Experiences from ProtecT:

Lessons I have learnt

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UNIVERSITY OF OXFORD

NUFFIELD DEPARTMENT OF SURGICAL SCIENCES

Articles

Randomised, prospective, single-blind comparison of laparoscopic versus small-incision cholecystectomy

A W Majeed, G Troy, J P Nicholl, A Smythe, M W R Reed, C J Stoddard, J Peacock, A G Johnson

THE LANCET

COMMENTARY

Surgical research or comic opera: questions, but few answers

"The way in which Majeed et al set out to answer their question is very much the exception rather than the rule in surgical research".....

"The study raises important issues about why surgeons do research, how they do it, what criteria they use, and how their research compares with the rest of the medical community."

Richard Horton, 1996

Surgical research: a myth?

“ I should like to shame surgeons out of the comic opera performances which they suppose are statistics of operation.”

Major Greenwood, 1923

“ The limitations on time and intellectual resources which are an inevitable consequence of the practice of surgery, can lead to poor quality work in the basic biological sciences.”

Hugh Dudley, BMJ 1981

Surgical research: a myth?

"*Lack of popularity is inescapable for any segment of the community that wishes to raise standards. I see little commitment to such a role in academic surgery today; we all want peaceful living, and if this is so, I doubt we have a viable future.*"

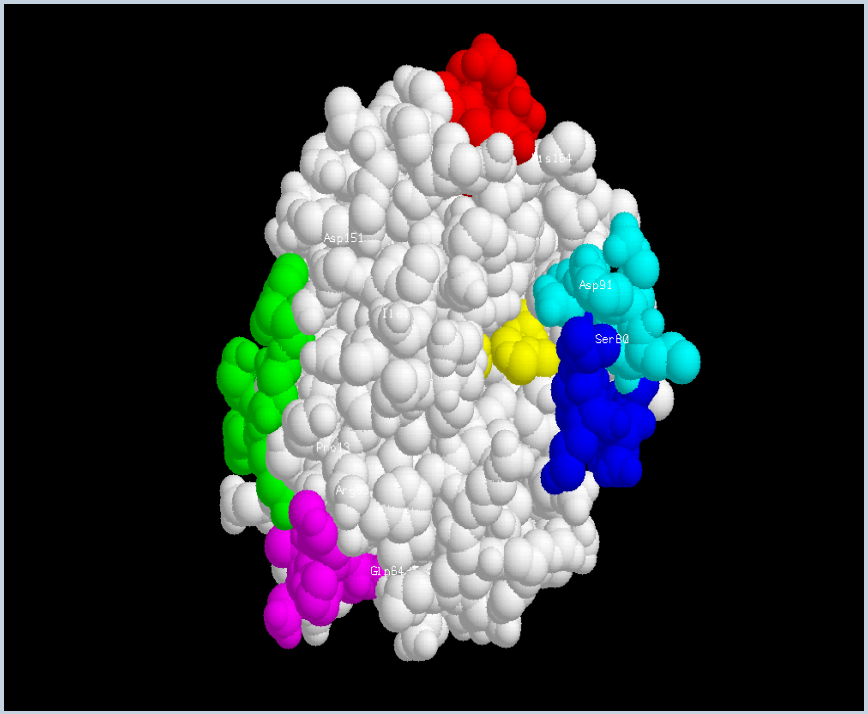
Hugh Dudley, BMJ 1981

What went wrong?

- Ivory towers
- Arrogance and self-sufficiency
- Lack of awareness:
  - Health Services Research
  - Levels of evidence
  - Statistics
  - Health Economics/modelling
  - Qualitative Research
  - Multidisciplinarity
- Time
- Molecular Biology and emphasis on basic science
- Difficulty with team work
- Ego…

Prostate Cancer: the 1980s

- **PSA:**

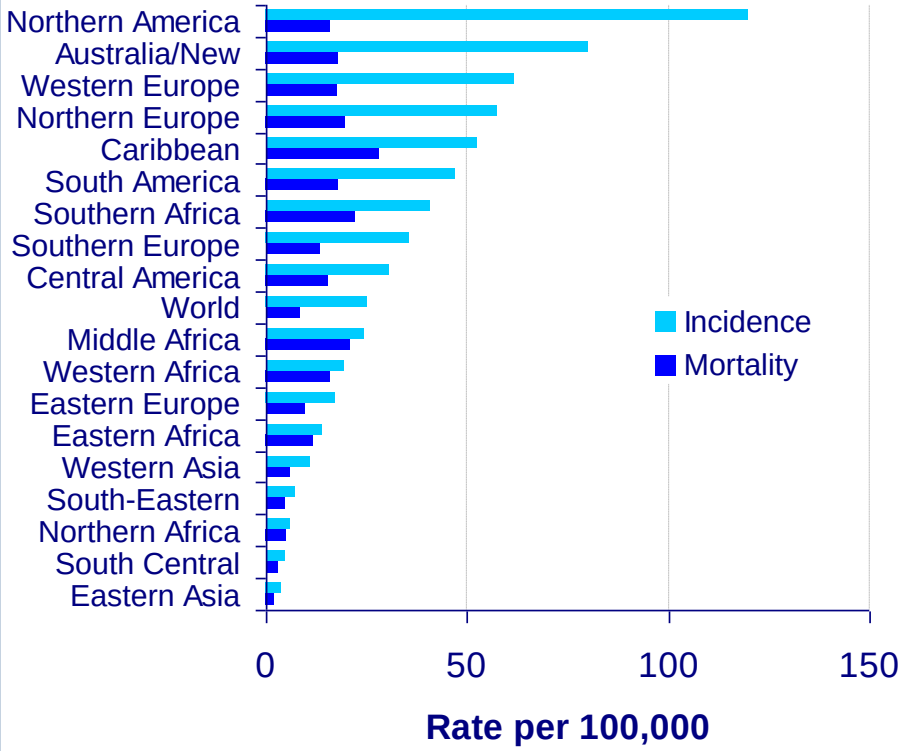


- **Anatomical Radical prostatectomy**

Stamey et al, NEJM 1987; Walsh et al, Prostate 1983

Incidence –Mortality : World

Figure 1.2: Age-standardised* incidence and mortality rates for prostate cancer by world regions, 2002 estimates



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The two faces of PSA testing

British Journal of Urology (1993), **71**, 375–377

EDITORIAL

Prostate Cancer Screening: Accepting the Consequences of PSA Testing

Chisholm, BJU 1993

There is now the prospect of a prostatectomy holocaust unless acceptable data can resolve this debate—and all of this is the result of a seemingly simple blood test.

It must be clear that this debate cannot be resolved because there has never been an appropriate trial either of screening or radical surgery or no immediate treatment. Indeed until randomised trials are performed we will not know if early detection with or without radical treatment improves cancer-specific survival

Screening for Prostate Cancer: The British Views in the early 1990

Opinions were divided

- Nihilistic conservatism still existed
- Screening must be introduced as a public health policy
- Screening studies must be performed
- Treatment studies must be performed first
- Multiplicity of guidelines, based on… lack of evidence

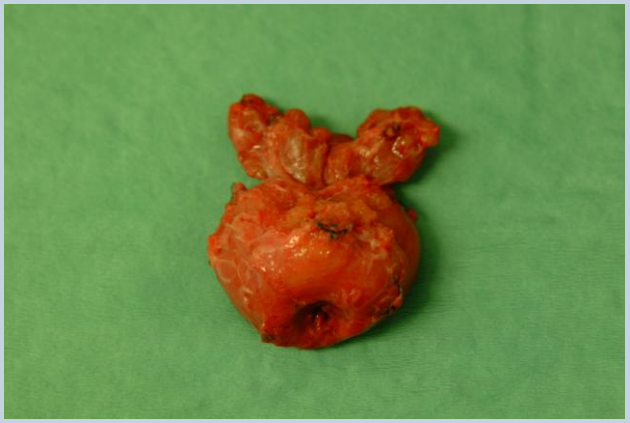
Prostate Cancer: the 1990s

- Radical prostatectomy
  - Curative surgical ‘gold standard’
- Radiotherapy
  - Advocated primarily by oncologists
- Watchful waiting
  - Men with less than 10 years life expectancy
  - Men with co-morbidities

Life on Earth

‘A sexually transmitted condition with 100% mortality’

Quality of life on Earth



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The Surgical Imperative

"If a surgeon tells you that without an operation you will die, and that as a result of the operation you may die, you have no choice but to have the operation".

