Institution: University of Bristol

Unit of Assessment: UoA2

Title of case study: Avoiding harm and evaluating benefit: establishing and implementing an evidence-based policy for prostate cancer screening in the UK

1. Summary of the impact

Research at the University of Bristol (UoB) led to the Department of Health (DH) decision in 1997 that screening for prostate cancer would not be introduced in the UK until there was evidence that benefits outweighed harms. UoB-led and collaborative research subsequently provided evidence to support informed decision-making in the NHS. A formal review by the DH in 2010 endorsed the policy and confirmed that any change would be based on evidence from the team's randomised trials. This research has ensured UK men have avoided known harms of prostate cancer screening in the context of uncertain benefits, and saved the UK economy £ billions.

2. Underpinning research

The research was initiated at UoB with a comprehensive systematic review of prostate cancer diagnosis, treatment and screening literature, funded by NHS R&D and led by Donovan (UoB).[1] Published in 1997, the review concluded "current evidence does not support a national screening programme for prostate cancer in the UK".[1] A major research programme was then designed and undertaken by UoB researchers in collaboration with Hamdy (Oxford) and Neal (Cambridge) to provide the required evidence, including:

- The ProtecT (Prostate testing for cancer and Treatment) feasibility study led by Donovan (UoB) investigated barriers inhibiting an RCT (randomised controlled trial) of treatment.[2] Over 8,500 men aged 50-69 years were recruited from general practices, and 224 men diagnosed with localised prostate cancer participated in the pilot RCT of treatments.[2] Integrated qualitative research supported clinicians and men in accepting randomisation between surgery, radiotherapy and 'active monitoring' (a management option developed with patients consisting of regular review and avoiding radical treatment).[2]
- The main ProtecT RCT (joint Principal Investigators (PIs): Donovan (UoB), Hamdy and Neal) was launched in 2001 to evaluate the comparative effectiveness of radical surgery, radical conformal radiotherapy and active monitoring for men with localised prostate cancer.[3] Recruitment of 111,000 men with a PSA (prostate specific antigen) blood test was completed in 2009, over 8,500 received biopsies, and 1,650 with prostate cancer were randomised between the treatment arms. The primary outcome (prostate cancer mortality) will be analysed in 2015 (with 10 years' median follow up). A nested cohort study of 1,100 men undergoing prostate biopsy investigated side-effects of prostate biopsy, including symptoms, health-care use,[4] and psychological impact.[5].
- The CAP (Cluster RCT of testing for Prostate Cancer) (joint PIs: Martin and Donovan (UoB), Hamdy, Neal) randomised 573 general practices to enable a comparison between PSA testing and treatment in ProtecT (screening) and usual NHS care (control) in 415,000 UK men.[6] An ecological study confirmed a much lower incidence of prostate cancer in the UK compared with the USA,[7] and a cohort study confirmed low rates of PSA testing in UK primary care[8] - reflecting much higher rates of screening in the USA compared with the UK.

The research programme began by exposing the lack of evidence for prostate cancer screening,[1] and then carried out a study to investigate the feasibility of mounting an RCT to provide robust evidence.[2] The success of the feasibility study,[2] led to the launch of the ProtecT RCT to evaluate the effectiveness of treatment[3] and the CAP RCT to evaluate the population impact of screening.[6] Studies embedded in these RCTs have produced policy-relevant evidence about the impacts on men of undergoing prostate biopsy,[4,5] and levels of PSA testing and cancer diagnosis compared with the USA,[7] and in UK primary care.[8]

Research team (positions held at UoB or dates of leaving; and researchers outside UoB)

Principal investigators: at UoB - Donovan (Professor), Martin (Professor); outside UoB - Hamdy (Professor, Oxford), Neal (Professor, Cambridge).

Key researchers at UoB: Collin (Research Fellow - RF), Metcalfe (Reader), Turner (Research Associate - RA), Lane (Senior RF), Peters (Professor), Wade (RA); outside UoB: Williams (RA Sheffield), Rosario (CSL Sheffield), Hughes (RA Cambridge).

Left UoB: Selley (RA, 1998), Faulkner (RF, 1999), Coast (Reader, 2005).

3. References to the research

[1] Donovan JL (PI), Faulkner A, Coast J et al. Prostate cancer: a systematic review. NHS R&D HTA Programme. 1/1/95 - 31/12/95. £52,052. (Peer-reviewed research grant.)

Selley S, Donovan JL, Faulkner A et al. Diagnosis, management and screening of early localised prostate cancer. *Health Technology Assessment* 1997; 1 (2). Doi: 10.3310/hta1020

[2] Donovan JL (PI), Peters TJ, Hamdy FC et al. The feasibility of conducting a multicentre randomised controlled trial of treatment for localised prostate cancer: early detection, recruitment strategies and a pilot (ProtecT) trial. NHS R&D HTA Programme. 1/5/99 - 30/4/01. £1.03 million. (Peer-reviewed research grant.)

