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J Donovan
F Hamdy
D Neal
T Peters
S Oliver
L Brindle
D Jewell
P Powell
D Gillatt
D Dedman
N Mills
M Smith
S Noble
A Lane

and the ProtecT Study Group: J Anderson, M Benney, S Burton, I Emmerson, J Goepel, L Goodwin, J Graham, D Gunnell, H Harris, B Hattrick, P Holding, C Kennedy, S Kilner, P Kirkbride, H Leung, T Mewes, J Oxley, I Pedley, M Robinson, L Salter, M Sidaway, C Torrington, L Wilkinson, A Wilson

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NHS R&D HTA Programme

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Prostate Testing for Cancer and Treatment (ProtecT) feasibility study

J Donovan[1*] L Brindle[1] N Mills[1]
F Hamdy[2] D Jewell[4] M Smith[7]
D Neal[3] P Powell[5] S Noble[1]
T Peters[4] D Gillatt[6] A Lane[1]
S Oliver[1] D Dedman[1]

and the ProtecT Study Group

[1] Department of Social Medicine, University of Bristol, UK
[2] Division of Clinical Sciences, University of Sheffield, UK
[3] School of Surgical Sciences, University of Newcastle-upon-Tyne, UK
[4] Division of Primary Health Care, University of Bristol, UK
[5] Freeman Hospital, Newcastle-upon-Tyne, UK
[6] Southmead Hospital, Bristol, UK
[7] Centre for Health Services Research, University of Newcastle-upon-Tyne, UK

[*] Corresponding author

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The ProtecT Study group:

J Anderson, M Benney, S Burton, I Emmerson, J Goepel, L Goodwin, J Graham, D Gunnell, H Harris, B Hattrick, P Holding, C Kennedy, S Kilner, P Kirkbride, H Leung, T Mewes, J Oxley, I Pedley, M Robinson, L Salter, M Sidaway, C Torrington, L Wilkinson, A Wilson

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Frankel SJ, Davey Smith D, Donovan JL, Neal DE. Screening for prostate cancer: a review. *Lancet*; in press.

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Contents

List of abbreviations

CI	confidence interval
CONSORT	Consolidated Standards for Reporting of Trials
DRE	digital rectal examination
FACT	Functional Assessment of Cancer Therapy
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
LUTS	lower urinary tract symptoms
PIN	prostatic intraepithelial neoplasia
PPV	positive predictive value
ProtecT	Prostate Testing for Cancer and Treatment (study)
PSA	prostate-specific antigen
RCT	randomised controlled trial
TRUS	transrectal ultrasound

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

There is currently insufficient evidence to introduce population screening for prostate cancer. While it is accepted that prostate cancer is an important public health problem, there is paucity of evidence on the natural history of the disease, the accuracy of diagnostic tests (e.g. prostate-specific antigen (PSA) testing) and the effectiveness of treatments.

Objectives

The overall aim was to evaluate the feasibility of a randomised controlled trial (RCT) of treatments for localised prostate cancer, including:

- feasibility of 'case-finding' in the community (including the reliability and psychosocial impact of PSA testing)
- determining the most efficient and effective design for a major trial of treatments
- randomised trial of recruitment strategies
- piloting outcome measures and procedures for the main trial of treatments.

Methods

The study was an RCT of treatment preceded by case-finding in the community, with qualitative research methods integrated at each stage. Case-finding took place in primary care centres in Sheffield, Newcastle and Bristol. The RCT was undertaken in urology clinics in these same centres. Men aged 50–69 years from specific primary care centres in the three cities were invited to attend a 30-minute prostate check clinic appointment in which they were informed about the study and asked to consent to a PSA test. Men with a raised PSA (initially ≥ 3.0 ng/ml if 50–59 years; ≥ 4.0 ng/ml if 60–69 years; but changed to ≥ 3.0 ng/ml for all men after 1 year) were invited for biopsy. Men with confirmed localised prostate cancer were invited to participate in a randomised trial of recruitment strategies.

Men with confirmed localised prostate cancer were asked to consent to randomisation between a nurse or urologist for an 'information' appointment to discuss recruitment to the treatment trial. In the information appointment, the need for a trial was explained in detail, along with the advantages and disadvantages of each treatment, and the recruiter attempted to randomise the patient to the treatment trial or reach a patient-led preference for a treatment. All men, whether randomised or not, were asked to consent to be followed-up, and these formed a pilot for the proposed main trial.

Main outcome measures

Case-finding

Numbers of men agreeing to attend prostate check clinics and then going on to have a PSA test, biopsy and diagnosis of prostate cancer were calculated. The accuracy of PSA testing was calculated by positive predictive values (PPVs) at various cut-off points. The psychosocial impact of case-finding was investigated through the use of the Hospital Anxiety and Depression Scale (HADS) and ICS*male* (urinary symptoms) questionnaire, completed by all men at baseline and those with raised PSA levels at the time of biopsy.

Randomised trial of recruitment

The primary outcome was the proportion of patients accepting randomisation to the treatment trial. Also calculated were the proportions consenting to randomisation to the three- (radical prostatectomy, radical radiotherapy and 'conservative' management) or two-arm (radical options only) trial and those accepting the random allocation. An economic analysis based on the duration of information appointments and recruiter salaries was performed to assess the most cost-effective recruiting staff.

Qualitative research

In-depth interviews were undertaken with several groups:

- men interviewed on several occasions as they progressed through the feasibility study from case-finding to randomisation
- men after they had received PSA test results
- men with confirmed localised prostate cancer after their information appointment.

In addition, tape-recorded information appointments were examined. Changes to information content and presentation were made and the proportions consenting to be randomised to the treatment trial and accepting the allocation were calculated regularly to examine the impact of these changes.

Proposed main randomised trial of treatment

All men with confirmed localised prostate cancer completed a baseline study questionnaire at the time of case-finding and biopsy. A further questionnaire was completed 6 months after the information appointment, with the major research follow-up to be at 12 months and annually thereafter in the main trial.

Results

Case-finding

A total of 8505 men from 18 primary care centres attended prostate check clinics (56% of those invited), and 7383 had a PSA test. Of these, 861 (12%) had raised PSA levels, and following biopsy, 224 cases of prostate cancer were found (165 clinically localised). The detection rate was 2.2% of clinic attendees. PPVs confirmed that a PSA cut-off point of 3 ng/ml was suitable. At the time of PSA testing, levels of depression were low (3.2% 'cases') and anxiety somewhat higher (11.6% 'cases'), but these remained virtually unchanged among those completing questionnaires at the time of biopsy.

Randomised trial of recruitment

Ninety per cent of eligible cases consented to randomisation between a nurse and urologist. Urologists achieved a higher rate of recruitment to the treatment trial (71% compared with 67% for nurses), but this was not statistically significant ($p = 0.60$). As effectiveness was essentially the same between the two arms, a cost-minimisation analysis was performed and showed that the urologist arm was more expensive because greater salary costs outweighed their tendency for shorter appointments and nurses often supported surgeon-led clinics.

Randomised trial of treatment

The three-arm trial was the most popular treatment trial option, with 84% opting for this rather than the two-arm trial ($p < 0.001$). The acceptance of the treatment allocation was 71% within the three-arm trial.

Qualitative research

The offer of PSA testing was construed as an opportunity to discover an unknown condition and the majority of men indicated that they understood that the study involved investigation of treatments. While the majority could recall clearly the principles of randomisation, issues around clinical equipoise caused many considerable difficulty. Recruitment to the treatment trial increased gradually during the feasibility study, from 30–40% at the outset to 70% by the end of the feasibility study. These improvements in recruitment were brought about by changes to the content and presentation of information, particularly avoidance of terms such as 'trial' and 'watchful waiting', and the clear specification of the non-radical treatment arm, as directed by the findings of the qualitative research.