Adolf Hitler

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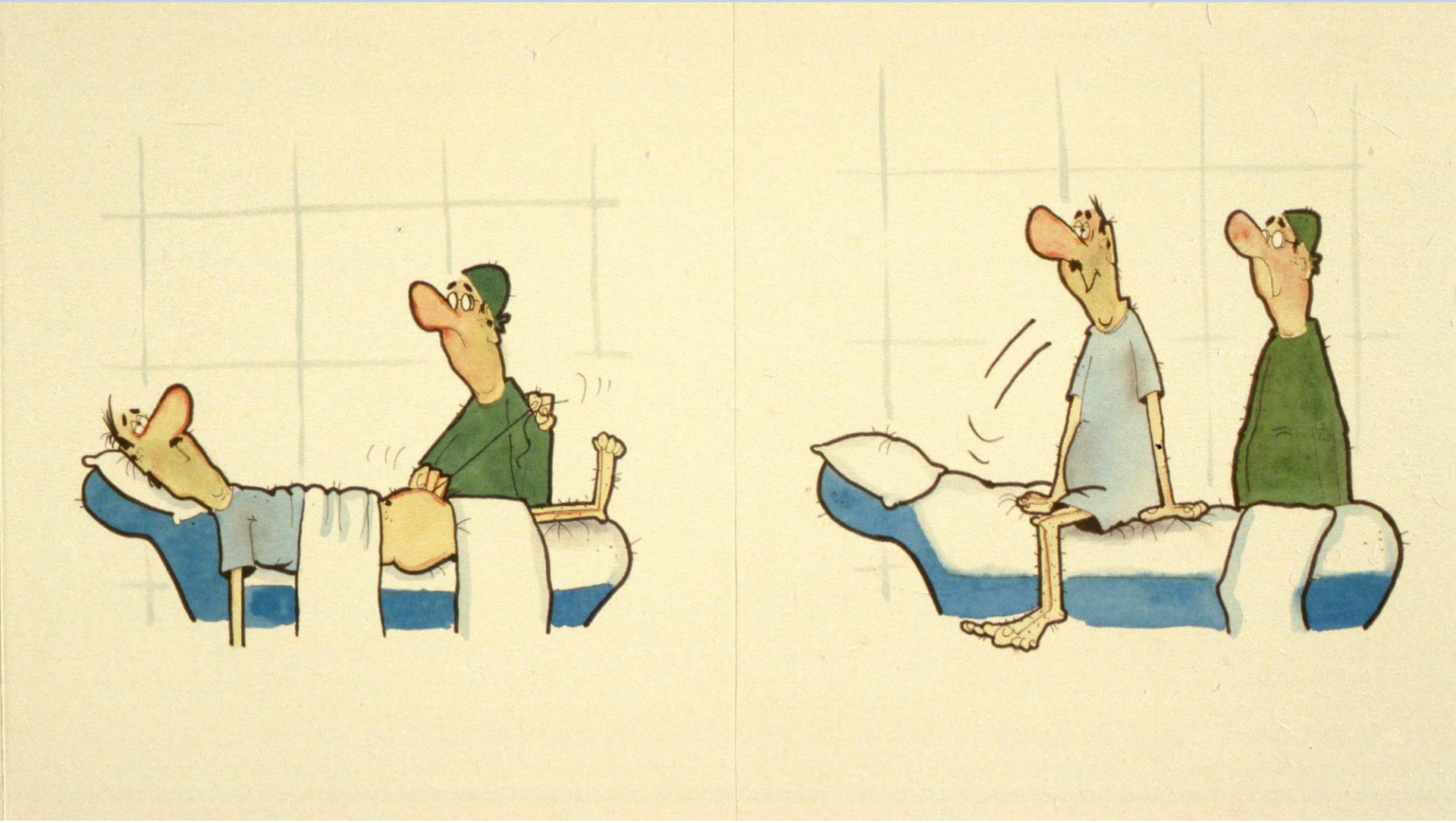
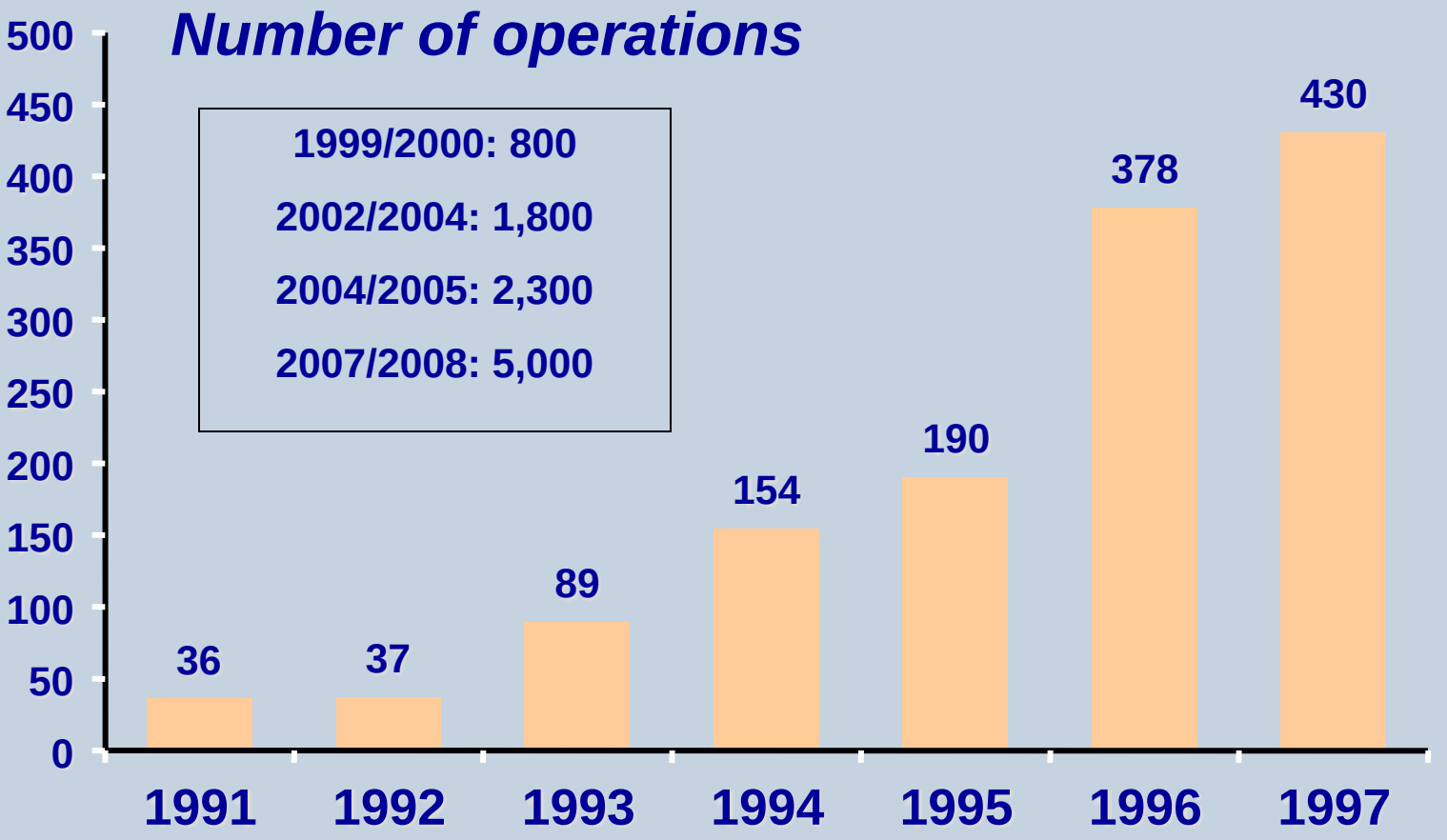



GENTS
ALAN PILTON

Number of radical prostatectomies performed in England (1991-1997)



Source: Hospital Episode Statistics

Research in the 1990s

- SPCG-4 (1989-1999)
- Systematic literature review in the UK 1996/7
- Failed MRC study
  - ‘Watchful waiting’ v RP v RT – no recruitment
- ERSPC RCT of screening - PLCO (1993-2009)
- PIVOT – closed

