Institution: University of Bristol		
Unit of Assessment: 2) Public Health, Health Services and Primary Care		
Title of case study: Prostate Cancer Screening trial informs guidelines, reduces harms to men from overdetection and avoids unnecessary health service costs internationally		
Period when the underpinning research was undertaken: 2001 - 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:**
Richard Martin	Professor of Clinical Epidemiology	1999 – present
Emma Turner	Research Fellow	2005 – present
Jenny Donovan	Professor of Social Medicine	1990 – present
Chris Metcalfe	Professor of Medical Statistics	2004 – present
Jonathan Sterne	Professor of Medical Statistics	1999 – present
Sian Noble	Senior Lecturer, Health Economics	2000 – present
Period when the claimed impact occurred: 2018 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

The cluster randomised trial of prostate specific antigen (PSA) testing to screen for prostate cancer (the CAP trial), conducted by the University of Bristol, found that while PSA testing increases the detection of low-risk prostate cancers, it does not save lives. These results published in 2018: (1) have informed UK and international guidelines on PSA-based screening; and (2) were used to update GP and Patient Information sheets produced by Public Health England (January 2020), aimed at enabling men to make a fully informed decision about whether or not to undergo screening. In intention to treat analyses, we showed that if PSA-based screening were to be offered to all men aged 50-69 in England and Wales, the impact over and above current practice, on the secondary care budget could be at least GBP250 million in the first year.

2. Underpinning research

Ideally, aggressive prostate cancers should be identified and treated early. However, for many men, prostate cancer is slow-growing and may never cause harm during a man's lifetime. Detecting these clinically insignificant cancers ('overdetection') may lead to overtreatment and seriously impact on quality of life through anxiety surrounding the diagnosis, the possibility of infection following a biopsy, and impotence and incontinence following surgery or radiotherapy. Healthcare providers may also be burdened with unnecessary costs.

Screening for prostate cancer can be conducted using tests that measure blood levels of a protein known as prostate-specific antigen (PSA). However, using PSA as a screening test is controversial because it cannot distinguish between aggressive and non-aggressive prostate cancers. Consequently, up to a half of all screen-detected prostate cancers may be 'overdetected'. It is therefore critical to ensure that any potential gains in mortality and quality of life achieved through PSA screening, are not outweighed by harms from overdetection and overtreatment.

The publication of two major trials in 2009, one from Europe and the other from the USA, failed to resolve the controversy surrounding PSA-based, population-wide prostate cancer screening. However, the CAP trial succeeded in providing high-quality UK-based evidence, by obtaining extensive and complete (>99%) long-term follow-up for over 400,000 men [3.1-3.5]. CAP, conducted by the University of Bristol (UoB) in collaboration with the Universities of Oxford and Cambridge, and funded by Cancer Research UK (CRUK) and the Department of Health [i,ii], was the largest randomised controlled trial ever to investigate prostate cancer screening. It set

out to find out if inviting men for a single PSA test would help detect high-risk / aggressive prostate cancers earlier and if treating these earlier would mean that the men live longer.

CAP randomised 415,357 men aged 50-69 years registered with 573 general practices in eight cities in England and Wales between 2001-2009. Men in the intervention-group practices were invited to undergo PSA testing. Control-group practices undertook standard (unscreened) UK practice. The trial compared 189,386 men who were invited to have a one-off PSA test with 219,439 men who were not invited for screening. The primary outcomes – prostate cancer-specific and all-cause mortality after a median 10-years follow-up – were published in JAMA in March 2018 [3.1].

Insights

The CAP trial detected significantly more prostate cancers in the screened (8,054, 4.3%) than the control (7,853, 3.6%) group, with a five-fold-increase in detection rate during the first 18 months of the screening period (10.42 versus 2.18 per 1,000 person-years in the screened vs control groups). The intervention mainly increased the detection of low-risk prostate cancers, and there was no evidence of any difference in prostate cancer mortality (the primary outcome [3.2]), between the screened and control groups after a median 10-year follow-up [3.1]: 549 out of 189,386 men died in the screened group (0.30 per 1,000 person-years) compared with 647 out of 219,439 in the control group (0.31 per 1,000 person-years). There was no difference in all-cause mortality (c.13%).

