HSR Protocol - project ref: 09/2000/63
Version: 1
Date: 10/11/2011

Development, validation and evaluation of a clinical instrument for active monitoring of men with localised prostate cancer

Chief investigator	Kate Tilling
Sponsor	University of Bristol
Funder	NIHR Health Services Research
NIHR Portfolio number	**09/2000/63**
ISRCTN registration (if applicable)	N/A

Development, validation and evaluation of a clinical instrument for active monitoring of men with localised prostate cancer

1. Aims/Objectives:

Our aim is to determine whether longitudinal age-related reference ranges that predict how PSA levels change over time in healthy men can be adapted to identify abnormal (cancer-related) PSA increases in men with localised prostate cancer, so that men with quiescent cancer can avoid unnecessary intervention while those with progressing disease can receive prompt and appropriate treatment.

Objectives:

1. To use data from three cohorts of men with prostate cancer to investigate whether data collected during diagnosis about the type, quantity and aggressiveness of the cancer (e.g. Gleason grade, number of positive biopsy cores) improve the accuracy of our previously published reference ranges.
2. To use data from three cohorts of men with prostate cancer to (a) calibrate the thresholds of the reference ranges to identify when an increase in PSA might be indicative of progressing cancer; (b) calculate the sensitivity, specificity and predictive value of the reference ranges to predict clinical cancer progression, and (c) compare these predictive abilities to those of standard PSA kinetics.
3. To develop an easy to use instrument based on the reference ranges that would assist in the clinical management of men with localised prostate cancer who have opted for active monitoring (regular PSA tests to monitor the cancer), and to explore the acceptability of various formats and presentations of the instrument to patients and clinicians.
4. To design a randomised controlled trial to evaluate the effectiveness of the most acceptable "active monitoring" instrument compared with existing active monitoring methods.

2. Background:

Prostate cancer is one of the most common newly detected cancers in men worldwide, primarily because of the increasing use of Prostate Specific Antigen (PSA) as a screening test. Prostate cancer screening is, however, one of the most controversial issues in contemporary healthcare (1). While screening using PSA can detect large number of cancers whilst still confined within the prostate (2) when radical prostatectomy or radiotherapy could achieve a cure, current tests cannot differentiate between tumours with biological potential for progression and the majority of slow-growing tumours which will not cause clinical disease in a man's lifetime. Radical treatments can cause serious side effects, particularly incontinence and impotence (3). The recent publication of the results of screening trials in Europe and the USA have further fuelled the controversies in this area, for example showing that 1421 men needed to be screened to find 48 cancers to prevent one cancer death (4).

There is currently a lack of trial evidence for the effectiveness of treatment for prostate cancer. The SPCG-4 trial showed a survival benefit for radical surgery over watchful waiting (no intervention), but this trial started recruitment prior to the use of PSA and consequently the majority of participants had clinically-detected localised disease (5). Interest in the safety and acceptability of monitoring localised prostate cancer and thus avoiding unnecessary intervention has grown over the past decade. While it is accepted that "active monitoring" protocols involve closer monitoring than that employed in the „watchful waiting" arm of SPCG-4, recent systematic reviews have concluded that there is little evidence or expert consensus over the most effective monitoring protocol (6;7). Serial measures of PSA level are used consistently, but various aspects of "PSA kinetics" are used to trigger further clinical review, including doubling time (length of time for PSA to double) and PSA velocity (both calculated in several different ways)(8-11). The Prostate testing for cancer and Treatment (ProtecT) trial is comparing active monitoring with radical treatment (surgery and radiotherapy) in men with PSA-detected localised prostate cancer, but the long periods of

follow-up required for clinically relevant outcomes to be observed means that it will not report for at least another five years (12).
Hence there is increasing interest in using PSA levels to monitor men with low risk localised tumours, and in strategies that would indicate when further clinical review and radical treatment would be appropriate, and when men could remain monitored without intervention (13).

3. Need:

Our research aims to meet several key health needs in the controversial area of prostate cancer, but particularly to enable men with prostate cancer of low biological aggressiveness to avoid serious side effects due to the overtreatment of screen-detected prostate cancer. The outcome of this project will be a simple method of constructing personalised reference ranges that can be used by patients and clinicians to monitor an individual's PSA levels with the aim being to: a) reassure the patient and clinicians if a man's reference ranges indicate changes in his PSA level are within the limits expected due to ageing; or b) trigger a clinical review and thus the opportunity for treatment if his reference ranges indicate possible progression of the prostate cancer (because changes in his PSA level are starting to exceed the limit expected due to ageing). Confirmation that longitudinal age-related reference ranges can be adapted to identify cancer-related PSA increases in men with localised prostate cancer will have important implications for current practice in the UK and elsewhere, as well as for any screening programmes. The specification of an effective and empirically supported method of active monitoring will avoid unnecessary radical treatment, avoiding the waste of NHS resources.