Conclusions

- It is feasible to mount a full-scale three-arm randomised trial of treatment for localised prostate cancer, preceded by a programme of case-finding in the UK.
- The full-scale three-arm Prostate Testing for Cancer and Treatment (ProtecT) randomised trial of treatment has now been commissioned by the NHS R&D Health Technology Assessment Programme. It will be undertaken in nine clinical centres in the UK, involving over 100,000 men, and recruitment will take 5 years, commencing September 2001.

Chapter 1

Background and aims

Background

A number of reviews, including two systematic reviews published by the NHS R&D Health Technology Assessment (HTA) Programme of the diagnosis, management and screening of localised prostate cancer, have shown that currently there is insufficient evidence to introduce population screening for prostate cancer.[1–4] While acknowledging that prostate cancer is an important public health problem, these reviews have highlighted the paucity of evidence concerning the natural history of prostate cancer, the accuracy and acceptability of available diagnostic tests, and, particularly, the effectiveness and acceptability of treatments. Each of these factors represents crucial background information for this project and each is summarised briefly below.

Burden of disease

There is no question that prostate cancer is a serious and common disease. In the USA, prostate cancer is the most common male cancer with an estimated 179,300 men expected to be diagnosed in 1999 and around 41,000 deaths per annum. After lung cancer, it is the second leading cause of cancer death in men in the USA. Prostate cancer is also the second most common malignancy in men in the European Union, with some 85,000 new cancers and 35,000–40,000 deaths each year. In England and Wales in 1993, there were over 17,000 new cases and over 8500 deaths.[3] With increasing life expectancy, improvements in diagnostic techniques, and a rise in public knowledge and demand for testing, the prevalence of the disease has been increasing in the 1980s and 1990s, although recent evidence suggests that mortality is falling both in the UK and the USA.[5] Interpreting these population trends is difficult because of a number of biases that are difficult to disentangle, for example:

- lead-time bias (that prostate-specific antigen (PSA) testing prolongs the length of time that a patient is known to have the disease, without prolonging life)
- length-time bias (that slow-growing, less-aggressive cancers with good prognoses are detected)
- evidence of substantial regional variations in US data with regard to incidence but not mortality[6]
- mislabelling of deaths as being from prostate cancer when they are actually from other causes[7,8]
- marked changes in the use of surgery for benign prostate disease.

There is, therefore, considerable debate over the evidence for, and interpretation of, recent changes in prostate cancer incidence and mortality and their relationship with PSA testing and screening.[9] There is, consensus, however, that prostate cancer is a major public health problem.

Natural history

The natural history of prostate cancer is poorly understood. It is primarily a disease of older men, with the median age at onset of clinically apparent disease around 72 years, and median age at death of 79 years.[3,10] Post-mortem studies make it clear that the vast majority of prostate cancers never develop into clinically apparent disease. At autopsy, small tumour foci are found in 30–40% of 60-year-old men in most countries. It has been estimated that the life-time risk of a 50-year-old man with a 25-year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer is 9.5%, and of dying of prostate cancer is 2.9%.[11] It is a well-known (and true) aphorism that "more men die with prostate cancer than of it."

The severity of prostate cancer ranges from non-fatal, asymptomatic slow-growing tumours, which probably require no treatment, to aggressive fast-growing tumours that metastasise quickly, often before symptoms are noticed. We do not yet know what factors are important in the progression of micro-focal tumours into symptomatic forms of the disease. There are cancers that are confined to the prostate in the early stages, but that will spread later; it is these tumours that screening seeks to identify. There is, however, doubt as to whether screening would be effective in identifying such tumours early enough in their natural history to alter the overall mortality from the

disease, particularly as it is not possible to predict which microscopic lesions will develop into malignancies. Some older studies of the natural history of untreated disease have pointed out that over time, tumours diagnosed on rectal examination or following transurethral prostatectomy do progress, the risk being largely dependent on grade.[12,13] However such studies are not readily applicable to present times because they do not provide information on the natural history of tumours detected through PSA testing.

Acceptability, cost and accuracy of diagnostic tests

Serum PSA testing is simple to perform and relatively inexpensive. However, estimates of the true sensitivity and specificity of PSA are difficult to obtain given the lack of knowledge about natural history, hampering the ascertainment of false-positives and false-negatives. Moreover, simple PSA testing identifies raised levels in as many as 10% of men aged 50–69 years and, following transrectal ultrasound (TRUS) and biopsy (a procedure causing some discomfort and small risk of infective complications), prostate cancer is confirmed in between 20–40%, ranging widely between studies.[1] Large numbers of men will therefore suffer unnecessary biopsies with the potential for discomfort and distress, when the acceptability of TRUS and biopsy has not been properly investigated.

Treatment

There are three main treatments for localised prostate cancer:

- radical prostatectomy
- radical radiotherapy
- non-radical option involving monitoring that is variously called 'watchful waiting', 'conservative management', 'monitoring' or 'surveillance'.

Each of the major treatments involves its own risks. While the active treatments offer the potential for cure, they can cause iatrogenic effects, including pain, hospitalisation, incontinence, impotence and, occasionally, death. It is likely, because of the slow-growing nature of some cancers, that patients undergoing radical treatments may experience harmful side-effects without the possibility of benefit.[14] With 'conservative management', the patient is at risk of progression which in a small number of cases may be fatal.

The question remains as to whether early detection of prostate tumours can enhance life expectancy and the quality of life. The aim of screening is to detect confined tumours that can be removed, effecting a cure. Clearly, current modes of screening are able to detect some such tumours, but they also detect both untreatable and non-fatal tumours, as well as leaving an unknown number of undetected tumours. Thus far, no adequate randomised controlled trials (RCTs) assessing the effectiveness and cost-effectiveness of treatments have been published.

Two trials, one comparing radical prostatectomy with radiotherapy and the other radical prostatectomy with placebo compared with placebo alone, have been published,[1,15] but both studies had serious methodological flaws that preclude firm conclusions based on their results. In particular, the numbers were too small to detect differences between groups, there were imbalances in age between the two arms, follow-up was poorly defined, and both studies were conducted prior to the introduction of PSA testing and did not employ an 'intention-to-treat' analysis.[1]

The evidence concerning the effectiveness of treatments is thus limited to observational studies with the full range of well-described limitations of such data, including differences in patient selection criteria, operative techniques and post-operative assessments, as well as variable definitions of terms, different lengths of follow-up, and sometimes poor quality methods of data analysis. Imbalances in patient selection are particularly common, including disease stage and grade, levels of initial PSA tests, nodal status, and age and co-morbidity, all of which make the accurate interpretation of the data extremely difficult. The main issues in terms of mortality, morbidity and quality of life are discussed below.

Mortality

The crucial issue with radical treatment is whether or not early intervention in men with localised tumours reduces mortality from prostate cancer. It is clear from data summarised in reviews[1,2] that survival following treatment for localised prostate cancer is high for all modes of treatment: 85–90% for radical prostatectomy, 65–90% for radiotherapy, and 70–90% for conservative management[1] (wide ranges are given because of the difficulties in comparing studies).

It is generally accepted that radical interventions are not recommended for men over the age of

70 years, or those who are likely to have a life expectancy of less than 10 years. In younger men, however, evidence concerning the optimum treatment is less clear. Some studies indicate that selected groups of men may benefit from radical intervention, particularly those who are youngest and fittest, and have high-grade tumours. However, problems with the accuracy of clinical staging using the classical triad of serum PSA levels, digital rectal examination (DRE), and TRUS of the prostate mean that up to 50% of men with apparently localised tumours are found to have extracapsular disease and positive margins following radical prostatectomy. Such accurate pathological staging is unavailable in patients receiving radiotherapy or conservative management, making comparisons extremely difficult. Ultimately, no treatment has been shown consistently to have a survival advantage.