Key researchers

CAP was jointly conducted by the Universities of Bristol and Oxford. Principal investigators at UoB: Martin (Lead PI); Donovan (Joint PI); University of Oxford: Hamdy (Joint PI) and Neal (Joint PI, initially based at Cambridge). University of Oxford PIs contributed clinical expertise. UoB researchers contributed expertise in RCT design, data management and analysis: Turner (trial coordinator); Metcalfe and Sterne (statisticians); Noble (health economists).

3. References to the research

3.1 **Martin RM**, **Donovan JL**, **Turner EL**, **Metcalfe C**, **Young GJ**, Walsh EI, **Lane JA, Noble S**, Oliver SE, Evans S, **Sterne JAC**, Holding P, **Ben-Shlomo Y**, Brindle P, Williams NJ, Hill EM, Ng SY, Toole J, Tazewell MK, Hughes LJ, Davies CF, **Thorn JC**, Down E, **Davey Smith G**, Neal DE, Hamdy FC, for the CAP Trial Group. (2018). Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. *JAMA,* 319(9):883–895. DOI:101001/jama.2018.0154 *Altmetric ranked in top 1% of all published research outputs (Altmetric score 885, 2 November 2020, jamanetwork.altmetric.com/details/34003282),120 citations and 32,429 views.*

3.2 **Turner EL, Metcalfe C, Donovan JL, Noble S, Sterne JAC, Lane JA,** Walsh E, Hill EM, Down L, **Ben-Shlomo Y**, Oliver SE, Evans S, Brindle P, Williams NJ, Hughes LJ, Davies CF, Ng SY, Neal DE, Hamdy FC, Albertsen P, Reid CM, Oxley J, McFarlane J, Robinson MC, Adolfsson J, Zietman A, Baum M, Koupparis A, **Martin RM**. (2016). Contemporary accuracy of death certificates for coding prostate cancer as a cause of death: Is reliance on death certification good enough? A comparison with blinded review by an independent cause of death evaluation committee. *British Journal of Cancer,* 115(1): 90-4. DOI:10.1038/bjc.2016.162

3.3 **Young GJ**, Harrison S, **Turner EL**, Walsh EI, Oliver SE, **Ben-Shlomo Y**, Evans S, **Lane JA**, Neal DE, Hamdy FC, **Donovan JL, Martin RM, Metcalfe C**. (2017). Prostate-specific antigen (PSA) testing of men in UK general practice: a 10-year longitudinal cohort study. *BMJ Open,* 7(10):e017729. DOI:10.1136/bmjopen-2017-017729

3.4 **Turner E, Metcalfe C, Donovan J, Noble S, Sterne J, Lane JA**, Avery K, Down L, Walsh E, Davis M, **Ben-Shlomo Y**, Oliver S, Evans S, Brindle P, Williams N, Hughes L, Hill E, Davies C, Ng SY, Neal D, Hamdy F, **Martin RM**. (2014). Design and preliminary recruitment

results of the Cluster randomised triAl of PSA testing for Prostate cancer (CAP). *British Journal of Cancer,* 110(12):2829-36. DOI:10.1038/bjc.2014.242

3.5 **Thorn JC, Turner EL**, Hounsome L, **Walsh E**, Down L, Verne J, **Donovan JL**, Neal DE, Hamdy FC, **Martin RM**, **Noble SM**, the CAP trial group. (2016). Validating the use of Hospital Episode Statistics data and comparison of costing methodologies for economic evaluation: an end-of-life case study from the Cluster randomised triAl of PSA testing for Prostate cancer (CAP). *BMJ Open,* 6:e011063. DOI:10.1136/bmjopen-2016-011063

Grant information

i) **Martin RM.** Evaluating population-based screening for localized prostate cancer in the United Kingdom: the (Comparison Arm for ProtecT) study. CRUK/DoH, 2004-2017, GBP4,644,314

ii) **Martin RM.** Evaluating the long-term effectiveness and cost-effectiveness of population-based screening and treatment for prostate cancer: the CAP and ProtecT RCTs. CRUK, 2017-2021, GBP961,403

4. Details of the impact

Prostate cancer places a significant burden on public health globally, causing an estimated 6 million years of life lost in 2016, a figure that is forecast to rise to 12 million by 2040. Amongst UK males, prostate cancer is the most commonly diagnosed cancer, affecting 1 in 8 men, and is the second commonest cause of cancer death.