4. Methods:

a. Setting

Longitudinal studies of active monitoring in men with prostate cancer.

b. Design

Observational longitudinal study.

c. Data collection

None – we are carrying out secondary analyses of data which have already been collected as part of other studies.

d. Data analysis

In this proposal, we will use data from three cohorts of men with prostate cancer to further develop and validate the models. Each of these cohorts will be randomly divided into a development sample (two-thirds of the men) and a validation sample (the remaining third). The development sample in each of the cohorts will be used to investigate relationships between the existing reference ranges for PSA change with age and important disease characteristics and baseline covariates. PSA measures on the same person are likely to be correlated, and men within a cohort may also share some similarities (e.g. in a cohort where men are PSA-detected no man will have an initial PSA below 3 ng/ml). We will thus use multilevel models with three levels: measurement occasion, clustered within subject, clustered within cohort. Individuals will be censored if they have radical treatment for prostate cancer, to avoid bias as such treatment may be triggered by changes in PSA level (14), and we will allow for possible non-normal random effects (15).

6. Plan of Investigation:

Month	Objective	Milestones
1-3	1	Assemble cohort data, divide into development (66%) and validation (33%) samples, clean data. Identify alternative PSA kinetic measures to be compared with reference ranges.
4-7	1	Using the development data set, apply previously developed longitudinal reference ranges for PSA in men without prostate cancer. Develop new reference range models for men with cancer, and compare these to those previously developed.
8-12	1	Using the development data set, examine inclusion in the reference ranges of diagnostic covariates and baseline characteristics. Write up development of reference ranges and disseminate.
13-17	2	Investigate prediction of progression using the development data set, including deriving alert thresholds, examining different definitions of progression.
18-21	1 and 2	Validate final longitudinal reference ranges for PSA (using all three cohorts in the validation data set), and their ability to predict progression.
22-23	1 and 2	Compare reference ranges to previously used methods (PSA velocity, doubling time, ProtecT protocol) using the validation and development data sets.
24	3	Develop a clinical active monitoring instrument using the best-performing PSA prediction (e.g. reference ranges or existing method) .
25-30	3	Explore the acceptability of the instrument to patients and clinicians, and modify the instrument (if necessary).
25-26	4	Design RCT to assess effectiveness of monitoring instrument.
27-30	1-4	Write up quantitative and qualitative research and disseminate results, submit proposed RCT design for funding.

7. Project Management:

Dr Tilling and Dr Metcalfe will manage the project, together with Prof Donovan, Prof Martin and Dr. Lane. Professors Holmberg, Neal, Hamdy, Albertsen, Taylor and Etzioni, and Dr. Carter will collaborate on the project and form the steering committee.

8. Service users/public involvement:

ProtecT study participants have been instrumental in the conception, design and implementation of the active monitoring programme. In this proposal, the views of samples of men will be gathered to determine the acceptability of the instrument and preferred modes of presentation. The views of these men about the feasibility of undertaking an RCT to evaluate the final version of the instrument will also be assessed.

9. References:

1 Hoffman RM. Randomized trial results did not resolve controversies surrounding prostate cancer screening. Curr Opin Urol 2010;20(3):189-93.
2 Catalona WJ, Ramos CG, Carvalhal GF, Yan Y. Lowering PSA cutoffs to enhance detection of curable prostate cancer. Urology 2000;55(6):791-5.
3 Frankel S, Davey Smith G, Donovan J, Neal D. Screening for prostate cancer. Lancet 2003; 361(9363):1122-8.
4 Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-8.

5 Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. New England Journal of Medicine 2002;347(11):781-9.
6 Martin RM, Gunnell D, Hamdy F, Neal D, Lane A, Donovan J. Continuing controversy over monitoring men with localized prostate cancer: a systematic review of programs in the prostate specific antigen era. J Urol 2006;176(2):439-49. **09/2000/63** 10
7 van den Bergh RC, Roemeling S, Roobol MJ, Wolters T, Schroder FH, Bangma CH. Prostate-specific antigen kinetics in clinical decision-making during active surveillance for early prostate cancer--a review. Eur Urol 2008;54(3):505-16.
8 Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 2006;176(4 Pt 1):1392-7.
9 Yu X, Han M, Loeb S, Gashti SN, Yeh JT, Roehl KA, et al. Comparison of methods for calculating prostate specific antigen velocity. J Urol 2006;176(6 Pt 1):2427-31.
10 Daskivich TJ, Regan MM, Oh WK. Prostate specific antigen doubling time calculation: not as easy as 1, 2, 4. J Urol 2006;176(5):1927-37.
11 Connolly D, Black A, Murray LJ, Napolitano G, Gavin A, Keane PF. Methods of calculating prostate-specific antigen velocity. Eur Urol 2007;52(4):1044-50.
12 Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, et al. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. Health Technol Assess 2003;7(14):1-88.
13 Klotz L. Active surveillance for favorable risk prostate cancer: rationale, risks, and results. Urol Oncol 2007;25(6):505-9.
14 Law NJ, Taylor JM, Sandler H. The joint modeling of a longitudinal disease progression marker and the failure time process in the presence of cure. Biostatistics 2002;3(4):547-63.
15 Subtil F, Rabilloud M. Robust non-linear mixed modelling of longitudinal PSA levels after prostate cancer treatment. Stat Med 2010;29(5):573-87.

This protocol refers to independent research commissioned by the National Institute for Health Research (NIHR). Any views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HSR programme or the Department of Health.