Morbidity

In view of the lack of apparent difference between the modes of treatment in terms of survival, greater attention could be taken of the morbidity caused by the treatment itself or consequent effects on quality of life. There are considerable variations in the complications reported, with various research methods used, but the majority relying on clinician report. Radical prostatectomy is a major surgical procedure which is safest in experienced hands, but carrying significant risks of often underestimated complications in the hands of surgeons performing the operation infrequently. Incontinence, for example, may be reported as 'total' with a rate of 3%, or 'dribbling' (up to 60%).[1] Impotence may similarly be reported as 'partial' or 'total', or between 20% and 80%, depending on previous sexual activity and the use of the nerve-sparing operative procedure.[1] Radical radiotherapy is also a major intervention, with risks of inflammation of adjacent organs such as the gastrointestinal tract and bladder (up to 40%), as well as incontinence (variably reported, but up to 10%) and impotence (also variable, but total when hormone therapy is used in combination, and up to 40% after radiotherapy treatment).[1] Morbidity from conservative treatment options is limited immediately to anxiety relating to the presence of cancer, but if local or distant progression occurs, the chance of curative treatment may be lost and other symptoms (urinary and systemic) may develop.

Quality of life

The measurement of quality of life has been neglected in this area, with a number of relatively weak studies producing somewhat conflicting results.[16–19] However, one important study, utilising the Short-Form 36-item (SF-36) generic health status measure, and two cancer-specific instruments, the Cancer Rehabilitation Evaluation System-Short Form (CARES-SF) and Functional Assessment of Cancer Therapy-General Form (FACT-G), found no differences in general aspects of quality of life between men with localised prostate cancer treated by radical prostatectomy, radiotherapy or observation.[20] The authors did find, however, considerably worse sexual and urinary dysfunction among those receiving radical interventions compared with those treated conservatively.[20] One study of the impact of treatment on quality of life has suggested that those receiving radical interventions suffer poorer disease-specific health-related quality of life than those receiving conservative management.[20] While some studies suggest that retrospectively, men are generally satisfied with having undergone radical treatment,[17,19] it is unclear whether this is real satisfaction or a subsequent rationalisation that attempts to put difficult experiences in a constructive light. Qualitative studies in this area are lacking.

Studies of patient preferences and randomisation

Although a recent editorial in the *Lancet* indicated the importance of research to understand the patient's perspective of participation in randomised trials,[21] little research in this area has been undertaken. Two exceptions are the studies by Snowdon and co-workers,[22] of parents of premature babies, and Featherstone and Donovan,[23,24] of men with benign prostatic disease. Snowdon described in detail the confusion and anger that may be present among those participating in randomised trials, particularly related to the misunderstanding of the purpose and practicalities of randomisation.[22] Featherstone and Donovan's study described the struggle that men engage in to come to terms with the difficult concepts inherent in the randomised design, and particular difficulties that arise with different perceptions of terms such as 'random' and 'trial'.[23,24] These studies indicate that considerable care needs to be paid to information for patients participating in trials.

There are also few clear suggestions about how patient preferences might be incorporated within or alongside standard randomised trials,[25] although many authors feel this might be desirable because of the influence such preferences might have on outcome.[26–29] A small number of studies have been conducted that consider patients' prefer-

ences for treatments. One such study aimed to elicit hypothetical preferences for the treatment of metastatic breast cancer in women with early-stage breast cancer.[30] Ninety per cent of the 115 patients interviewed expressed clear preferences for specific treatments for metastatic disease, with only 10% allowing randomisation between high-dose compared with standard chemotherapy. These findings suggest that such trials will be difficult. The findings have limited relevance to this study as the women had already received treatment for breast cancer and were discussing possible future hypothetical scenarios for themselves if they experienced recurrence. In addition, the issue of randomisation was considered very briefly and in terms of 'allowing the flip of a coin to determine which therapy they received'.[30] In the conclusion, the authors conceded that the presentation of the scenarios had a 'dramatic impact' upon the patients' decisions,[30] and this has been confirmed in other studies.[31]

It was possible to find only one randomised trial in surgery that included patient preferences as well as randomisation. This study considered women's preferences for medical abortion or vacuum aspiration in the early first trimester of pregnancy, and the acceptability of randomised allocation.[32] A total of 363 women were recruited, and while 26% preferred vacuum aspiration and 20% medical abortion, 195 (54%) were willing to be randomised.[32] Although this was only one study, it could be said to set a benchmark for randomisation in trials where patients are likely to express strong preferences of around 50%.

The need for a feasibility study

The sections above have shown the high levels of uncertainty that exist around prostate cancer and in conducting trials. It was (and remains) our view that the greatest and most pivotal uncertainty surrounds the effectiveness of treatments for localised prostate cancer. Our approach was thus to focus on providing evidence concerning treatment, and particularly to explore the feasibility of mounting a full-scale randomised trial of the main treatments for localised prostate cancer in the UK.

There was a need for a feasibility study in this area because previous attempts to mount trials, for example, the US Prostate Cancer Intervention Versus Observation Trial (PIVOT)[33,34] and the UK MRC PR06 studies, experienced considerable difficulties. These difficulties emerged from a number of sources, each of which was tackled in the feasibility study.

- Patients with truly localised disease do not arise incidentally in sufficient numbers, and need to be sought from the community.
- In the absence of good-quality evidence, clinicians and patients often have strong preferences for particular treatments – some will tend to favour radical approaches, making trials including a conservative arm apparently unacceptable; yet others will prefer conservative treatment.
- Existing observational data suggest that 10-year survival in men with localised prostate cancer is high, and trials need to be large in order to detect relatively small differences between treatment groups.

Outline of the feasibility study

The feasibility study aimed to address previous difficulties in mounting a treatment trial by:

- evaluating the feasibility of mounting **either** a three-arm (including conservative management) **or** two-arm (radical options only) trial before commencing the main study
- securing sufficient numbers of patients to enter into the trial by a programme of 'case-finding' in the community
- ensuring that men were aware of **all** three treatments from the outset of case-finding, to attempt to counter the idea that radical treatment should inevitably follow early detection
- examining the most effective and cost-effective method of gaining informed consent from men to enter into the treatment trial by comparing information provision by urologists and nurses, using material from the HTA-funded systematic reviews, and carrying out qualitative research to understand recruitment patterns
- undertaking a pilot study for the main trial in three different parts of the country (Sheffield, Newcastle and Bristol) to develop suitable outcome measures and procedures for conducting the major multicentre trial.

Aims and objectives

The overall aim of the feasibility study was to evaluate the feasibility of undertaking a randomised trial of 'conservative management', radical prostatectomy and radical radiotherapy (three-arm), or radical prostatectomy and radical radiotherapy (two-arm), in men with localised prostate cancer. The feasibility study had three major elements: case-finding, trial of recruitment

strategies, and pilot for the main trial – each with its own objectives:

Objectives – case-finding

- To establish the feasibility of inviting men aged 50–69 years registered with primary care centres in Sheffield, Newcastle and Bristol to attend for PSA testing with a view to entering those with confirmed localised prostate cancer into a trial of treatments.
- To evaluate the reliability of PSA testing for localised prostate cancer detection among men willing to attend for case-finding.
- To assess the psychosocial impact of case-finding.