1993


MAIN ENTRANCE

INTERNATIONAL
CONTINENCE
SOCIETY
28th
ANNUAL

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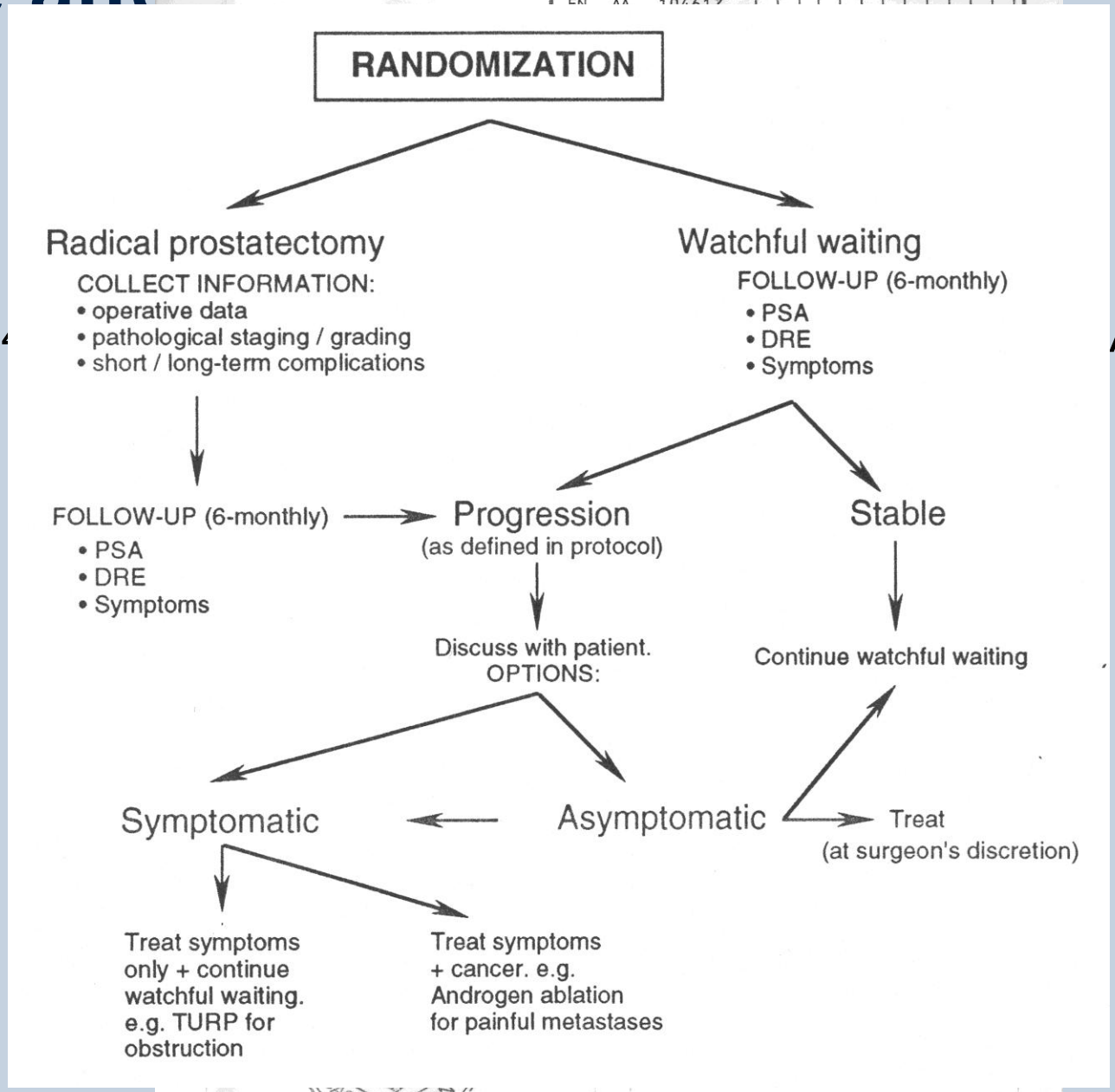
- 199 AP



The attempts

- 19

Evaluation of radical prostatectomy *versus* 'watchful-waiting' in the management of early, organ-confined prostate cancer

PROPOSAL FOR A MULTI-CENTRE RANDOMISED TRIAL

F. C. HAMDY AND D. E. NEAL
University Urology Unit
Freeman Hospital, Newcastle upon Tyne, NE7 7DN.

J. DONOVAN, T. J. PETERS, J. COAST,
I. M. HARVEY AND S. J. FRANKEL
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N. J. R. GEORGE
Department of Urology
Whitington Hospital, Manchester, M20 8LR.

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Department of Urology
Southmead Hospital, Bristol BS10 5NB.

M. HEHIR
Department of Urology
Stirling Royal Infirmary, Stirling, FK8 2AU.

A. GRANT
Health Services Research Unit
Dept. of Public Health
Aberdeen AB9 2ZD

The opportunities

- 1996: HTA commissioned 2 systematic reviews on screening and treatment of prostate cancer

  [Selley et al 1997; Melia et al, 1997]
- Recommendations:
  - Insufficient evidence to suggest benefits of screening as publica health policy
  - Randomised controlled trials of screening and treatment are required urgently
- 1997: Call from HTA
  - Primary research projects
  - Screening for prostate cancer

ProtecT study design

Feasibility *(Donovan et al)*

- To evaluate the feasibility of a RCT of the major treatments for localised prostate cancer
  1. Is community-based PSA testing possible in the UK?
  2. Would men accept randomisation to surgery, radiotherapy and a non-immediate intervention arm
  3. Could nurses recruit men as effectively as urologists?

Main Trial *(Hamdy et al)*

- To conduct a major PSA-testing programme and 3-arm randomised trial of treatment effectiveness in prostate cancer
  - Active Monitoring *versus* surgery *versus* DXT
  - 1ry end-point: survival at 10 years

Both grants submitted December 1997

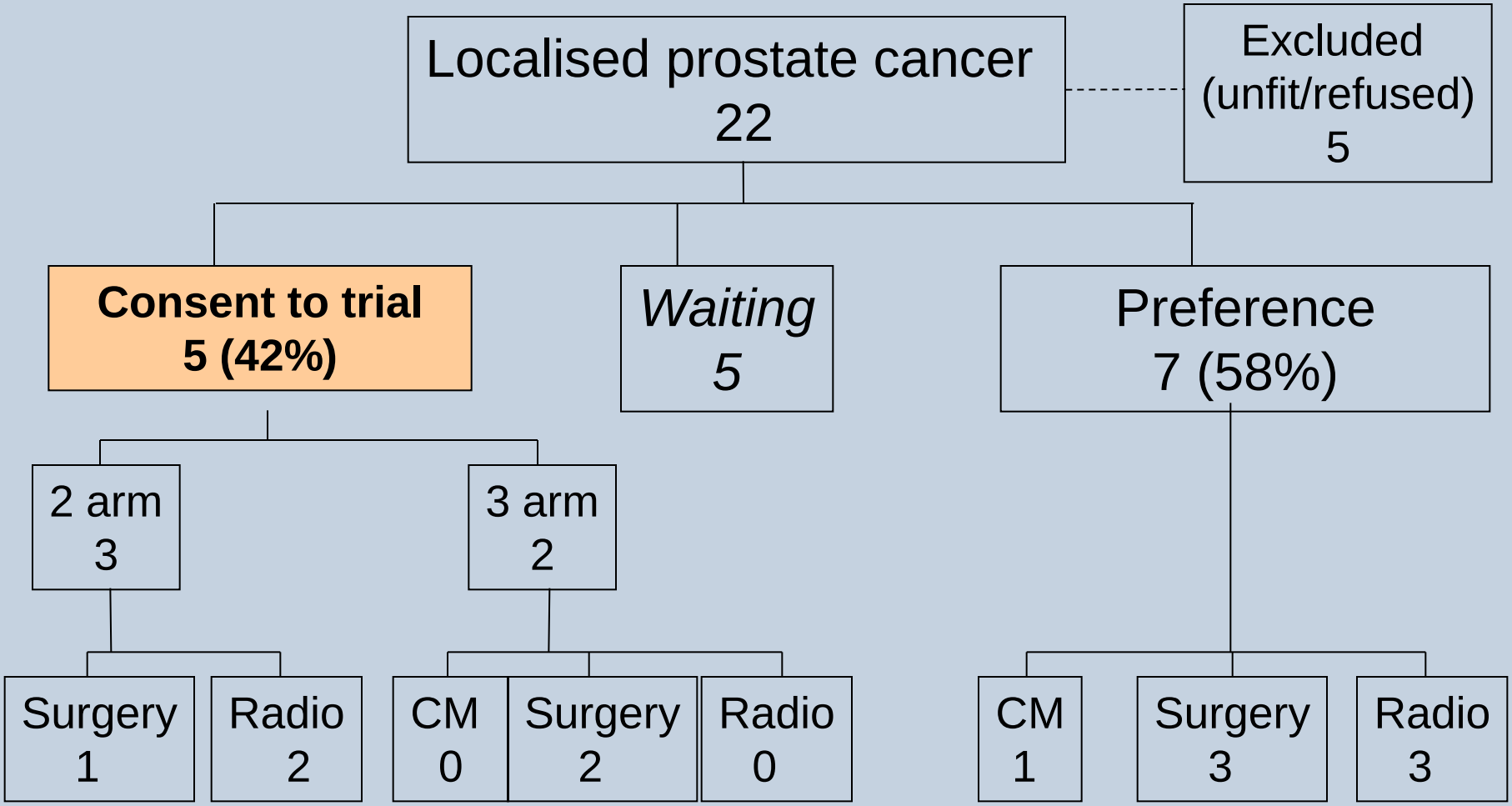
ProtecT: the milestones

June 1998:

