/sj.bjc.6605648

G. (i) National Prostate Cancer Audit Annual Report (2016)
(ii) National Prostate Cancer Audit Annual Report (2017)
(iii) National Prostate Cancer Audit Annual Report (2018)

H. Screening for Prostate Cancer: External review against programme appraisal criteria for the UK National Screening Committee, October 2020. Evidence document available from summary of recommendation at https://legacyscreening.phe.org.uk/prostatecancer