Objectives – trial of recruitment strategies

- To determine the proportions of men consenting to randomisation to the three- or two-arm trials and those expressing preferences for particular treatments, to inform the design of the main treatment trial.
- To compare the recruitment rates of research nurses and consultant urologists.
- To elicit the men's understanding of randomisation and clinical equipoise, understand reasons for consenting to randomisation or preferences for particular treatments and identify items of information or methods of recruitment which would increase men's willingness to consent to randomisation.
- To understand the process of treatment decision-making as it occurs in the consultation and as interpreted afterwards by men.

Objectives – pilot of main treatment trial

- To determine the most effective and efficient design for the main treatment trial.
- To carry out preliminary piloting of appropriate measures of outcome and procedures for use in the main treatment trial.

Chapter 2
Methods

The study was named the Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. The ProtecT feasibility study employed quantitative and qualitative research methods throughout, and these are described in the sections that follow.

Case-finding

Case-finding involved inviting men aged 50–69 years from specific primary care practices in each of the three study areas (Newcastle, Sheffield, Bristol) to attend a 30-minute prostate check clinic appointment. Men considered by the general practitioner (GP) to be unfit for any of the potential treatments (i.e. those terminally ill or with serious co-morbidity) were excluded. The remaining men were invited to attend prostate check clinic appointments in their primary care centre or the local hospital by letter and with an information sheet explaining about PSA testing and the purpose of the study. At the prostate check clinic appointment, they received detailed information from trained nurse-researchers about the implications of having a PSA test, the uncertainties about treatments and need for a randomised trial of treatment. If they consented, blood was taken for a PSA test and basic socio-demographic and medical history data were collected. Men were asked to complete the baseline study questionnaire. There was then a 24-hour 'cooling-off' period during which the men had to return a further consent form to have the blood sample tested for PSA level. The majority of men (~ 90%) were expected to have a normal result and would exit the study at this point.

Initially, age-based PSA ranges were used (≥ 3.0 ng/ml if 50–59 years; ≥ 4.0 ng/ml if 60–69 years). This was changed to a level of ≥ 3.0 ng/ml for all men after 1 year of recruitment following publications indicating this to be a more efficient cut-off point.[35]

Men with a raised PSA result were invited to undergo a further PSA test and TRUS-guided biopsy. After 1 year, the biopsy protocol was changed from sextant to 8–10 cores, also following the publication of papers indicating this to be more efficient.[36–38] Men found to have advanced disease received a rapid appointment and were treated routinely outside the study. Men with high-grade prostatic intraepithelial neoplasia (PIN) or persistently raised PSA levels were offered a further biopsy. Men with a persistently raised PSA but no evidence of prostate cancer were offered the opportunity to be seen again in primary or secondary care. Men with a negative biopsy and normal second PSA test were informed that they did not have prostate cancer, were told about the reasons for sporadic PSA rises, and advised to consult their GP in the future if they had concerns.

Numbers of men responding to the single invitation to the prostate check clinic were recorded and calculated, as were numbers of men with raised PSA levels in each of the major age groups (50–59 years, 60–69 years). The detection rate for localised prostate cancer was determined using the numbers attending prostate check clinics as the denominator. Positive predictive values (PPVs) for PSA tests were calculated. The psychosocial impact of case-finding was investigated using levels of anxiety and depression recorded in the Hospital Anxiety and Depression Scale (HADS)[39] and levels of lower urinary tract symptoms (LUTS) using the ICS*male* questionnaire.[40]

In order to evaluate the accuracy of PSA testing, including the implications for selecting different cut-off points overall and by age group, PPVs were obtained for a series of (retrospectively applied) thresholds above the main cut-off point used for the study (i.e. ≥ 3 ng/ml). These were derived in the standard way by dividing the number of cases of cancer subsequently diagnosed by the number of men whose PSA level was at or above the given cut-off point; 95% confidence intervals (CIs) were derived for these proportions using the exact Binomial method in Stata. The PPVs and CIs were obtained for the two age groups of 50–59 years and 60–69 years separately, and plotted against (integer) cut-off points from ≥ 3 ng/ml to ≥ 10 ng/ml inclusive. (Given the change in threshold applied during the study for 60–69 year olds, those older men with

PSA in the range 3.0–3.9 ng/ml before this change were omitted from the denominator for the relevant PPV for 3+ ng/ml.) For the purposes of this analysis, and for simplicity the PSA level was just the first PSA taken, and cases were all cancers rather than just localised cases.

Trial of recruitment strategies

Men with confirmed localised prostate cancer attended a short diagnostic/eligibility appointment with the study urologist who explained the diagnosis and asked for consent to randomise the patient to see either a nurse or urologist in a longer 'information' (recruitment to treatment trials) appointment. Men were given a detailed information sheet describing the advantages and disadvantages of each of the treatments and the need for a randomised trial to read before the information appointment. This 'two-stage' process was used both for convenience in terms of organising the recruitment trial, but also because patients receiving a diagnosis of cancer need time to absorb the diagnosis and consider the treatment options.

In the information appointment, the need for a trial was explained in detail, along with the advantages and disadvantages of each treatment. The nurse or urologist answered any questions raised by the patient. The nurse or urologist then attempted to gain consent to randomise the patient to the treatment trials – first to the three-arm trial, and then to the two-arm (radical treatments only) trial if the conservative option was not acceptable. If the men were not happy to be randomised, a patient-led preference for a treatment option was reached. All men, whether randomised or not, were asked to consent to be followed-up.

Four major issues were investigated in this part of the study:

- the comparative effectiveness of the nurses and urologists in recruiting men to the trials
- the comparative cost-effectiveness of the nurses and urologists in recruiting men to the trials (based on time taken in appointments and salary levels)
- the acceptability of randomisation to the three- and two-arm trials
- the acceptance of allocation by treatment arm.

Statistical methods

CONSORT-style flow charts were compiled to indicate the numbers of eligible cases, those randomised in the trial of recruitment strategies and the outcome of this trial in terms of effectiveness in recruiting men to the treatment trials. Analysis was conducted according to the principles of intention-to-treat, with analysis by chi-squared, Fisher's exact and the sign test, with 95% CIs for proportions and differences between them obtained from exact methods or the Normal approximation, as appropriate. *A priori*, a power calculation suggested that 150 men with localised prostate cancer randomised between the nurse and urologist would be required to enable the detection of a 23% difference in the proportion agreeing to randomisation (i.e. 50% versus 73% comparing nurse with urologist) with a power of 80% and a two-sided alpha of 0.05. The margin of error around each separate estimate of the proportion agreeing to participate was expected to be 11–14% with 50–70 in each arm.

Methods of economic evaluation

Two types of analysis were planned, depending on the results of the main comparison of effectiveness of the nurse and urologist. If a difference emerged between the two, a cost-effectiveness analysis was planned; if the level of effectiveness was essentially the same, a cost-minimisation analysis would be performed. Data to be used in the economic evaluation were the resources used in the appointment – namely the duration of the visit and the grade of recruitment staff. Staff time was valued using annual salaries, including employer on-costs, obtained from one centre. This was adjusted for number of weeks worked per year, number of hours worked per week, and the proportion of patient contact. Sensitivity analyses were planned to explore the impact of, for example, number of appointments and staff present.

Qualitative research

As the trial was controversial and previous attempts had encountered such serious difficulties, it was decided that qualitative research methods would be used throughout the feasibility study. Interviews with participants and tape-recordings of information appointments were undertaken so that we could understand how and why problems arose, and attempt to improve efficiency and patient/clinician satisfaction as the feasibility study progressed. Qualitative research methods were used to explore men's views about being involved in the study, their interpretations of the

study information and documentation, their understanding of randomisation, the acceptability of randomisation, and the acceptability of the treatments. Information appointments were tape-recorded so that we could understand how information was being presented by recruiters and interpreted by patients.