- Feasibility grant awarded
- (Bristol, Newcastle, Sheffield)

- Main trial grant on hold, pending results of feasibility

Recruitment by Feb 2000



ProtecT randomisation rates

Date	Eligible	Consent to randomisation	Accept allocation
October 1999 to May 2000	up to 30	ranged 30-40%	ranged 60-70%
August 2000	45	23 (51%)	18 (78%)
November 2000	67	39 (58%)	30 (77%)
January 2001	83	51 (61%)	38 (75%)
May 2001	155	108 (70%)	76 (70%)

- Changes…
  - Order of treatments
  - Present study as a solution to the problem
  - Terminology
  - Non-radical arm: not ‘watchful waiting’

- Changes…
  - Equalise treatments
  - Challenge patient preferences
  - Randomise by end of appointment
  - Non-radical arm: ‘active monitoring’

Qualitative Research Methods

- Scrutiny of information appointments and follow-up interviews
- Extraction of themes relating to maximising recruitment
  - Lay beliefs about prostate cancer
  - Perceptions of treatment
  - Understanding/acceptability of randomisation

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

It's not just what you say, it's also how you say it: Opening the 'black box' of informed consent appointments in randomised controlled trials

Julia Wade [a,*], Jenny L. Donovan [a], J. Athene Lane [a], David E. Neal [b], Freddie C. Hamdy [c]

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[b] University of Cambridge Department of Oncology, Box 279 (S4), Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom
[c] Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

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Quality improvement report

Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study

Jenny Donovan, Nicola Mills, Monica Smith, Lucy Brindle, Ann Jacoby, Tim Peters, Stephen Frankel, David Neal, Freddie Hamdy for the Protect Study Group

Editorial by Thornton *Papers* pp 737,7

Abstract

[illegible] randomised trials is often [illegible] important trials are not mounted

Background

The randomised controlled trial is the widely acknowledged design of choice for evaluating the effectiveness

Qualitative Research

ELSEVIER

Controlled Clinical Trials 24 (2003) 272–282

Controlled Clinical Trials

Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study

Nicola Mills, Ph.D.[a,*], Jenny L. Donovan, Ph.D.[a], Monica Smith, M.A.[b], Ann Jacoby, Ph.D.[c], David E. Neal, M.S., F.R.C.S.[d], Freddie C. Hamdy, M.D., F.R.C.S. Ed.[e]

Equipoise

ELSEVIER

[illegible] Clinical Epidemiology 56 (2003) 605–609

Journal of Clinical Epidemiology

Who can best recruit to randomized trials? Randomized trial comparing surgeons and nurses recruiting patients to a trial of treatments for localized prostate cancer (the ProtecT study)

Jenny L. Donovan[a,*], Tim J. Peters[b], Sian Noble[a], Philip Powell[c], David Gillatt[d], Steven E. Oliver[a], J. Athene Lane[a], David E. Neal[e], Freddie C. Hamdy[f], for the ProtecT Study Group

Research Nurses

ProtecT: the milestones

- January 2001:
  - Invited by HTA to submit full proposal

£13m prostate cancer drive

MINISTERS will today launch a £13million drive to find an effective treatment for prostate cancer.

Experts from the universities of Sheffield, Newcastle and Bristol will head a seven-year study involving 230,000 men in a bid to beat the 'forgotten disease' which kills 10,000 men every year.

Public health minister Yvette Cooper will introduce a new 'informed choice' leaflet to give men more information about the blood test used to detect prostate cancer.

Tomorrow the Government will unveil a new website where men who have discovered they have the disease can watch 'video diaries' in which other sufferers recount their experiences.

By **Graeme Wilson**

Ministers hope this will ease the anxieties of newly-diagnosed patients and help inform them about what lies ahead.

The moves follow the Daily Mail's Dying of Embarrassment campaign, which saw readers raising £1million for prostate research.

Ministers believe the treatment trials – which will start later this month – could offer real hope to men diagnosed with a disease which is soon expected to overtake lung cancer as the biggest cause of male cancer death. At present, doctors do not know which of the three main approaches – active monitoring, radiotherapy or removal of the prostate – is the most effective.

There is similar uncertainty over the test for the disease, which measures PSA (prostate specific antigen) in the blood.

● The blood test information leaflet is available from two websites – www.doh.gov.uk/cancer or the National Electronic Library for Health on www.nelh.nhs.uk/psatesting/. The video diary website is www.dipex.org.

g.wilson@dailymail.co.uk

The ProtecT study

(*Pro*state *te*sting for *c*ancer and *T*reatment)

Principal Investigators:

FC Hamdy (Oxford)
JL Donovan (Bristol)
DE Neal (Cambridge)

Study Co-ordinator:
Athene Lane (Bristol)

1999-2008

Bristol
Birmingham
Cambridge

Cardiff
Edinburgh
Leeds

Leicester
Newcastle
Sheffield

ProtecT study design

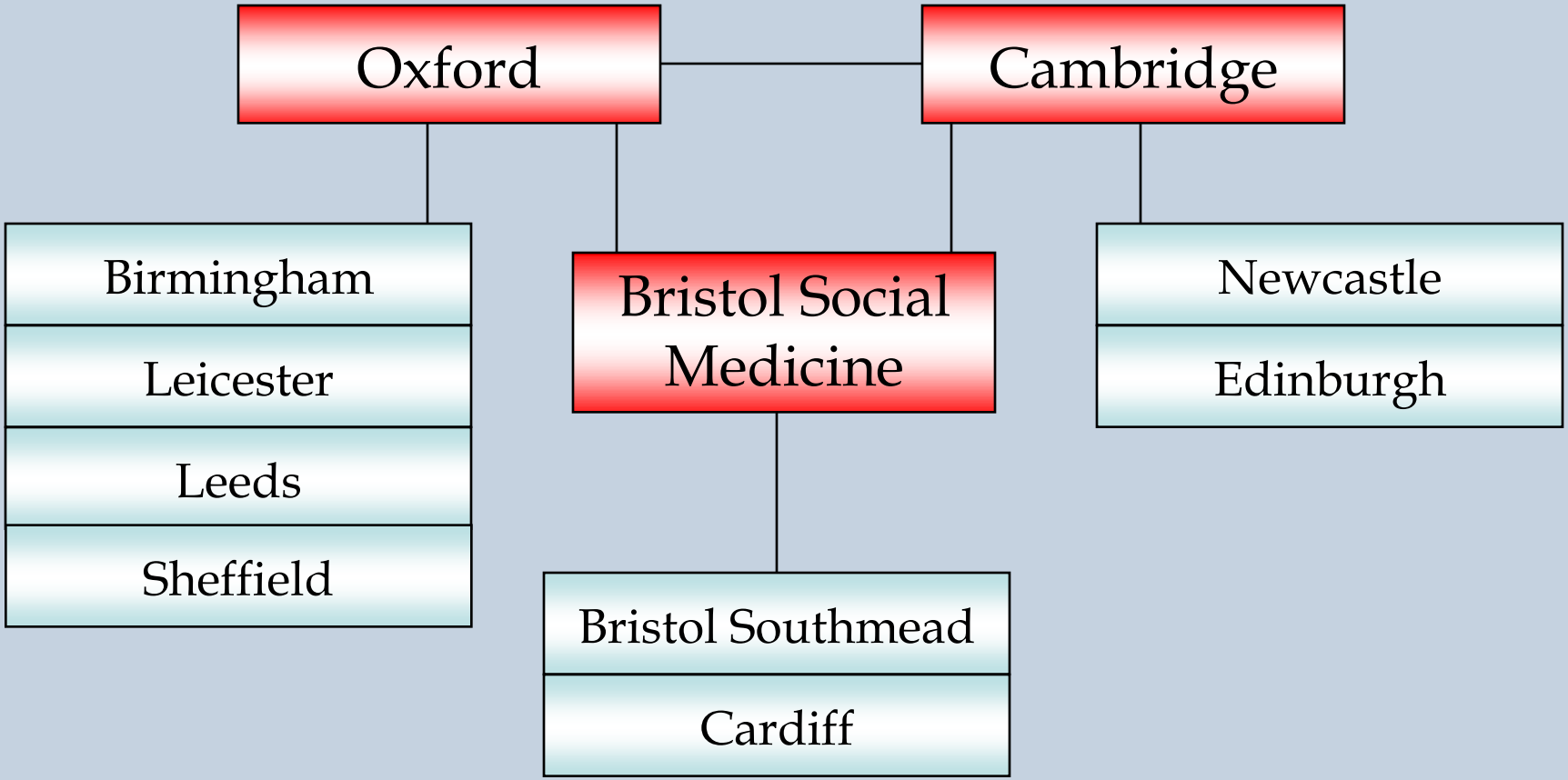
Pilot (1999-2001)

