

CANCER  
RESEARCH  
UK



**NHS**  
*National Institute for  
Health Research*

Effect of a lower-intensity PSA-based  
screening intervention on prostate  
cancer mortality: the CAP randomized  
clinical trial

Edinburgh & Lothians Prostate Cancer Support Group

8<sup>th</sup> Nov 2018



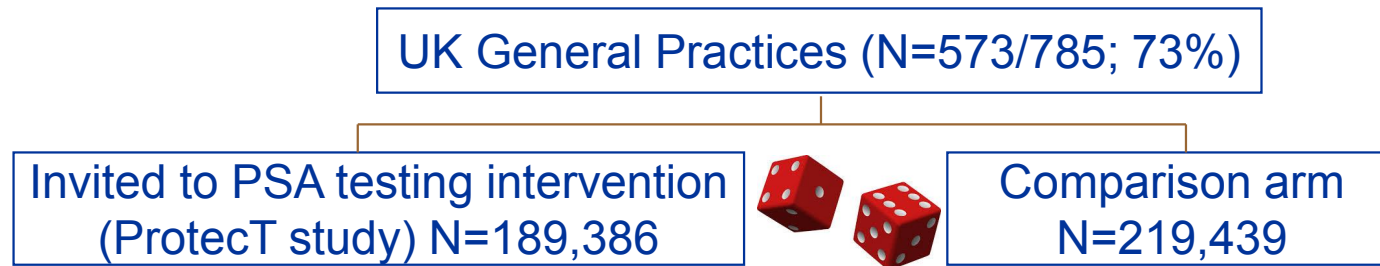
# Context of PSA based screening

- ERSPC and PLCO highlighted that the balance of benefits and harms in men remains close
- Small mortality benefit with 2-4 yearly repeated screening, 5 instead of 6 deaths in 1000
- Overdiagnosis between 20-50%, increasing with the intensity of screening
- Men receiving surgery or radiotherapy experience serious impacts on sexual, urinary & bowel function - clearly quantified in ProtecT