The qualitative research was in three major parts.

- In-depth interviews with men before or after receipt of PSA results and/or biopsies, and repeated interviews (case studies) with men with confirmed localised prostate cancer – to elicit lay beliefs about prostate cancer, perceptions and experiences of the study, understandings of randomisation, and the acceptability of treatments.
- Information appointments were routinely audio tape-recorded – to allow detailed examination of the content and style of the information imparted to patients. Reasons for different levels of recruitment between centres and over time were investigated.
- Follow-up interviews with patients after information appointments – the scrutiny of pairs of audio-taped appointments and interview transcripts allowed the examination of the delivery of the study information by recruiters and its recall and interpretation by patients.

All interviews were semi-structured, carried out using a checklist of topics to ensure that the same basic areas were covered with each informant but allowing any issues of importance to the men to emerge. Interviews and information appointments were carefully transcribed. The data were being analysed using the methods of 'constant comparison' in which transcripts are scrutinised for similar themes, segments of text are assigned codes, and then examined in detail within themes.[41,42] Detailed analyses are being prepared for publication. The data presented in this report focus on:

- preliminary findings about perceptions and experiences of participating in the ProtecT feasibility study, and
- findings used to inform changes to recruiter training and randomisation rates.

Pilot of the main trial outcome measures

All men identified with localised prostate cancer in the feasibility study (whether randomised or not) were asked to consent to being followed-up. Various questionnaires and schedules were subjected to preliminary piloting for use in the main trial. Measures for the following outcomes were piloted:

- survival
- disease progression
- treatment complications
- generic health status
- anxiety and depression
- LUTS
- sexual function
- quality of life related to treatments for prostate cancer.

Chapter 3
Results

Results from the ProtecT feasibility study are reported below in four major sections. It should be borne in mind that the calculation of rates at each of the stages of the study is subject to some variation because of the time-lags inherent in testing, diagnosing and organising appointments. In the sections that follow, the most appropriate census times were chosen for each part of the study to ensure the most accurate and complete data. As a consequence, numbers of 'eligible' cases are not always identical and reports in publications may vary slightly.

Case-finding

As can be seen in *Figure 1*, 8505 men (from 18 primary care centres in the three study areas) attended prostate check clinic appointments (56% of those invited). The majority favoured appointments in primary care centres rather than the hospital. The age distribution of men invited to the study matched that for the health authorities within which the practices were based. Very small numbers of men were excluded by GPs from the lists passed to the study team.

A total of 7383 (87%) had a PSA test. Of the attendees who did not have a PSA test, the majority (66%) were excluded on health grounds. Men excluded at this stage were, on average, older (mean age 61 years versus 59 years, $p < 0.0001$) and less likely to be in social classes I and II (48% versus 53%, $p < 0.0001$). Full study participants were almost exclusively white (95%), with more from social classes I and II than the general population.

Of the 7383 study participants, 861 (12%) had raised PSA levels. The majority (754, 88%) agreed to biopsy, and of these 592 (79%) had only one biopsy. A total of 224 cases of prostate cancer were found (30% of those with raised PSA who agreed to biopsy), and of these 165 (74%) were clinically localised. The detection rate was 165/7383 (2.2% of tested clinic attendees).

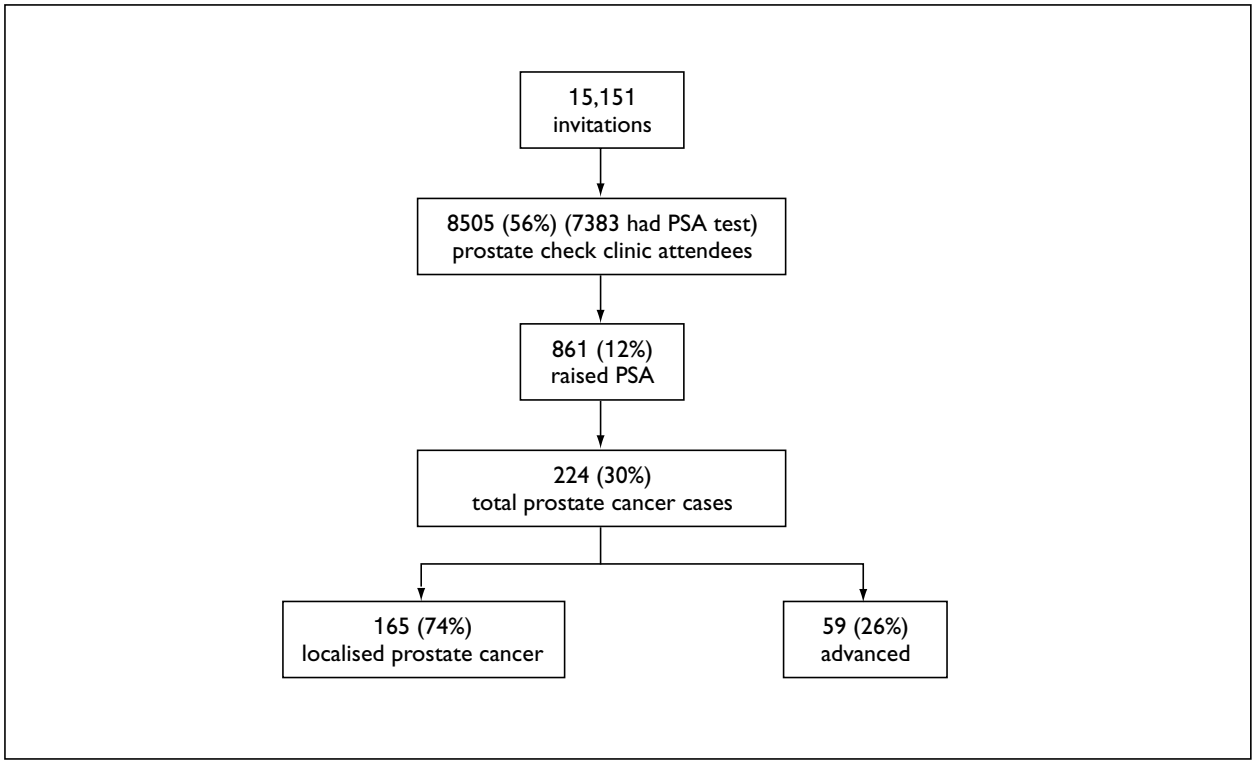

FIGURE 1 *Case-finding results*

Changes to the PSA cut-off point and increased biopsies after 1 year led to an increase in the proportion with a raised PSA (from 8% to 12%) and cancers detected (from 1% to 2%).

Accuracy of PSA testing

The PPVs at various cut-off points applied retrospectively to the study data are presented along with 95% CIs in *Figure 2*, with the numbers underlying them given in *Table 1*.