Donovan JL, Hamdy FC, Neal DE et al. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. *Health Technol Assess* 2003; 7(14) pp.1-42. DOI : 10.3310/hta7140 http://www.hta.nhs.uk/fullmono/mon714.pdf

[3] 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:1/5/01- 31/5/08 (£20 million); 1/6/08-31/12/13 (£14 million); 1/1/2014-31/12/2016 (£5.4 million). (Peer-reviewed research grant.)

[4] Rosario DJ, Lane AJ, Metcalfe C et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. *BMJ* 2012;344:d7894. http://dx.doi.org/10.1136/bmj.d7894. (Included in REF2.)

[5] Wade J, Rosario DJ et al, Donovan JL. Psychological impact of prostate biopsy: physical symptoms, anxiety, and depression. Journal of Clinical Oncology, 2013: published ahead of print, 21st October 2013 as 10.1200/JCO.2012.45.4801. (Included in REF2.)

[6] Martin RM, Donovan JL, Hamdy FC, Neal DE (PIs) et al. Evaluating population-based screening for localised prostate cancer in the UK: an extension to ProtecT – the CAP trial. Cancer Research-UK/DoH. 1/3/02-31/12/06 (£1.19 million); 1/1/07-31/12/09 (£931,232); 1/1/10–31/12/12 (£1.3 million); 1/1/13-31/12/16 (£1.2 million). (Peer-reviewed research grant.)

[7] Collin SM, Martin RM, Metcalfe C et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncology* 2008; 9: 445-52. Doi: 10.1016/S1470-2045(08)70104-9. Listed in REF2.

[8] Williams N, Hughes LJ, Turner EL et al. Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. BJU Int. 2011, 108(9):1402-8. Doi: 10.1111/j.1464-410X.2011.10163.x.

4. Details of the impact

Prostate cancer screening is one of the most controversial healthcare topics globally. Prostate cancer kills over 11,000 men per annum in the UK. Many prostate cancers can be identified when potentially curable following screening with a PSA blood test and prostate biopsy, but it is not possible to identify which tumours will become aggressive or life-threatening (the vast majority will not). Screening leads to large numbers of men being diagnosed and suffering harms related to the diagnosis and treatment of prostate cancer in the context of small and uncertain benefits - hence the current UK policy not to recommend screening. Our research has provided the evidence-base for this policy and has had the following specific impacts:

The establishment of UK policy and origin of the impact

UK policy was established in a letter from the DH to all UK health authorities and clinicians in 1997, stating that: “Population screening for prostate cancer, including the use of prostate specific antigen (PSA) as a screening test, should not be provided by the NHS or offered to the public until there is new evidence of an effective screening technology for prostate cancer”.[a] This was based directly on two cited systematic literature reviews, one led from UoB.[1] The policy has remained unchanged throughout the REF impact reporting period, based on this original policy statement.

Implementing UK policy

A National Screening Committee (NSC) Scientific Reference Group (including UoB Donovan and Lane as members) launched the Prostate Cancer Risk Management Programme (PCRMP) in 2002. PCRMP issued on-line and paper documents containing information about PSA testing, prostate cancer diagnosis, and treatment, based on evidence from the UoB systematic review[1] to enable patients to make informed decisions about screening.[b] PCRMP documents were revised in 2009[c] with UoB Donovan given first acknowledgement (p.2) for contributing evidence from the review[1] and ProtecT feasibility study.[2] The PCRMP remains the primary source of information for UK GPs and men.

Low levels of UK PSA-testing have been corroborated by independent research in 2004 showing the rate of PSA-testing in primary care of 6% of eligible men;[d] UoB research confirmed this rate (6.2%) in 2008.[8]

Evaluating the benefits and harms of screening

UK policy has led to much lower levels of incidence and treatment of localised prostate cancer compared with countries where PSA testing has been widespread since the 1980s: for example in the USA (as shown by our research[7]), and Canada, Australasia, Northern and Western Europe.[e] Evidence for a potential prostate cancer-specific mortality benefit from screening comes from a relatively robust European RCT,[f] published alongside a USA RCT showing no benefit from screening.[g] Our research has provided evidence about the harms of screening. A 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] Among the two-thirds of men who received a negative or inconclusive biopsy result, around 20% reported high distress persisting up to 12 weeks.[5] Concerns about the harms caused by prostate cancer diagnosis and treatment in the context of uncertain benefit, and increasing realisation that high levels of PSA-testing did not reflect clinical need, led to a policy review in the USA in 2011. The review focussed on the harms and uncertain benefits[h] and so in 2011, USA policy changed explicitly not to recommend prostate cancer screening - 14 years after the 1997 UK policy decision.