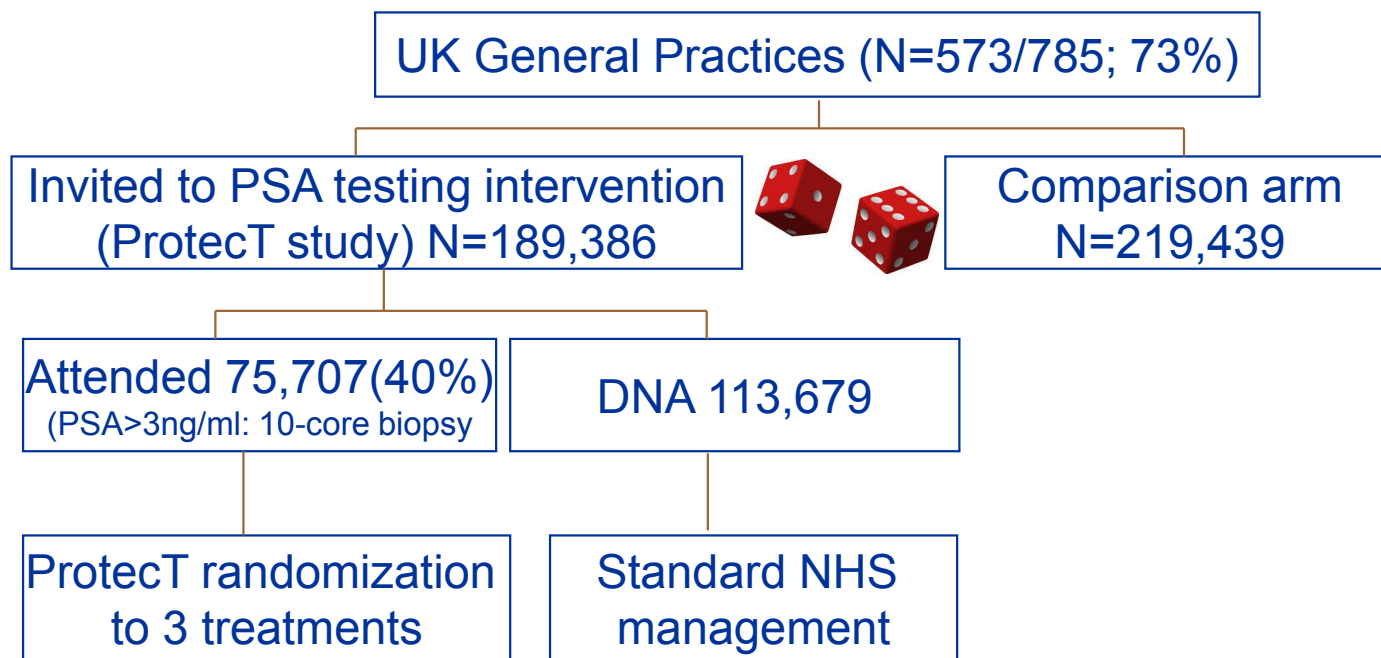
# Objectives

- Estimate the effect of an invitation to a single PSA-screen (vs standard practice) on median 10-yr:
  - PCa-specific mortality (1ary outcome)
  - All-cause mortality (2ary outcome)
  - PCa detection, stage & grade (2ary outcomes)
- Other 2ary outcomes not reported here: PCa & all-cause mortality at 15 yrs, HRQoL, cost-effectiveness

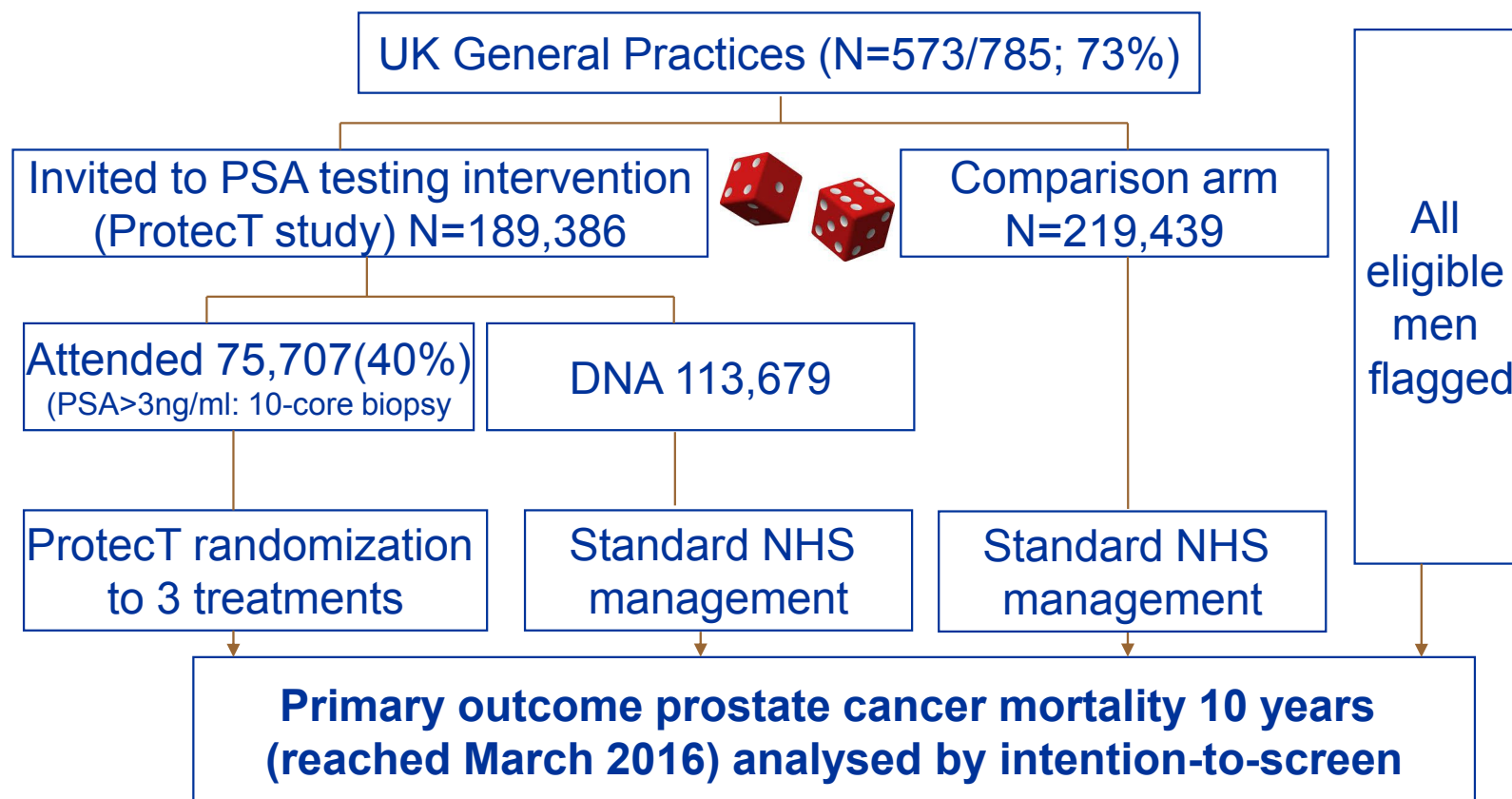
# CAP (2001-2009, Zelen design)