Psychosocial impact of case-finding

Data are available on 7688 men who completed the HADS and ICS*male* questionnaires at baseline, and on 313 men who completed the same questionnaires at the time of biopsy (*Table 2*). At baseline, levels of depression were low (3.2% with symptoms consistent with being a 'case'), and levels of anxiety somewhat higher (11.6% 'cases'). At the time of biopsy, when anxiety might be expected to increase, both anxiety

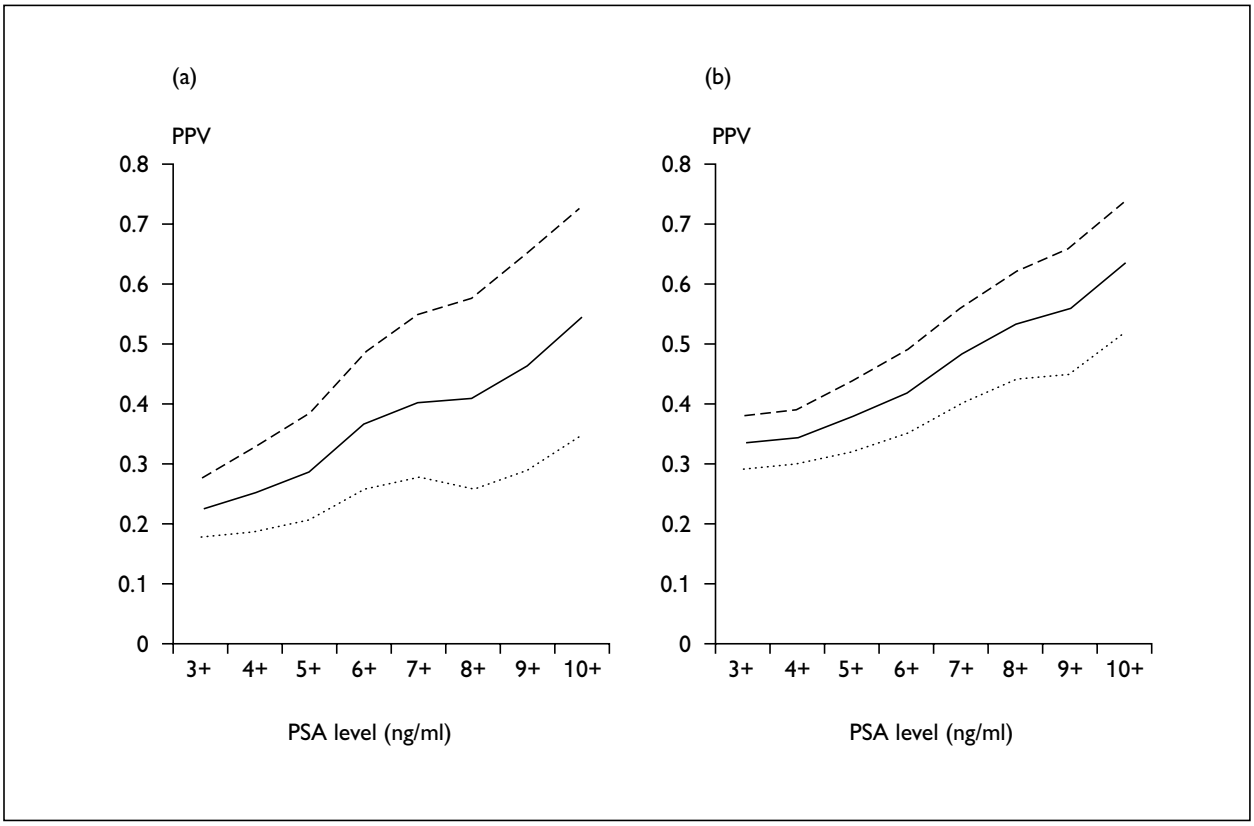

FIGURE 2 *PPVs (and 95% CIs) in relation to all cancers according to a series of (retrospectively applied) cut-off points for the PSA level at first testing, presented separately for a) 50–59-year-olds and b) 60–69-year-olds*

TABLE 1 *Numbers, proportions and 95% CIs for PPVs presented in* Figure 2

	50–59 years				60–69 years			
PSA level	**No. cancers (all)**	**No. tested**	**PPV**	**95% CI**	**No. cancers (all)**	**No. tested**	**PPV**	**95% CI**
3+	62	274	0.23	0.18 to 0.28	157	473	0.33	0.29 to 0.38
4+	41	161	0.25	0.19 to 0.33	128	372	0.34	0.30 to 0.39
5+	28	97	0.29	0.21 to 0.39	102	269	0.38	0.32 to 0.44
6+	22	60	0.37	0.26 to 0.49	83	199	0.42	0.35 to 0.49
7+	19	47	0.40	0.28 to 0.55	72	150	0.48	0.40 to 0.56
8+	14	34	0.41	0.26 to 0.58	66	124	0.53	0.44 to 0.62
9+	12	26	0.46	0.29 to 0.65	48	86	0.56	0.45 to 0.66
10+	12	22	0.55	0.35 to 0.73	45	71	0.63	0.52 to 0.74

TABLE 2 *Anxiety, depression and LUTS at baseline and biopsy*

	% All men at baseline (*n* = 7688)	% Men undergoing biopsy (*n* = 313)			
		Baseline	Biopsy	% Change	(95% CI)
HADS					
Anxiety – case (score > 10)	11.6	9.9	10.5	+0.7	–2.7 to 3.9
Depression – case (score > 10)	3.2	3.0	1.3	–1.7	–1.7 to 0.1
Ever feel tense	76.8	75.2	77.5	+2.2	–7.0 to 2.8
Worrying thoughts	64.5	66.7	57.0	–9.7	–15.3 to –3.5
Frightened feelings	51.4	48.9	49.2	+0.3	–5.5 to 6.1
Ever panic	45.5	43.2	38.6	–4.6	–10.0 to 1.3
***ICS*male**					
Frequency	26.7	32.4	36.2	+3.9	–0.7 to 7.9
Nocturia	16.6	25.4	24.4	–1.0	–4.1 to 2.4
Hesitancy	46.0	60.6	66.7	+6.1	0.7 to 10.9
Urgency	46.9	58.1	54.6	–3.5	–8.2 to 1.6
Urge incontinence	20.4	30.0	28.4	–1.6	–5.0 to 2.2
LUTS interfere with life	21.2	32.6	30.7	–1.9	–6.3 to 2.7

and depression remained at about the same level, with the numbers of men categorised as 'cases' for depression actually falling. LUTS at baseline were consistent with levels among men of this age-group in the community,[43] and were largely unchanged at the time of biopsy. However, among men undergoing biopsy (i.e. with raised PSA levels), LUTS were higher than all men at baseline, and this will be further investigated.

Trial of recruitment strategies

This trial is in two parts. First, the comparison between nurses and urologists in terms of the proportions randomised to the treatment trials will be considered, followed by the acceptability of the three-arm compared with the two-arm trial, with the proportions consenting to the treatment allocation and preferring particular options.

Nurse/urologist comparison

For the purposes of this trial, 167 cases of localised prostate cancer make up the eligible sample. Of these, the majority (150, 90%) consented to randomisation between the nurse and urologist for the information appointment (*Figure 3*). Of those who opted to see one or the other, the majority chose to see a urologist.

As can be seen in *Figure 3,* of the 75 who saw a nurse, 50 (67%) were subsequently randomised as part of the treatment trial, compared with 53 (71%) of the 75 who saw a urologist. This difference in recruitment rates of 4.0% (95% CI, –10.8% to +18.8%) is not statistically significant ($p = 0.60$ from a chi-squared test). Although the upper confidence limit does approach the target difference set for the power calculation in the protocol, the lower confidence limit enables us to rule out any appreciable advantage of the nurses in terms of effectiveness.