- To evaluate the feasibility of a RCT of the major treatments for localised prostate cancer
  1. Is community-based PSA testing possible in the UK?
  2. Would men accept randomisation to surgery, radiotherapy and a non-immediate intervention arm
  3. Could nurses recruit men as effectively as urologists?

Main Trial (2001-2008)

- To conduct a major 3-arm randomised trial to test the effectiveness and cost-effectiveness of radical prostatectomy, radical conformal radiotherapy and active monitoring for localised prostate cancer
  - Survival at 5, 10 and 15 years
  - Disease progression (biochemical and clinical)
  - Impact of treatment: urinary/bowel symptoms, quality of life, sexual function, complications
  - Economic evaluation
  - Biorepository for basic/translational research
  - Qualitative evaluation of recruitment and experience

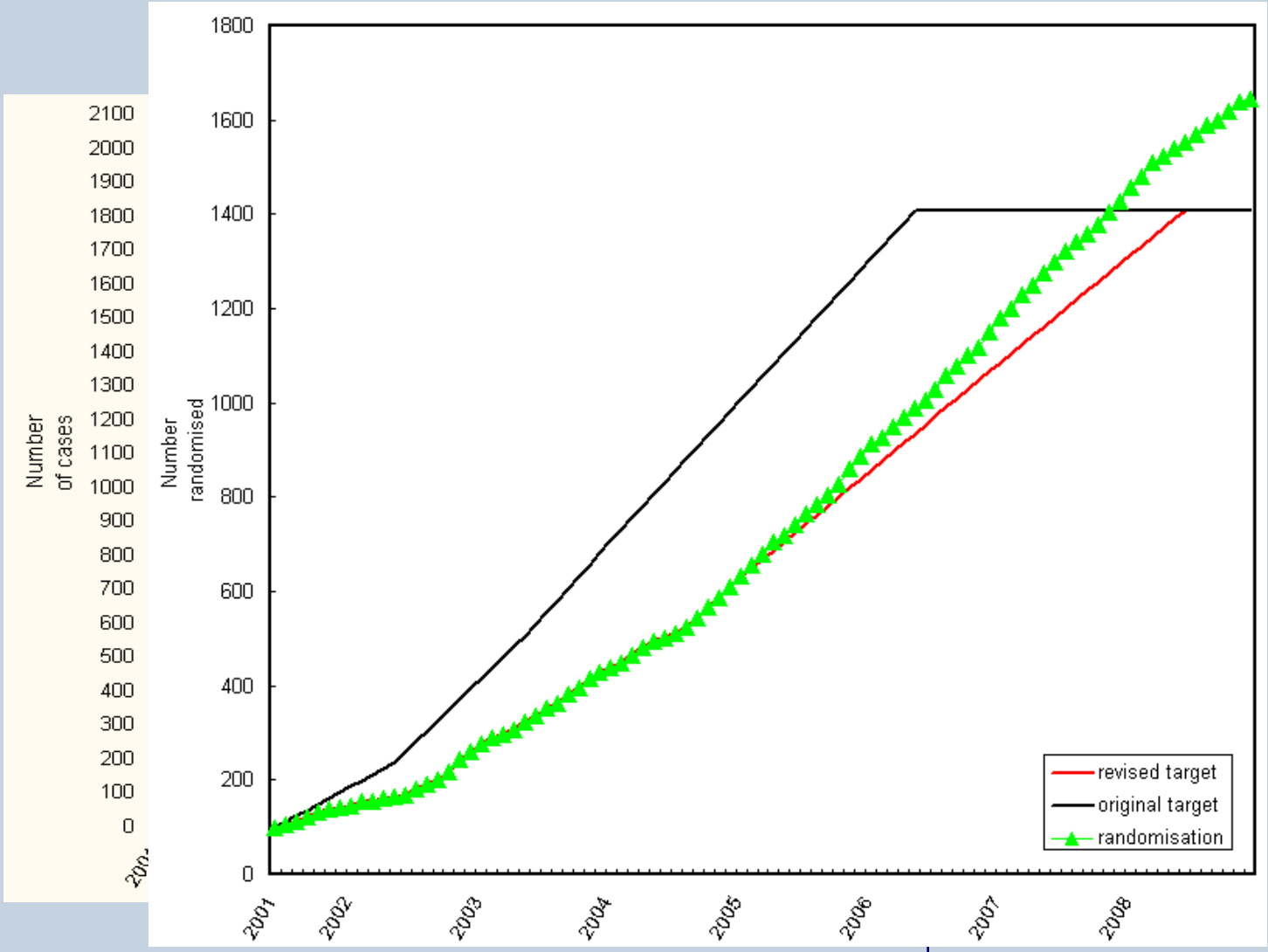
ProtecT
Study hubs & centres



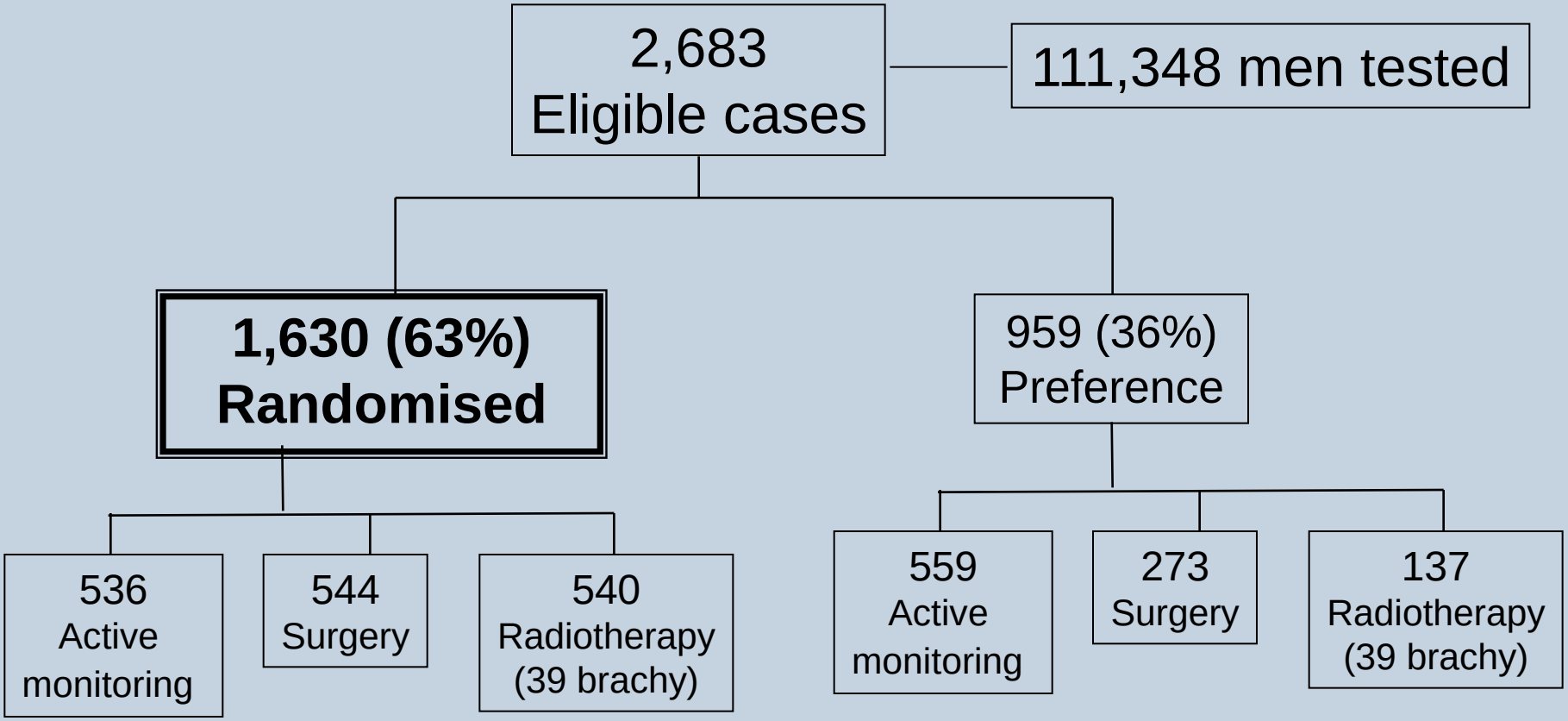
ProtecT: The roles

- Trial Co-ordinator: Athene Lane
- Lead Nurse Group
- Clinicians group
- Trial Steering Committee: Chair: Mike Baum
- Data Monitoring Committee: Chair: Adrian Grant
- Quality Control in RT
- Site monitoring group
- Specimen Management Group
- Pathology Group
- Training Sessions for nurses/secretaries
- Database training