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*Power to detect an overall PCa mortality rate ratio (ORR) of 0.84, 80% power (5% alpha)*

# Post-randomization exclusions did not introduce selection bias

No important differences in:

- Characteristics of randomised practices that did vs did not agree to participate
- Characteristics of intervention vs control-group practices or men
- The distribution of non PCa deaths between intervention vs control-group

# Adherence

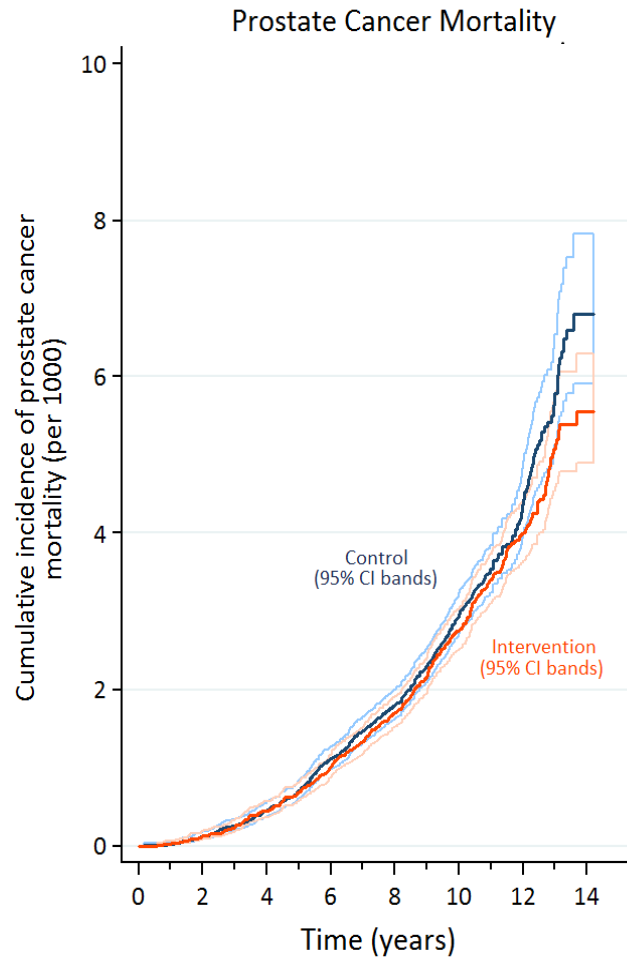
- Of 189,386 intervention group men:
  - 75,707 (40%) attended for PSA-testing
  - 67,313 (36%) had a blood sample taken
  - 64,436 had a ‘valid’ test result
- Of these 64,436 men:
  - 6,857 (11%) - PSA 3-19.9ng/ml ( ProtecT eligible )
  - Of whom 5,850 (85%) had a prostate biopsy
- Cumulative PSA testing in controls indirectly estimated at  $\approx 10-15\%$  over 10-years

# **PRIMARY ANALYSIS**

# Effect of CAP PSA invitation intervention on 10 yr median PCa mortality

- PCa deaths
  - Intervention arm: n = 549 (0.30/1000 pyrs)
  - Control arm: n = 647 (0.31/1000 pyrs)
- Rate ratio, ITT
  - 0.96 (95% CI: 0.85, 1.08); p=0.50
- Rate difference per 1000 person years
  - - 0.013 (95% CI: - 0.047, 0.022)