The CAP trial provided the first and only robust evidence comparing a low-intensity PSA-based screening strategy (a single screen) for prostate cancer with no screening, minimal contamination [3.3], and was designed to reduce overdetection and overtreatment while seeking a mortality benefit. It showed that while PSA-based screening increases the detection of low-risk prostate cancers, it does not save lives. The results were disseminated widely, including through print and broadcast media locally, nationally and internationally that involved interviews with Martin and Turner. The CAP trial won the 2018 Office for National Statistics (ONS) Research Excellence Awards, recognising outstanding use of ONS research data for public benefit. *("The award winning submission from Emma and her team shows the fantastic public benefit that can be achieved through innovative methodology, exceptional collaboration and excellent use of Secure Research Data"* Director for Methods Data Research at the ONS). The CAP trial is cited as a highlight in CRUK's timeline of lifesaving research [5.1ii].

In the current REF period, the results of the CAP trial have informed UK and international guidelines on the use of the PSA test for prostate cancer screening, helping to avoid harms to men and reduce unnecessary costs to the NHS and globally (such as in the USA).

1. Impacts on UK and international health policy and professional practices

The research has helped policymakers make evidence-based decisions about the population impact of PSA-based screening for prostate cancer. The CAP trial led to changes in health policy and professional guidelines around the world, with clinicians and health services now advised to encourage individualised shared decision-making (informing men of the possible harms and benefits and supporting decision making) rather than routine screening. These new guidelines help ensure that patients (men aged 50-69 years), GPs and urologists are better informed about the benefits and harms of PSA screening for prostate cancer.

1.1 New UK guidance on PSA tests

The CAP trial provided the UK National Screening Committee (NSC) with high-quality, UK-based evidence to inform new Public Health England (PHE) guidance for GPs on the balance of benefits and harms of PSA-based prostate cancer screening, published in January 2020. The importance of the CAP results in these guidelines is confirmed in writing by the Director of the UK NSC [5.2i].

On 6 March 2018, the Royal College of General Practitioners released a statement [5.3] in response to the CAP paper published the same day [3.1]. This stated that "*the College does not recommend that the PSA test is offered routinely to men who do not present with prostate*

cancer symptoms". Further, it praised CAP as a "*large, high-quality study"* that is *"really useful in backing up our calls for GPs to have better access to a more specific and sensitive test than the PSA test*" [5.3].

1.2 New international guidance on PSA tests

In the USA, the results of CAP had a major influence on the recommendations of the United States Preventative Services Task Force (USPSTF), a public health body, published in May 2018 [5.4]. These advised that the decision to screen is a complex one, and that men should be carefully counselled about the benefits and harms of screening to make a fully informed decision. The Bristol research team liaised regularly with the USPSTF in the year prior to publication once they had undertaken the CAP analysis, providing USPSTF with a draft manuscript and advising on the timing of publication. The USPSTF recommendations, published May 2018, cited CAP's results [3.1] and were delayed until the CAP trial publication (March 2018) so that the results of CAP could be included in the Evidence Report that informed USPSTF's recommendations [5.4]. The American Urological Association (AUA) also included CAP (citing 3.1) in its body of evidence underpinning clinical guidelines on Early Detection of Prostate Cancer (June 2018) [5.4]. The AUA also argues for shared decision-making for men aged 50-69 years who are considering PSA screening.

In other countries, the trial results [3.1] were cited in updated urological and oncological guidelines for the early detection of prostate cancer. For example, Clinical Guidelines for the Screening and Early Detection of Prostate Cancer in Denmark were updated in 2019: *"Neither systemic nor opportunistic screening of prostate cancer is recommended"*, evidence rated as strong [5.5i]. Italian guidelines also updated in 2019 "informed of the (many) risks and (limited) benefits associated with the test" [5.5ii]. The European Urology Association (EAU) cites CAP results in their review of the frequency and intervals of PSA testing [5.5iii]. The Canadian Urological Association (CUA) cited initial CAP results [3.4] in its guidelines published in 2017. The Canadian guidelines precede the publication of CAP's full trial results in 2018, but it recognised that these results would likely feed into future reviews [5.6].

In September 2018, a rapid recommendation on prostate cancer screening with PSA testing was published in the BMJ [5.7]. This guidance, developed by an international panel for urological surgeons, was triggered by the results of CAP [3.1], published earlier that year: "*The Rapid Recommendations executive felt* [CAP]*—taken together with extended follow-up data from existing trials—required a new appraisal of the body of evidence for patients and clinicians*." Drawing on evidence from CAP and other studies, the Recommendation advises: "*Shared decision making is needed for men considering screening to make a decision consistent with their individual values and preferences. However, clinicians need not feel obligated to systematically raise the issue of PSA screening with their patients*".

