Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
The ProtecT Trial and Associated Translational Research – Management of Localised Prostate Cancer.

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

ProtecT (Neal, Cambridge; Donovan, Bristol; Hamdy, Oxford), funded by NIHR in 1999, is the largest randomised controlled trial in localised prostate cancer; and compares a deferred conservative approach (Active Monitoring – developed by the Trial PIs) with surgery and radiotherapy. Avoiding "over-treatment" in low risk cancer is important and Active Monitoring (AM) and Surveillance (AS) have now had a major impact on patients and on national health policy through NICE guidance, which recommends such management approaches. The linked bio-repository was critical to characterising the genetic pre-disposition alleles (SNPs) in prostate cancer, which are now being used to identify high risk populations.

2. Underpinning research (indicative maximum 500 words)

Neal is Group Leader in the CRUK Cambridge Institute and Urologist (Chair of Surgical Oncology, 2002, tenured). Prostate cancer is the most common cancer in men and results in 41,000 new cases and 10,700 deaths in the UK *p.a.;* it is predicted to increase to over 60,000 cases *p.a.* in the coming two decades because of an ageing population. Early diagnosis is based on measurement of prostate specific antigen (PSA), but this is of low sensitivity and specificity. Neal and Donovan have for many years highlighted the considerable controversy over screening, early detection and treatment because of risks of "over-diagnosis" and "over-treatment" (1). Most men with "low risk" localised disease do not die of prostate cancer and radical treatments carry sexual, rectal and urinary morbidity.

In 1998, because of the long natural history and low rate of progression of prostate cancer, the three ProtecT PIs (Neal, Cambridge; Donovan, Bristol; Hamdy, Oxford) developed the novel concept of Active Monitoring (AM) and comparing this with surgery and radiotherapy in a RCT (2). AM aims to keep men in a "window of curability" whereby only those showing progression on careful re-assessment triggered by PSA change and / or change on rectal examination, are treated radically, this is very different from "watchful waiting" (where there is no intervention till advanced disease is present).

ProtecT approached 229,000 men in nine centres in the UK: 82,000 were enrolled, 8,000 men had high PSA levels and underwent prostate biopsy. Almost 3,000 men were diagnosed with prostate cancer and 62% of eligible men were recruited (2). Current trials of screening and of treatment have confirmed the continued international importance of ProtecT, because only ProtecT has a "screen-detected" cohort treated by AM. ProtecT is due to reach its primary clinical outcome in late 2015, but has already produced over 100 papers.

Intermediate end-points

Firstly, we showed in ProtecT that novel collaborative methodologies between Social Science and Clinical Researchers could ensure recruitment to trials that were seen as difficult to recruit to (3), leading to the adoption of such approaches to other trials *via* the NIHR.

Secondly, many high impact discoveries have been made. We developed an internationally important clinically well-annotated **bio-repository** of tissue, blood and serum from 82,000 randomly selected men.

Research involving Easton and Pharoah (Strangeways, Cambridge) and Eeles (ICR, London) was funded by Cancer Research UK (£ 4M) in 2007 to carry out genome-wide association studies (GWAS). Neal, Eeles and Easton reasoned that the use of an extreme experiment (comparing very low risk and very high risk men) would uncover significantly more single nucleotide polymorphisms (SNPs) in prostate cancer (4). This proved to be the case. This collaboration has led to almost 20 papers in high impact journals leading to almost 1,000 cites since 2008. To date, 73 SNPs (4, 5) have been found, accounting for around a third of the known genetic background in

prostate cancer; and this will be used to identify populations for targeted screening.

Other important discoveries have included the observation that genetic corrections for PSA can be made, improving sensitivity and specificity (6); new biomarkers have been discovered (7) which are dependent on SNP risk alleles; and that the known impact of diet on prostate cancer development may be mediated by IGF family members (8).

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

1. Frankel S, Smith GD, Donovan J, **Neal D**. 2013. Screening for prostate cancer. Lancet. 2003 Mar;361(9363):1122-8. Impact Factor 38, (Citations > 100).
2. Lane JA, Hamdy FC, Martin RM, Turner EL, **Neal DE**, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. Eur J Cancer. 2010 Nov;46(17):3095-101.(Cited > 50)
3. DONOVAN, J., MILLS, N., SMITH, M., BRINDLE, L., JACOBY, A., PETERS, T., FRANKEL, S., **NEAL, D**. & HAMDY, F. 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. *British Medical Journal,* 325**,** 766-769. Impact factor 14. (Citations >190).
4. EELES, R. A., KOTE-JARAI, Z., GILES, G. G., ……., **NEAL, D. E**. & EASTON, D. F. 2008. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet,* 40**,** 316-21. Impact factor 35. (Citations > 350).
5. Ghoussaini M, Song H, Koessler T,….. **Neal DE**, Pharoah PD, Ponder BA, Eeles RA, Easton DF, Dunning AM. Multiple loci with different cancer specificities within the 8q24 gene desert. J Natl Cancer Inst. 2008 Jul 2;100(13):962-6. (Cited > 150)
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7. WHITAKER, H. C., KOTE-JARAI, Z., ROSS-ADAMS, H, …….., EASTON, D., COOPER, C., EELES, R. & **NEAL, D. E**. 2010. The rs10993994 Risk Allele for Prostate Cancer Results in Clinically Relevant Changes in Microseminoprotein-Beta Expression in Tissue and Urine. *PLoS One,* 5.
8. Gunnell D, Oliver SE, Peters TJ, et al, …… **Neal DE,** Holly JM. Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. Br J Cancer. 2003 Jun 2;88(11):1682-6.