Interestingly, of the 17 who refused randomisation to nurse or urologist, 11 later consented to be randomised in the treatment trial (eight by a urologist, three by a nurse), suggesting that they did not reject randomisation *per se.*

Economic evaluation

Given the similar effectiveness of the nurse and urologist in terms of the proportion of patients accepting randomisation, a cost-minimisation analysis was performed. A decision of whether or not to participate in the trial was reached by the majority of patients after only one information appointment. For the remaining patients this decision was made following further contact with the centres, such as additional information appointments and/or informal telephone discussions. Given the uncertainty surrounding the actual amount of staff contact these patients received, a sensitivity analysis was performed using a range of assumptions about the proportion of second and third information appointments which took place. Information from the centres indicated

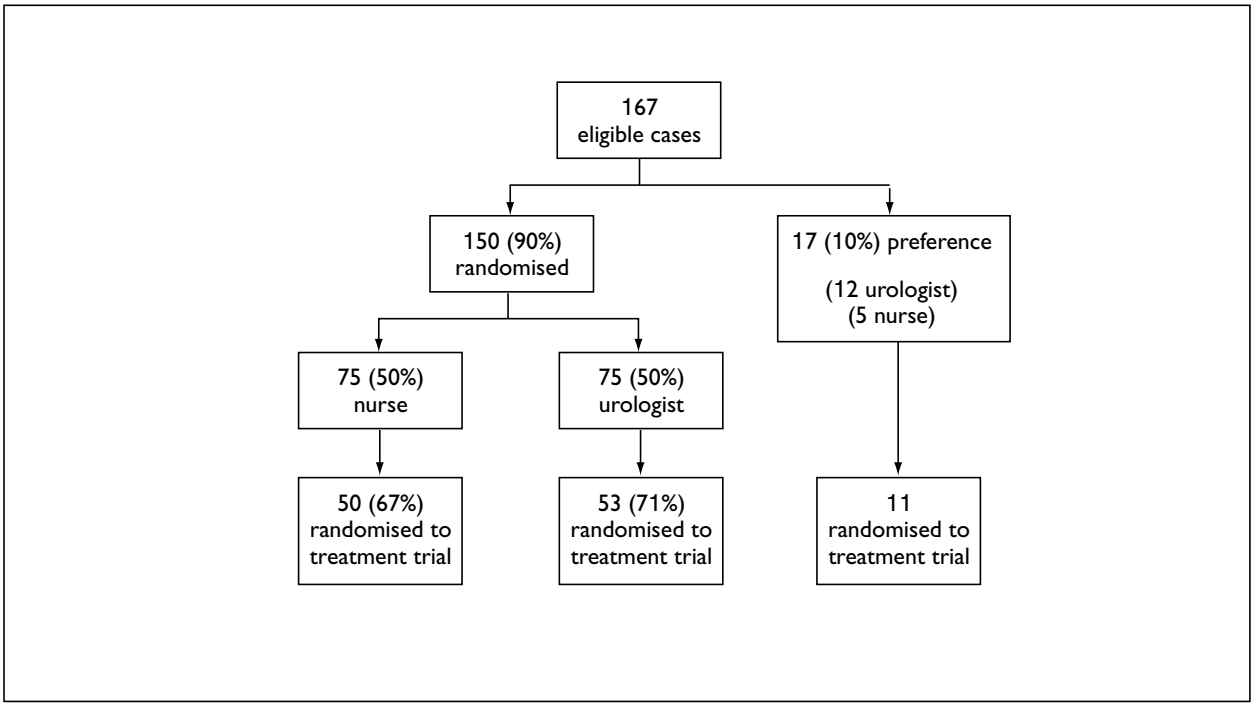

FIGURE 3 *Nurse/urologist comparison*

that Scenario 1 in *Table 3* was the most likely to occur. It was also noted that a second staff member (generally a nurse) was sometimes present during the information appointments and so a sensitivity analysis was performed to account for this.

Table 4 shows the valuation and costs of the documented information appointment. The mean appointment time was greater in the nurse arm, but higher urologist staff costs outweighed the shorter appointment time. Thus in the initial analysis the urologists were more expensive than the nurses. The sensitivity analyses (*Table 3*) showed that varying the proportion of second and third information appointments did not alter this initial finding. Only if it was assumed

TABLE 3 *Results of the sensitivity analysis with differences from the original costs shown in parentheses*

Scenario	Total mean costs (£)	
	Nurse	Urologist
1) Assuming 20% had two information appointments and 10% had three information appointments*	50.96 (+14.56)	60.61 (+17.32)
2) Assuming 75% had two information appointments and 25% had three information appointments*	81.90 (+45.50)	97.41 (+54.12)
3) Assuming 15% had two information appointments and 10% had three information appointments with a nurse, and 20% had two information appointments and 10% three information appointments with a urologist*	49.17 (+12.77)	60.53 (+17.24)
4) Assuming 20% had two information appointments and 10% had three information appointments with a nurse, and 15% had two information appointments and 10% had three information appointments with a urologist*	50.94 (+14.54)	58.52 (+15.23)
5) Assuming 90% of urologists and 10% of nurses had another nurse present	40.53 (+4.13)	89.93 (+46.64)
6) Assuming 10% of urologists and 10% of nurses had another nurse present	40.05 (+3.65)	48.62 (+5.33)
7) Assuming 50% of nurses had another nurse present	54.36 (+17.96)	44.07 (+0.78)
8) Assuming 50% of urologists had a nurse present	36.70 (+0.30)	69.11 (+25.82)

* *It is assumed that all subsequent appointments are of the same duration and conducted by the same member of staff as the documented information appointment*

TABLE 4 *Mean (standard deviation) resource use and cost per patient for the information appointment*

Resource item	Nurse			Urologist		
	N	Time (minutes)	Cost (£)	*N*	Time (minutes)	Cost (£)
Nurse-F grade	53	20.5 (31.2)	12.08 (18.43)			
Nurse-G grade	53	36.1 (32.6)	23.85 (21.50)	38	2.4 (10.2)	1.56 (6.72)
Consultant urologist	53	0.5 (3.4)	0.48 (3.47)	38	41.3 (19.8)	41.73 (19.95)
Total	**53**	**57.1 (22.1)**	**36.40 (13.86)**	**38**	**43.7 (17.1)**	**43.29 (17.58)**

that 50% of the nurse-led appointments had another nurse present (scenario 7) was the nurse arm more expensive than the urologist arm of the trial, and this was unlikely. However, if a large proportion of urologists had a nurse present at the appointments, the costs of the urologist arm rose considerably (scenario 5). Information provided by the centres indicated that a second nurse was more likely to be present during a urologist-led appointment. It can thus be concluded that using nurses was the most cost-effective method for recruitment of patients into the trial.

Acceptability of the three-arm and two-arm treatment trials

The willingness of men to consent to randomisation overall and to either the three- or two-arm trials was calculated. For this analysis, the number of cases for whom complete data were available was 155 (i.e. including the 151 randomised to either a nurse or urologist and the 11 randomised following a preference information appointment, but excluding seven individuals whose decision about the allocation remains pending).

As can be seen from *Figure 4*, 108 men overall consented to randomisation to the treatment trials. This represents a high recruitment rate (70%) with even a lower confidence limit in excess of 60% (95% CI, 62% to 77%). Of the two options, the three-arm trial was considerably more popular than the two-arm (84% opted for the three-arm trial; $p < 0.001$ from the sign test of the null hypothesis of equal preference for the two trials). Even just considering the three-arm trial alone, the recruitment rate was 91/155 or 59% (95% CI, 51% to 67%).