2. Economic impacts: reduced costs to healthcare providers

Health policy changes occurring as a result of the trial, will reduce unnecessary costs to the health authorities around the world who adopt the revised screening guidelines. In the UK, the costs of annual routine screening have been estimated to be GBP1 billion, were it to be introduced by the NHS, according to a School of Health and Related Research (ScHARR) report to the NSC in March 2013 [5.8]. The ScHARR report explains: "*Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself.* [Annual screening] *would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease*."

The impact of introducing PSA-based screening test has a measurable effect on secondary care costs. In an intention-to-treat analysis of the CAP trial [3.5], offering PSA-based screening was associated with additional secondary care costs of circa GBP40 per man in the intervention compared with the control arm in the first year following randomisation, suggesting that if PSA-based screening was to be offered to all men aged 50-69 in England and Wales, the impact on

the secondary care budget (over and above current NHS practice) could be over GBP250 million in the first year.

3. Impact on patient and clinician understanding through new information sources on PSA-based screening

- A CRUK public information page on prostate cancer screening [5.1i] has received 55,574 unique views since the CAP trial results were published, with a spike of 3,089 views on the day of publication, which CRUK described as "by far the biggest driver to the page".
- PHE developed a leaflet for well men [5.2iii], published in January 2020 (with the impact of the CAP trial confirmed in writing by the Director of the UK NSC [5.2i]).
- Authoritative summaries of the CAP trial results (NIHR Signal; CLAHRC Bite) [5.9] were written to provide information to clinicians about the trial and its implications.

4. Impacts on health and wellbeing

The conduct of the trial underpinned the UK NSC longstanding policy of awaiting the publication of the primary results of CAP before making a final decision on the introduction of a national screening programme (Minutes, Nov 2015) [5.10]. The decision to await the results has potentially prevented harms of overdetection for between 129,948 (reasonably assuming a lower limit of 20% overdetection) and 259,896 (reasonably assuming an upper limit of 40% overdetection) men aged 50-74 per year.

5. Sources to corroborate the impact

5.1 i) CRUK (2018). Blog: Why a one-off PSA test for prostate cancer is doing men more harm than good
ii) CRUK (2019). Beating cancer: our progress

5.2 i) UK NSC (2020). Testimonial letter – Director - *Refers to the recommendation that population-based screening for prostate cancer should not be introduced.*
ii) UK NSC (2020). Rapid Review: Screening for Prostate Cancer
iii) PHE (2020). Prostate specific antigen testing: advice for well men aged 50 and over
iv) PHE (2020). Advising well men about PSA test for prostate cancer: information for GPs

5.3 Royal College of General Practitioners (2018). PSA tests should not be offered routinely to men without symptoms of prostate cancer, says College

5.4 i) USPSTF (2018). Screening for Prostate Cancer US Preventive Services Task Force Recommendation Statement
ii) USPSTF (2018). Prostate-Specific Antigen–Based Screening for Prostate Cancer Evidence Report and Systematic Review for the US Preventive Services Task Force
iii) AUA (2018). Early Detection of Prostate Cancer

5.5 i) Danish Prostate Cancer Group (DAPROCA) (2019) Clinical Guideline for the Screening and Early Detection of Prostate Cancer
ii) Italian Association of Medical Oncology (AIOM), with Italian Society of Urology (SIU) and Italian Society of Uro-Oncology (SIUrO) (2019). Prostate Cancer Guidelines
iii) European Association of Urology (EAU) (2019). Guidelines on Prostate Cancer

5.6 CUA (2017). Canadian Urological Association recommendations on prostate cancer screening and early diagnosis

5.7 i) Tikkinen *et al.* (2018). BMJ, 362:k3581. DOI:10.1136/bmj.k3581
ii) Ilic *et al.* (2018). BMJ, 362:k3519. DOI:10.1136/bmj.k3519 *International meta-analysis conducted to inform rapid recommendation above [5.2ii].*

5.8 ScHARR report (2013) to the NSC

5.9 i) NIHR (2018). Single routine offer of a blood test for prostate cancer did not save lives
ii) CLAHRC Bite (2018). A study investigating a single blood test to screen for prostate cancer (the CAP trial)

5.10 UK NSC (2015). Meeting minutes November 2015