Accrual of cases 2001-2006



ProtecT study accrual



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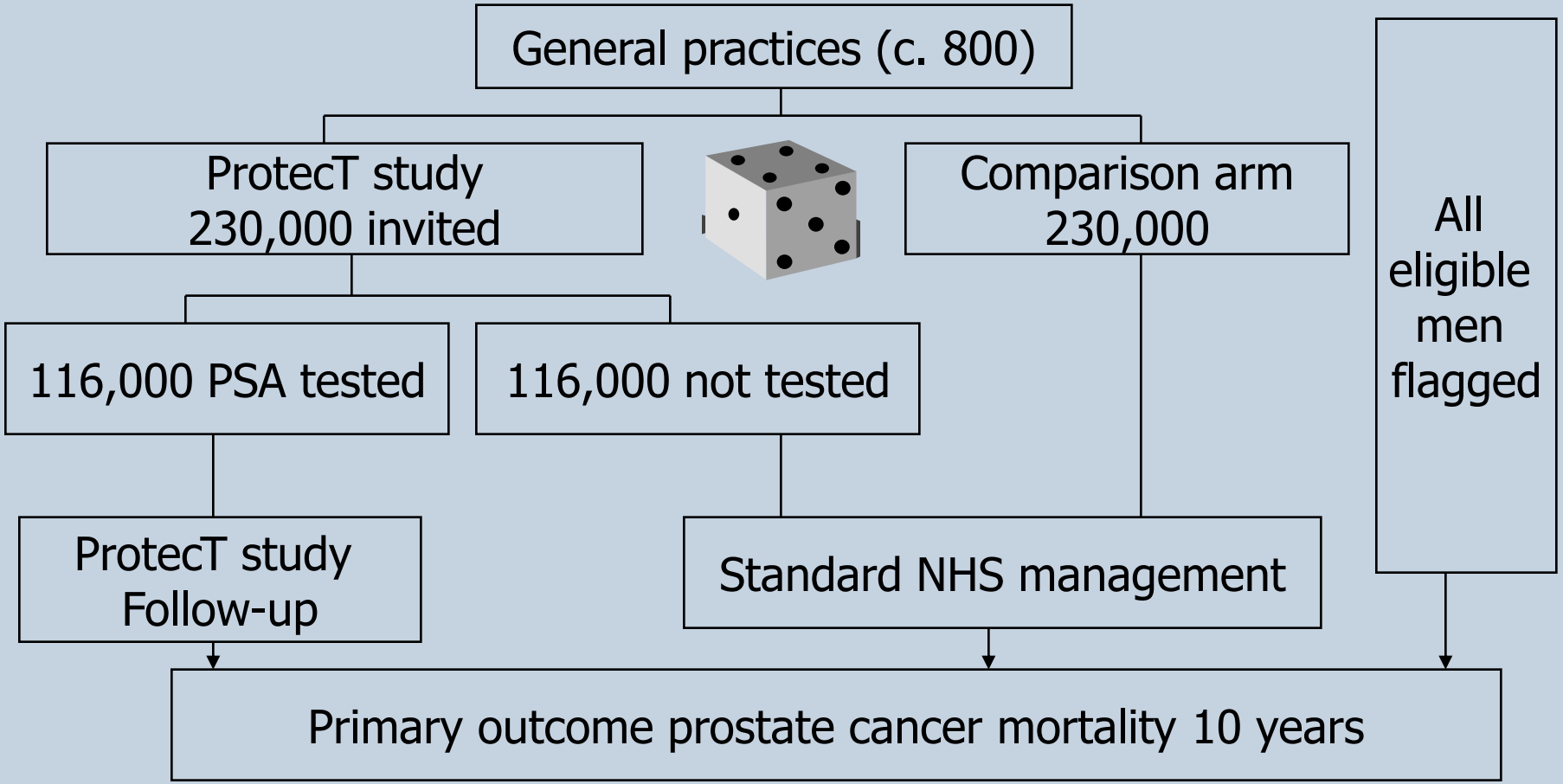
CAP and ProtecT



ProtecT outcomes: when?

ProtecT - opportunities

ProtecT Research Resources

- 110,000 men aged 50-69
  - Epidemiological and biological data
  - Serum, Plasma, DNA
- 3000 prostate cancers
  - Clinical data and long-term follow-up
  - Tissue, serum, plasma, DNA

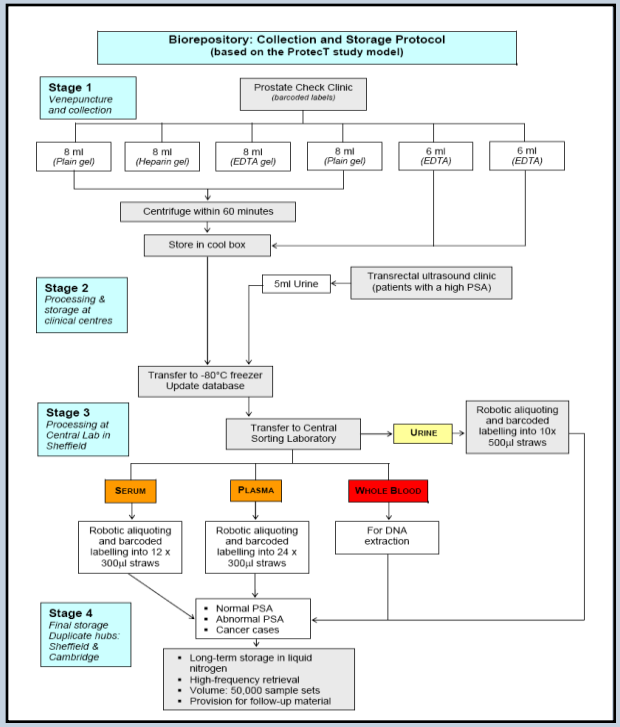
Other Research resources

- Case-mix of patients and controls recruited from urological clinics in the collaborative (>1000 sets)
- Sequential blood sampling: serum, plasma, DNA)
- Robust electronic database

Funding for biorepository equipment

- State-of-the-art robotic aliquoting and storage

Processing, storage and Database



SOPs

Dedicated Website for access by authorised partners

Long-term storage

Authentication

Database on dedicated Oxford University Server

ProtecT Network linked research 1999-2011

EUROPEAN JOURNAL OF CANCER 46 (2010) 3095–3101

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available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Latest results from the UK trials evaluating prostate cancer screening and treatment: The CAP and ProtecT studies

J.A. Lane [a,*], *F.C. Hamdy* [b], *R.M. Martin* [a,c], *E.L. Turner* [a], *D.E. Neal* [d], *J.L. Donovan* [a]

[a] *School of Social and Community Medicine, University of Bristol, Bristol, UK*
[b] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK*
[c] *MRC Centre for Causal Analysis in Translational Epidemiology, University of Bristol, Bristol, UK*
[d] *Oncology Centre, Addenbrooke's Hospital, Cambridge, UK*

Genome Wide Association Study Design
PIs: Ros Eeles, Doug Easton- stages 1 & 2 funded CR-UK

Stage 1: 550,000 tagged SNPs (Ilumina Infinium)

"High-risk" prostate cancer cases
Dx <60/FH+ve (n=2000)

compared with

ProtecT controls
(age>60 PSA<0.5ng/ml)
(n=2000)