# Kaplan Meier cumulative PCa mortality



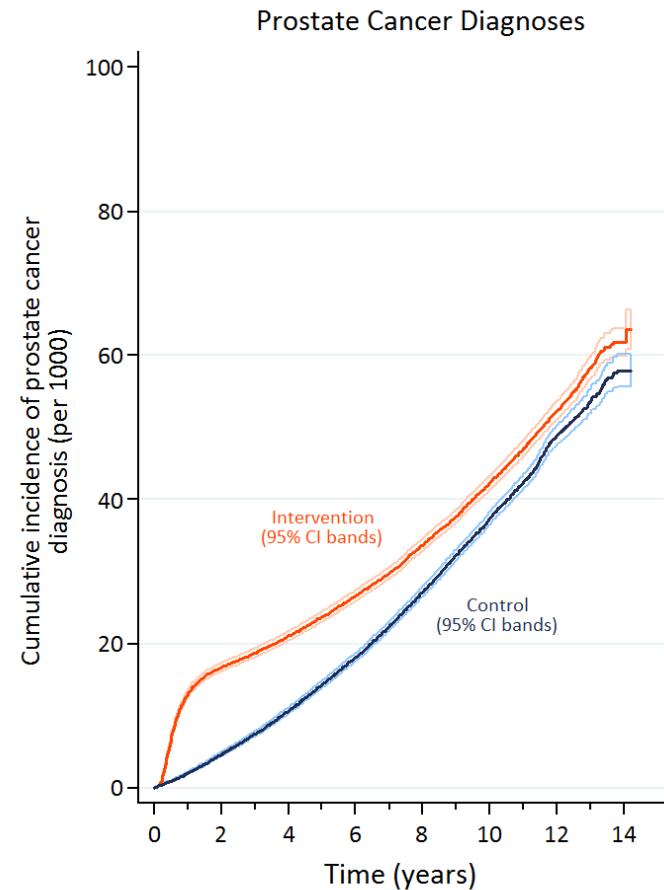
**Median (IQR) follow-up:**  
Int: 10.03 (8.80, 11.50)  
Control: 9.92 (8.74, 10.93)

**Non-proportional hazards:**  $p=0.38$

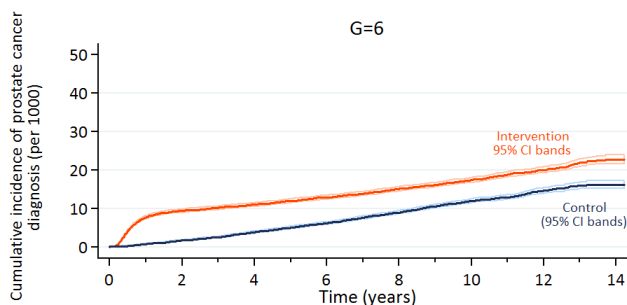
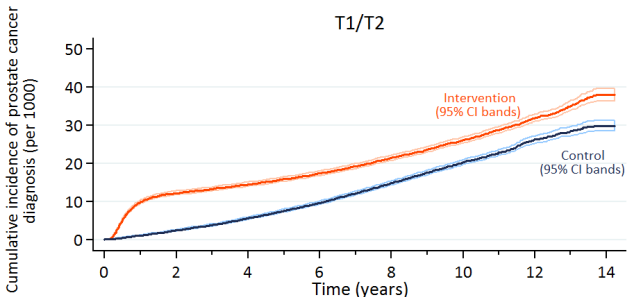
# **SECONDARY ANALYSIS**

# Effect of the CAP PSA invitation intervention on cumulative PCa risk

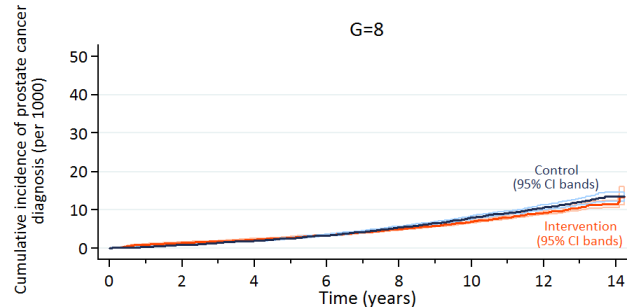
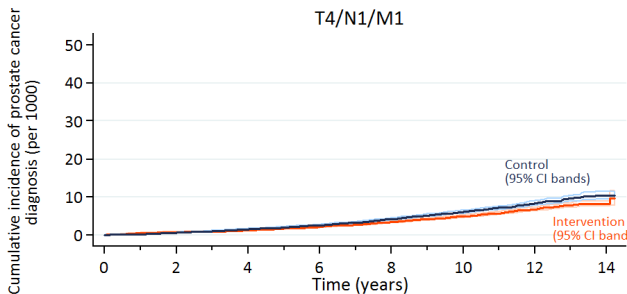
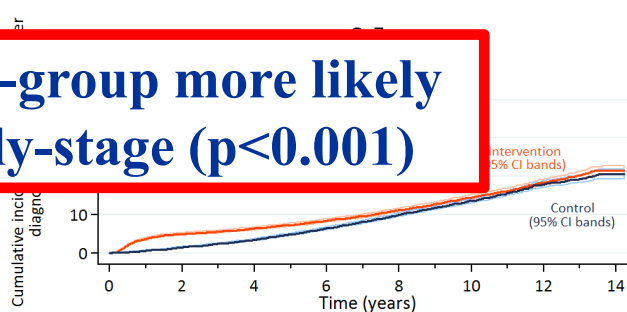
- Incident PCa
  - Intervention: n=8,054 (4.3%)
  - Control: n = 7,853 (3.6%)
- Detection per 1000 pyrs:
  - 4.45 (95% CI: 4.36, 4.55) vs. 3.80 (3.72, 3.89)
- Difference per 1000 pyrs
  - 0.65 (0.52, 0.78; p<0.001)
- During screening phase
  - 10.42 v 2.18 (p<0.001)