Associated Funding

Hamdy FC, Donovan J, Neal DE. NIHR funding for ProteCT. **£36M**.; Neal DE, Hamdy FC, Maitland NJ, Donovan JL, Clarke N. The Northern (and Bristol) Prostate Cancer Collaborative. MRC **£5M**.; Neal DE. CRUK **£3M;** Neal DE CRUK: **£0.9M;** Donovan JL, Hamdy FC, Neal DE, Martin R. CRUK **£2.4M;** Eeles R, Easton D, and Neal DE. CR UK **£ 4M;** Eeles R, Cooper C, Neal DE and Stratton M. Next generation sequencing for prostate cancer (CRUK: ICR, Sanger and Cambridge) **£4M**

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

Although not due to complete until 2015, the importance of AM and the critical role of the final outcome of ProtecT have already had major impact on National Health Policy through developing the role of conservative approaches that underpin NICE Guidance, and decisions on screening.

Active monitoring (AM) was developed in late 1998 within ProtecT as a method for deferring radical treatment in men with low risk prostate cancer, whilst keeping them in a “window of curability”. Over-treatment is clearly identified world-wide as the major problem of early detection of prostate cancer. AM has been adopted and adapted internationally through the use of additional biopsies into a management protocol known as active surveillance (AS). Critically, these conservative

approaches have been incorporated into the NICE Guidance published in 2008 (1) and later clarified through a joint statement with the British Association of Urology (led by Neal) (2). The guidelines stated that men with low risk prostate cancer should be offered conservative approaches such as Active Surveillance.

The trial underpinned the hugely important medico-political decision not to introduce screening for prostate cancer in 2010. Screening would only be introduced if it was known what the best treatment was for screen-detected cancers, and that this was cost-effective. A recent overview for the Department of Health by ScHARR (3) has explicitly and extensively referred to knowing the outcome of ProtecT as being a key benchmark. A reference from ProtecT (4) was one of only five quoted in the expert review for the main national screening document (5) and the requirement for ProtecT to report was by one leading international opinion leader (Wilt) as being of critical importance to national health policy on prostate cancer screening (6). A recent independent review; published in the Lancet confirmed that "ProtecT has affected clinical practice, even before announcement of its results, by allowing the UK to reaffirm its policy of no routine screening". (7) Also we recognised within the ProtecT Trial the critical importance of presenting men with information in a neutral way to allow them to make an informed decision, so that they understood the uncertainty behind the requirement for a RCT. Our experience of developing such information was recognised through the appointment of Neal to a group tasked by the Department of Health to produce an "informed decision making aid". This involved collaboration with health service researchers in Boston and Ontario and the urological input to the final document was led by Neal. This decision aid was then rolled out within the NHS via NHS Direct (8). The work on shared decision making between patients and their advisors is now part of Health Policy: "no decision about me without me" and the Urological Decision Aid has been used as an exemplar in documents produced for the Health Foundation by Coulter (9). Neal also led the Clinical Advisory Group for the Department of Health on the development of a new patient website where the role of conservative approaches to the management of localised prostate cancer is fully explained (10).

Advice about prostate cancer and the pros and cons of early detection has been sent out by the Department of Health to all General Practitioners under the government's Prostate Cancer Risk Management Programme, which builds on quoted evidence that has already come out of ProtecT (11, 12). The report noted: *"The Prostate Cancer Risk Management Programme …. will be piloting a recent finding from the ProtecT study which showed that two PSA tests performed 7 weeks apart allowed more accurate risk prediction and may assist in decision-making as to whether or not to proceed with referral…*

ProtecT has made a major difference to the quality of care for men with prostate cancer in that more men nationally and internationally with low risk disease are now being offered conservative approaches such as AM to keep them "in a window of curability", which will have reduced significantly the impact of morbidity associated with unnecessary radical treatments: an approach supported by the US NIH (13). The concept of strategies to keep men in a window of curability so that those who progress are offered radical treatments, is the principle within the active monitoring arm within ProtecT and other active surveillance protocols being developed.

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

1. NICE. Prostate Cancer, diagnosis and treatment. 2008. http://www.nice.org.uk/nicemedia/live/11924/39687/39687.pdf
2. BAUS and NICE. Joint Implementation Statement. 2009. http://www.nice.org.uk/nicemedia/live/11924/44396/44396.pdf
3. Chilcott J, Hummel S, Mildred M. SCHARR. 2010. Option appraisal: screening for prostate cancer. Report to the UK National Screening Committee. May 2010. Version 2.0. Option appraisal: screening for prostate cancer [ScHARR] (PDF document, 1.11MB, 02/08/10): www.screening.nhs.uk/policydb_download.php?doc=79
4. MOORE, A. L., DIMITROPOULOU, P., LANE, A., POWELL, P. H., GREENBERG, D. C., BROWN, C. H., DONOVAN, J. L., HAMDY, F. C., MARTIN, R. M. & NEAL, D. E. 2009. Population-based prostate-specific antigen testing in the UK leads to a stage migration of prostate cancer. BJU Int, 104**,** 1592-8.

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6. Wilt TJ. 2008. SPCG-4: a needed START to PIVOTal data to promote and protect evidence-based prostate cancer care. J Natl Cancer Inst. 100(16):1123-5. doi: 10.1093/jnci/djn259. Epub 2008 Aug 11.
7. Raftery J, and Powell J. Health Technology Assessment in the UK. Lancet. 2013. 382: 1278-85.
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9. Coulter A. Implementing shared decision making in the UK. A report for the Health Foundation. Produced as a scoping paper for the Health Foundation in 2009. (http://www.health.org.uk/public/cms/75/76/313/595/Implementing%20shared%20decision%20making%20in%20the%20UK.pdf?realName=vgvUMW.pdf)
10. http://admin.decisionaids.nhsdirect.nhs.uk/localisedprostatecancer/node/6
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13. http://www.nih.gov/news/health/dec2011/od-07.htm