Compare genotype frequencies
P<0.05

Stage 1 Genotyping completed

Stage 2: ~47 120 SNPs

4,000 prostate cancer cases

Australian case/control
Australian dx<55 (2000)
UK dx<60 (1300)
UK systematic series (700)

compared with

4,000 controls

Australian
UK case control study
ProtecT

nature genetics

Identification of seven new prostate cancer susceptibility loci through a genome-wide association study

Rosalind A Eeles[1,2,*], Zsofia Kote-Jarai[1], Ali Amin Al Olama[3,52], Graham G Giles[4,5,52], Michelle Guy[1,52], Gianluca Severi[4,5,52], Kenneth Muir[6,52], John L Hopper[5,52], Brian E Henderson[7,52], Christopher A Haiman[7,52], Johanna Schleutker[8,52], Freddie C Hamdy[9,52], David E Neal[10,52], Jenny L Donovan[11,52], Janet L Stanford[12,13,52], Elaine A Ostrander[14,52], Sue A Ingles[15,52], Esther M John[16,52], Stephen N Thibodeau[17,52], Daniel Schaid[17,52], Jong Y Park[18,52], Amanda Spurdle[19,52], Judith Clements[20,52], Joanne L Dickinson[21,52], Christiane Maier[22,52], Walther Vogel[22,52], Thilo Dörk[23,52], Timothy R Rebbeck[24,52], Kathleen A Cooney[25,52], Lisa Cannon-Albright[26,52], Pierre O Chappuis[27,52], Pierre Hutter[28,52], Maurice Zeegers[29,30,52], Radka Kaneva[31,52], Hong-Wei Zhang[32,52], Yong-Jie Lu[33,52], William D Foulkes[34,52], Dallas R English[5,52], Daniel A Leongamornlert[1], Malgorzata Tymrakiewicz[1], Jonathan Morrison[3], Audrey T Ardern-Jones[2], Amanda L Hall[1,2], Lynne T O'Brien[1], Rosemary A Wilkinson[1], Edward J Saunders[1], Elizabeth C Page[1,2], Emma J Sawyer[1], Stephen M Edwards[1,51], David P Dearnaley[1,2], Alan Horwich[1,2], Robert A Huddart[1,2], Vincent S Khoo[1,2], Christopher C Parker[1,2], Nicholas Van As[2], Christopher J Woodhouse[2], Alan Thompson[2], Tim Christmas[2], Chris Ogden[2], Colin S Cooper[1], Melissa C Southey[35], Artitaya Lophatananon[6,36], Jo-Fen Liu[6], Laurence N Kolonel[37], Loic Le Marchand[37], Tiina Wahlfors[8], Teuvo L Tammela[38], Anssi Auvinen[39], Sarah J Lewis[11], Angela Cox[40], Liesel M FitzGerald[12,21], Joseph S Koopmeiners[12,41], Danielle M Karyadi[14], Erika M Kwon[14], Mariana C Stern[15], Roman Corral[15], Amit D Joshi[15], Ahva Shahabi[15], Shannon K McDonnell[17], Thomas A Sellers[18], Julio Pow-Sang[18], Suzanne Chambers[42], Joanne Aitken[42,43], R A (Frank) Gardiner[44], Jyotsna Batra[20], Mary Anne Kedda[20], Felicity Lose[19,20], Andrea Polanowski[21], Briony Patterson[21], Jürgen Serth[45], Andreas Meyer[46], Manuel Luedeke[22], Klara Stefflova[24], Anna M Ray[25], Ethan M Lange[47], Jim Farnham[26], Humera Khan[29], Chavdar Slavov[48], Atanaska Mitkova[31], Guangwen Cao[32], The UK Genetic Prostate Cancer Study Collaborators/British Association of Urological Surgeons' Section of Oncology[49], The UK ProtecT Study Collaborators[50], The PRACTICAL Consortium[51] & Douglas F Easton[3]

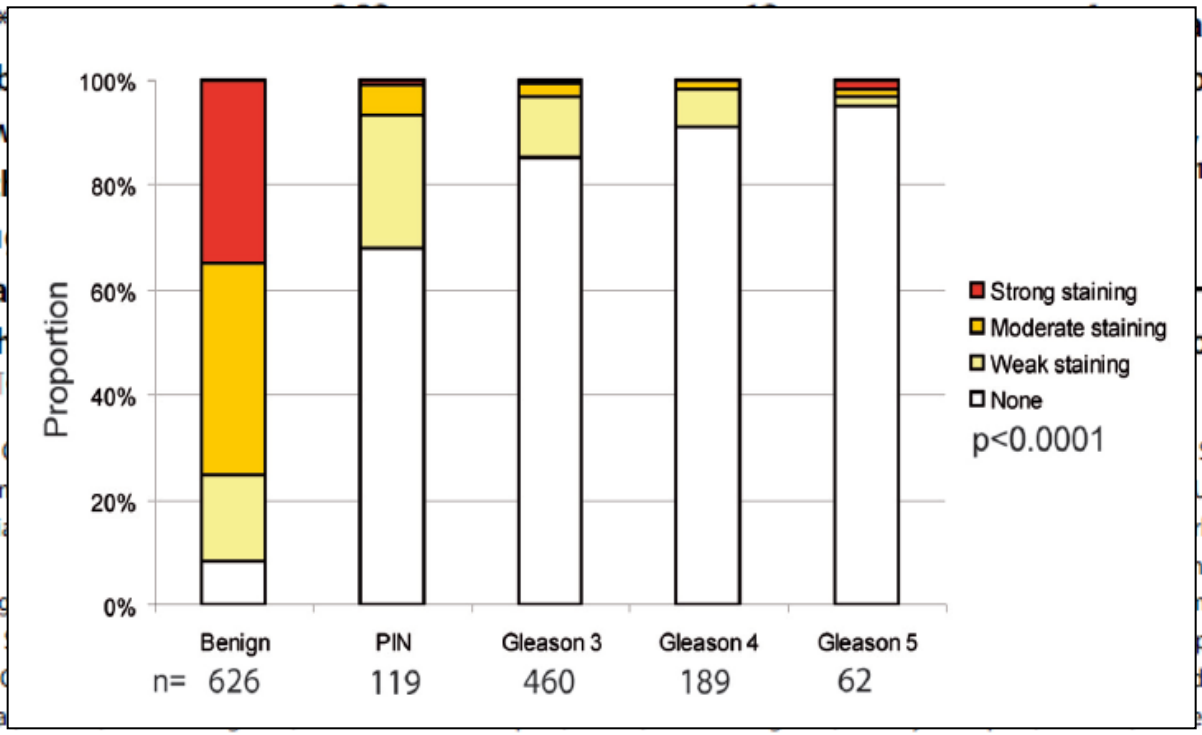
OPEN ACCESS Freely available online

PLoS one

The rs10993994 Risk Allele for Prostate Cancer Results in Clinically Relevant Changes in Microseminoprotein-Beta Expression in Tissue and Urine

Hayley C. Whitaker[1]*, ...anna Burge[1], Anne George[1], Elizab... ...orzata Tymrakiewicz[2,3], Edw... Geoffrey J. Lindeman[6], D. Garetl... [10], Virginia Clowes[11], Fiona Dou... Izatt[16], Huw Dorkins[17], Alison Ma... Hans Lilja[22], Douglas Easton[23], Th... orators[¶b], UK GPCS Collaborators[¶]

1 Uro-Oncology Research Group, ... Surrey, United Kingdom, 3 Royal Marsden NHS Foundation... United Kingdom, 5 Peter Maccallum Cancer Centre, Victoria... rkville, Victoria, Australia, 7 Genetic Medicine, Manchester ... hester, United Kingdom, 8 Catalonian Institute of Oncolog... npton, United Kingdom, 10 NorthShore University Health ... pital, Cambridge, United Kingdom, 12 Institute of Human ... dom, 14 Oxford Regional Genetics Centre, Churchill Hospita... d Kingdom, 17 Kennedy Galton Centre, Northwick Park Hospital, Harrow, Middlesex, United Kingdom, 18 Institute of Child Health, London, United Kingdom, 19 Prince of Wales Hospital, Sydney, New South Wales, Australia, 20 Repatriation General Hospital, Adelaide, Australia, 21 Familial Cancer Service, Westmead Hospital, Westmead, New South Wales, Australia, 22 Departments of Clinical Laboratories, Surgery, Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, United States of America, 23 Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom



British Journal of Cancer (2011) 00, 1–6

www.bjcancer.com

Full Paper

Suitability of PSA-detected localised prostate cancers for focal therapy: experience from the ProtecT study