# Cumulative incidence by stage & grade



**PCa in the intervention-group more likely to be low-grade & early-stage ( $p < 0.001$ )**



# Other secondary/subgroup analysis

- IV analysis (causal effect amongst attenders)
  - 0.93 (95% CI 0.67, 1.29);  $p=0.66$
- All cause mortality:
  - Intervention arm:  $n = 25,459$  (13.7/1000 pyrs)
  - Control arm:  $n = 28,306$  (13.5/1000 pyrs)
  - RR: 0.99: 95% CI 0.94, 1.03;  $p=0.49$
- No differences in effect by age or SES
- Intervention-related deaths
  - 8 in the intervention-group, 7 in controls

# Missed lethal cancers in the intervention-group

- Of 549 men who died in the intervention-group
  - Attended a screening appointment: 188 (34%)
- Of the 188 attendees who died, 129 (69%) had not been identified by a PSA test:
  - Not received a PSA test: n = 42
  - Eligible men not receiving a biopsy: n = 15
  - PSA level < 3ng/ml: n = 68
  - Benign prostate biopsy result: n = 4

# Limitations

- Single screen - multiple rounds in ERSPC & PLCO
  - But over-detection with repeat screens
- Lower-intensity strategy under-detected lethal cases
  - High intensity wrt TRUS biopsy: 85% adherence; 10-core
  - Identification of this is a design strength
- 40% adherence vs 59-69% in ERSPC
  - IV analysis (effect of attendance) found similar results
- mpMRI will improve diagnostic pathway
- Median 10-yr follow-up may be too short
  - In ProtecT, PCa mortality was 1% across treatments
  - If lower-intensity strategy with TRUS biopsy has a long-term effect, would still be informative for mpMRI

## At a median 10 yrs, a lower-intensity screening intervention (a single PSA test):

- Had no discernible effect on PCa-specific mortality
- Increased detection of early-stage, low-grade PCa
- Did not detect some lethal cancers
- Long-term follow-up will ascertain if lower-intensity screening reduces over-detection while achieving mortality gains
- **The current findings do not support single PSA-testing for population-based screening**

# Dissemination

- [www.youtube.com/channel/UCc0AUjDL7q89p3IGyIigB0g](https://www.youtube.com/channel/UCc0AUjDL7q89p3IGyIigB0g)
- <https://discover.dc.nihr.ac.uk/content/signal-000602/single-routine-offer-of-a-blood-test-for-prostate-cancer-did-not-save-lives>
- CLAHRCBite

CLAHRC West  
June 2018

  
National Institute for  
Health Research

**CLAHRCBITE**

Brokering Innovation Through Evidence

**A study investigating a single blood test to screen for prostate cancer (CAP)**



# Further funded work

- Effect on 15-year PCa-specific & all-cause mortality
- Age-specific lead time & over-diagnosis rates
- Projected lifetime effectiveness & cost-effectiveness of alternative, UK-focused PCa screening options
  - UK-specific decision analytic (Markov) model
  - Incorporate parameters computed from CAP & ProtecT
  - MPES to enable assessment of risk stratified screening & use of mpMRI





# Acknowledgements



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ProtecT Research, Nursing & Administrative staff

## Comparison of RCTs

	CAP	ERSPC	PLCO
Mean age (yrs)	59.0	61.5	NA
N controls	219,439	89,353	38,350
% PSA-tested, intervention	36%	64%	85%
Biopsy rate	85%	86%	41% <sup>8</sup>
PSA testing in controls	≈10% over 10 yrs	≈15%	≈50%
PCa risk, intervention	4% over 10 yrs	5% over 9 yrs <sup>6</sup>	8% over 10 yrs
<b>PCa's in controls</b>			
Gleason grade ≤6	35%	55%	62%
Gleason grade 7	41%	29%	27%
Gleason grade ≥8	24%	16%	12%
Stage T1/2	60%	79%	95%
<b>PCa's in intervention grp</b>			
Gleason grade ≤6	45%	72%	67%
Gleason grade 7	37%	20%	24%
Gleason grade ≥8	18%	7%	9%
Stage T1/2	69%	90%	97%
Mean age at diagnosis (yrs)	67	61	NK