Formal review of UK policy in 2010

The UK NSC formally reviewed policy for prostate cancer screening in 2010 using evidence from an independent option appraisal analysis based on ProtecT trial data (acknowledged, p.xi).[i] The appraisal analysis estimated rates of diagnosis, potential benefits and harms of treatment, as well as impact on survival and costs to the UK economy of introducing prostate cancer screening at age 50 years, annually, or every two or four years, using statistical modelling. The harms of treatment always outweighed any possible benefit of screening in each potential scenario.[i] The clinical costs alone, without administrative costs, were estimated to be £0.6 to £1.7 billion per year.[i] The 2010 review concluded that UK policy should remain as established in 1997, and re-iterated that any change needed to await evidence from this research team’s ProtecT[3] and CAP[6] RCTs.[j]

Health Technology Assessment in the UK, review 2013

This review, written by an independent team, specifically identified the ProtecT study as “The outstanding example of 143 projects for screening and diagnostics funded by the HTA programme,” and noted ProtecT had “affected clinical practice ... by allowing the UK to reaffirm its policy of no routine screening” and through its qualitative research that “pioneered ways to involve patients” in recruitment, and research on the psychosocial effect of screening.[k, page 1280]

In summary, UoB-led research established UK policy in 1997, and UoB-led and collaborative research has supported policy implementation since then, including providing evidence for the formal confirmation of UK policy in 2010. UK policy, underpinned by this research, has ensured that knowledge about prostate cancer screening has increased, very many men have avoided known harms of testing, and the UK economy has saved billions of £s every year.

5. Sources to corroborate the impact

[a] Letter EL(97)12 from Graham Winyard, DoH Medical Director (Room 3N12, Quarry House, Leeds LS2 7UE), June, 1997, to Health Authority and NHS Trust Chief Executives and all UK health practitioners. It stated that "systematic reviews commissioned by the NHS R&D HTA Programme have concluded that current evidence does not support a national screening programme for prostate cancer in the United Kingdom. Current screening technologies (including the PSA test) have a limited accuracy that could lead to a positive result for those without the disease. Follow up procedures could thus cause unnecessary harm to healthy individuals." One of the cited reviews was UoB[1].

[b] UK Prostate Cancer Risk Management Programme (PCRMP). This webpage links to PCRMP documents providing information for GPs and patients to make informed decisions. http://www.cancerscreening.nhs.uk/prostate/about-pcrm.html cites the UoB systematic review[1] in paragraph eight, after bullet points.

[c] http://www.cancerscreening.nhs.uk/prostate/prostate-booklet-text.pdf is the 2009 revised booklet with UoB Donovan given first acknowledgement on p.2 for contributing evidence from the UoB review.[1]

[d] Melia J, Moss S, Johns L. Rates of PSA-testing in general practice in England and Wales. BJU International, 2004: 94: 51-56. Doi: 10.1111/j.1464-4096.2004.04832.x. Paper from independent group corroborating policy implementation leading to low rates of PSA testing in the UK.

[e] Center MM, Jemal A, Lortet-Tieulent et al. International variation in prostate cancer incidence and mortality rates. European Urology. 2012, 6: 1079-1092. Doi: 10.1016/j.eururo.2012.02.054. Paper from independent group corroborating higher levels of diagnosis and treatment of prostate cancer in the absence of UK-like policy.

[f] Schröder FH, Hugosson J, Roobol MJ et al. Screening and prostate cancer mortality in a randomized European study. NEJM 2009, 360 (13): 1320-1328. Doi: 10.1056/NEJMoa0810084. Paper from independent group indicating small mortality benefit from screening with considerable over-diagnosis and over-treatment.

[g] Andriole GL, Crawford ED, Grubb RL et al. Mortality results from a randomized prostate-cancer screening trial. NEJM 2009; 360 (13): 1310-19. Doi: 10.1056/NEJMoa0810696. Paper from independent group showing no mortality benefit from screening and considerable harms.

[h] Chou R, Croswell JM et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011. 155(11):762-71. Doi: 10.7326/0003-4819-155-11-201112060-00375. Most recent systematic review to inform USA policy review decision.

[i] Chilcott J, Hummel S, Mildred M. Report to the UK National Screening Committee, May 2010 Option appraisal: screening for prostate cancer [ScHARR] (PDF document, 1.11MB, 02/08/10). Report from the independent option appraisal analysis commissioned by the NSC from the University of Sheffield for the policy review. Potential benefits and harms of screening, and costs to the economy were estimated using ProtecT data (directly acknowledged on p.xi.).

[j] This web-link: http://www.screening.nhs.uk/prostatecancer confirms the 2010 National Screening Committee review decision that UK policy should remain as established in 1997, and directly cites documents produced by PCRMP ([b] above), UoB systematic review[1] and ProtecT study data.

[k] Raftery J, Powell J. Health Technology Assessment in the UK. *Lancet* 2013; 38:1278-85; doi: 10.1016/S0140-6736(13)61724-9. Report from an independent group specifically citing the impact of ProtecT study on prostate cancer screening policy and identifying other health impacts, p.1280.