JWF Catto[1,16], MC Robinson[2,16], PC Albertsen[3,16], JR Goepel[4], MF Abbod[5], DA Linkens[6], M Davis[7], DJ Rosario[1], AY Warren[8], M Varma[9], DF Griffiths[9], KM Grigor[10], NJ Mayer[11], JD Oxley[12], NS Deshmukh[13], JA Lane[7], C Metcalfe[7], JL Donovan[7], DE Neal[14] and FC Hamdy*[,15] on behalf of the ProtecT study group

[1]Academic Urology Unit and Institute for Cancer Studies, University of Sheffield, UK; [2]Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle, UK; [3]Department of Surgery, University of Connecticut Health Center, CT 06030, USA; [4]Department of Pathology, Royal Hallamshire Hospital, Sheffield, UK; [5]School of Engineering and Design, Brunel University, UK; [6]Department of Automatic Control and Systems Engineering, University of Sheffield, UK; [7]School of Social & Community Medicine, University of Bristol, UK; [8]Department of Pathology, University of Cambridge, UK; [9]Department of Pathology, University Hospital of Wales, Cardiff, UK; [10]Department of Pathology, Western General Hospital, Edinburgh, UK; [11]Department of Pathology, University of Leicester, Leicester, UK; [12]Department of Cellular Pathology, Southmead Hospital, Bristol, UK; [13]CRUK Institute of Cancer Studies, University of Birmingham, UK; [14]Department of Oncology, University of Cambridge, UK; [15]Nuffield Department of Surgical Sciences, University of Oxford, Headley Way, Headington, Oxford OX3 9DU, UK

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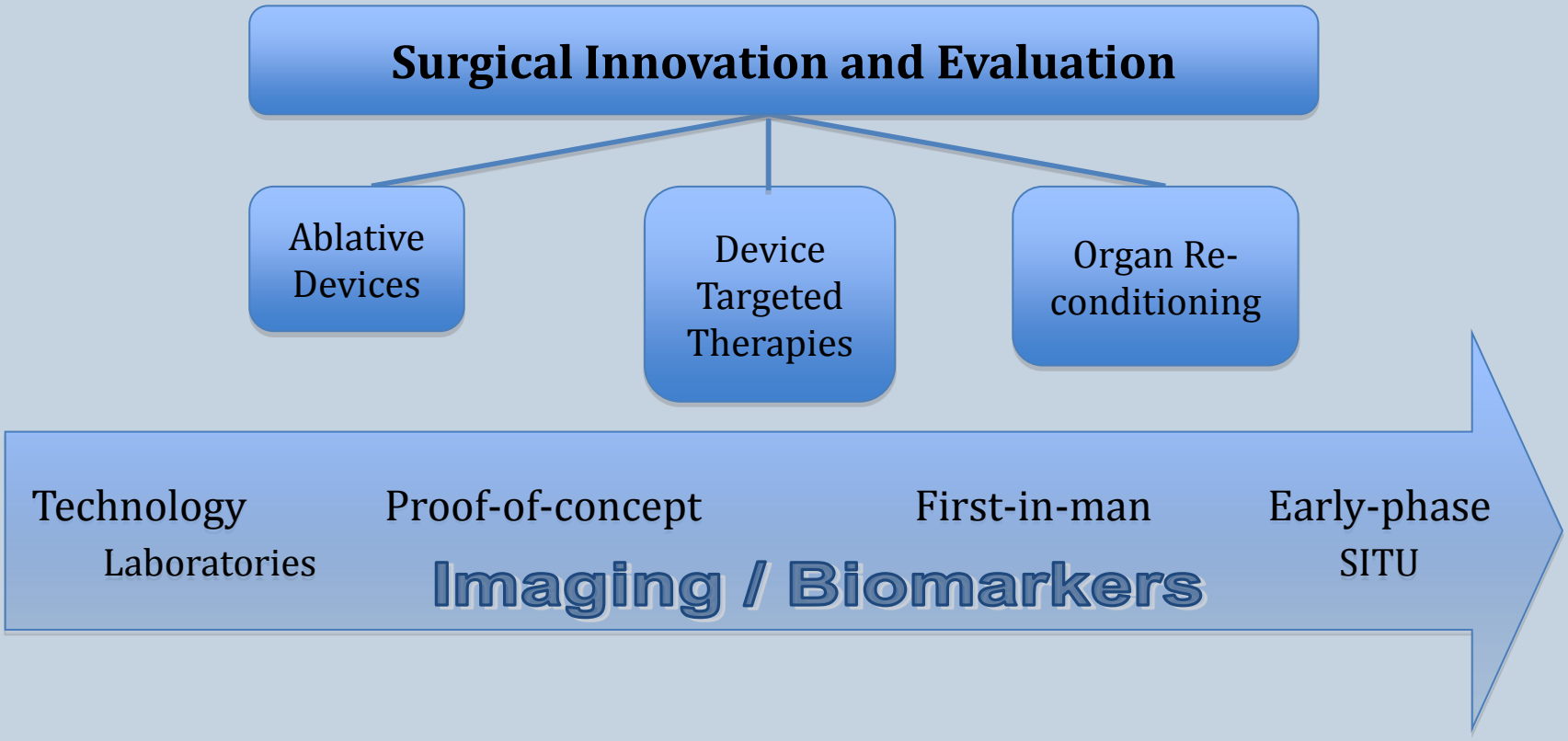
Oxford Biomedical Research Centre



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ProtecT: lessons for surgeons (1)

- Come down from Ivory Tower, then use explosives to destroy, and stay at ground “0”
- Find the question
- Find out who to work with as well who to avoid
- Invite your worst enemies to join – better to have them inside the tent p******* out than outside the tent p******* in
- Forget ego, motivate others and sit at a round table
- Do what you are best at doing and don’t be amateurish

ProtecT: lessons for the surgeons (2)

- Pick your partners outside surgery
  - A credible trials unit
  - A multidisciplinary team
    - Health service researcher
    - Statistician
    - Health economist
    - Qualitative researcher
    - Data manager
  - A good trial co-ordinator
  - A competent TSC Chair
  - A competent DMC Chair
- Show that ‘it can be done’…
- Choose the right funder and build a good relationship with them
- Build a comprehensive, high quality biorepository
- Persevere, do not give up, and finish the race!...

ProtecT: lessons for the surgeons (3)

- Engage, motivate and empower research nurses
- Be ruthless with quality of research, consult colleagues, practice humility, shed pedestrian work, have high expectations
- Train recruiters and monitor them
- Evaluate impact of new evidence and guidelines
- Keep the fire going, become a ‘role model’ for trainees
- Cynicism, scepticism and complacency must belong to the past
- Be clear about the end, and surround yourself with people who have the means

If you are going through hell, keep going…

Do not do just what you can, but reach what you cannot…

The Future?

“ Traveller, there is no path. The path is made by walking…”

Antonio Machado

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Screening and
in a Rando

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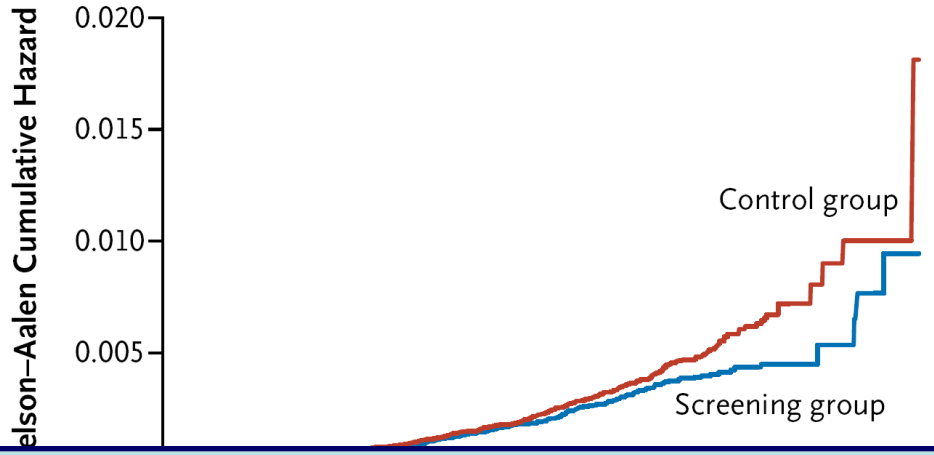

To prevent one man from dying of prostate cancer:

- **1400 need to be screened**
- **48 need to be treated**

Figure 2. Cumulative Risk of Death from Prostate Cancer.

As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.