The level of acceptance of the treatment allocation was also high for both trials (*Figure 4*), and slightly

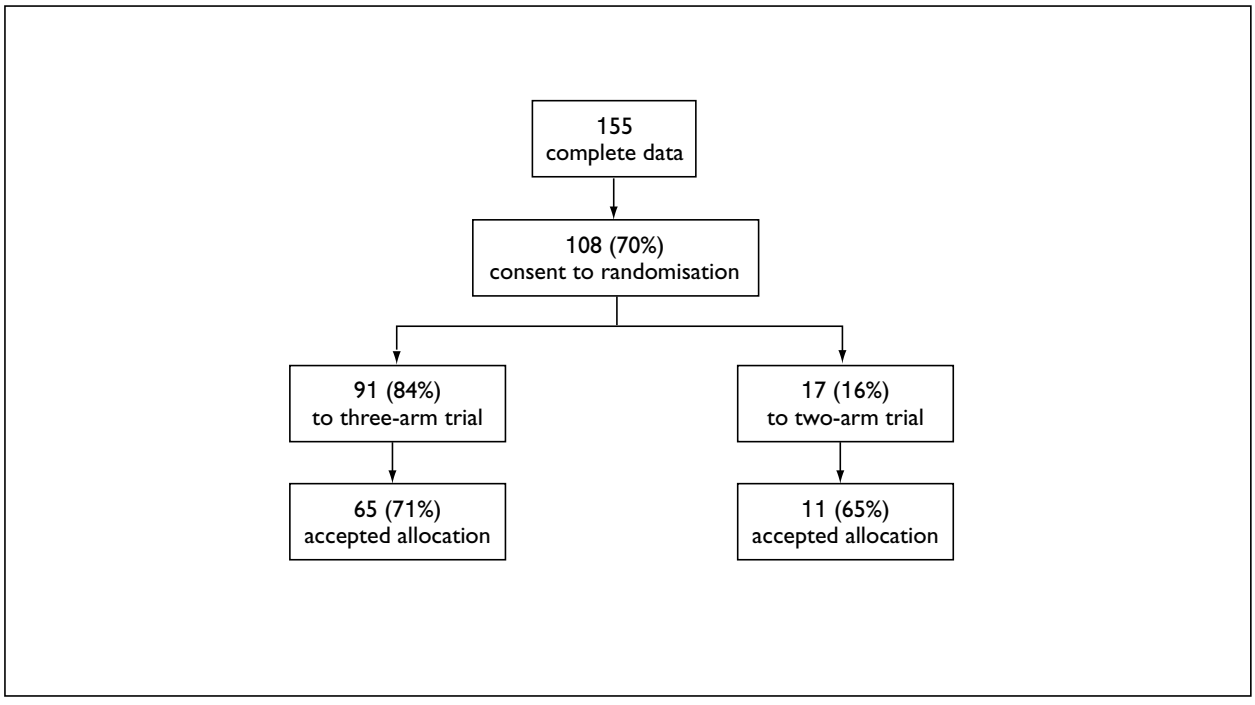

FIGURE 4 *Acceptability of three-arm and two-arm trials*

higher for the three-arm trial. Specifically, 71% (95% CI, 61% to 80%) accepted allocation within the three-arm trial compared with 65% (95% CI, 38% to 86%) among the smaller number opting for the two-arm trial. The difference between these proportions is not statistically significant ($p = 0.58$ from a chi-squared test), though the small numbers in the two-arm trial yield a wide CI around the observed difference of 6.7% (95% CI, –17.8% to +31.3%).

Table 5 shows that acceptance of allocation is considerably higher among those randomised to active monitoring (exact $p = 0.002$ comparing the three groups in the three-arm trial), with little evidence of differences between surgery and radiotherapy in this respect in either trial (exact $p = 0.64$ for the two-arm trial). Consistent with this, among the 45 preference patients whose decision is now known (*Table 6*), about half as many preferred each of surgery and radiotherapy compared with active monitoring. It is important to add, however, that those opting for the two-arm trial are, in effect, rejecting the active monitoring arm, and taking these into account, preferences are similar across the arms.

TABLE 5 *Acceptance of allocation*

	n	Accept allocation	95% CI
Three-arm trial			
Surgery	27	15 (56%)	35 to 75
Radiotherapy	25	13 (52%)	31 to 72
Active monitoring	25	23 (92%)	74 to 99
Two-arm trial			
Surgery	10	7 (70%)	35 to 93
Radiotherapy	7	4 (57%)	18 to 90

TABLE 6 *Treatment preferences expressed by those refusing randomisation and whose treatment decision is known*

Treatment preference	*n*
Surgery	12
Radiotherapy	11
Active monitoring	22

Qualitative research

A great deal of qualitative data has been collected and detailed analyses of a number of topics are underway. The following qualitative data have been collected.

- Case studies with four men interviewed on several occasions during their progress through the study: after the PSA result, biopsy, diagnostic appointment and information appointment.
- In-depth interviews with 39 men – six before receipt of the PSA result and 33 after this – most of whom had a negative biopsy result.
- Twenty pairs of information appointments and subsequent patient interviews – men with confirmed localised prostate cancer.
- Recordings and transcripts of 15 other information appointments – men with confirmed localised prostate cancer.

Analyses so far undertaken of the data from the feasibility study fall into two major areas, both of which are described below.

Perceptions and experiences of prostate cancer and the ProtecT study

Detailed analyses of data are still ongoing. The data presented below are mainly descriptive, with interpretations illustrated by quotations from interviews or clinical appointments. The following major themes emerged:

- experience of case-finding
- experience of negative biopsy
- experience of a positive diagnosis
- acceptability of treatment options
- understanding of randomisation.

(Note: Quotations in this chapter have been recorded verbatim: the pauses (indicated in seconds by the numbers in brackets) and hesitations have been included to give the reader a more accurate idea of the response to various issues and questions put to the patients.)

Experiences of case-finding

All the men made positive comments about the prostate check clinics and the staff they saw. Although, on the whole, the study information was well received and appreciated, there was some concern that there was a lot of it.

Consenting to the PSA test

Only 5% of those who were eligible declined to have a PSA test after receiving the detailed information in the prostate check clinic. Men were asked why they had agreed to have the test.

The offer of PSA testing was construed as an opportunity to discover previously unknown conditions. There was a clear assumption that such discovery could only be a 'good thing':

> No I ..(2).. as I said from my point of view if I had a problem, regardless of whether it's cancer or blood pressure or you know heart problems or any of this, then to me let's have them checked then worry about them when you're told about it. … If the opportunity's there, take it … So I'm quite happy to follow a pattern through and um hopefully ..(2).. it won't go to a stage where there is major decision-making occurring at the end of the day. Hopefully but um that's unknown, that's in the lap of the Gods.

Early detection of prostate cancer was associated with prevention which was, in turn, portrayed positively in contrast to finding out later, when it might be too late:

> **Int: What do you think about programmes that test people for cancer when they aren't actually ill?**
>
> I'm all in favour – prevention is better than cure, no doubt about it.
>
> **Int: Do you think there are any circumstances in which it isn't a good idea to test people who aren't ill for cancer?**
>
> I suppose there are excessively nervous individuals (..) perhaps they ought to be persuaded that that anything that finds out sooner rather than later **must** be a good thing (.) in all types of cancer for sure (1).
>
> I know a couple that have gone with it gone you know have died with it [prostate cancer]. They've probably left it too late, you know.

Further support for this came from knowledge of the existence of preventive screening programmes for other diseases:

> It was just as I said, a letter that offered you this opportunity to have an examination and (I mean) like my wife, umm I'm 54 my wife's 51, ermm like you know it it was sort of inviting for a smear test and all these sort of things, and err you go along because it's preventative. …I felt like it was a similar sort of letter in a different way that you get from opticians …or your dentist. They say come along and you know 6 months or whatever and err (.) I mean you see quite honestly if they offered me a check for anything else, I'd go along quite happily.

Many of the men did not want to consider the negative implications of PSA testing. They reasoned that the odds of being found to have prostate cancer were low, and so a major reason for consenting to testing was to gain peace of mind from knowing that they did not have the disease:

> Well, being as I didn't have any problem that way, umm I thought I would (2) err be OK… I don't have any reason to assume that I would have it, but umm the 3 out of a 100 seemed erm (.) seemed very good odds I think ((laughs))
>
> What I went for was, was peace of mind actually. That's the sort of thing. I mean (2) if there's something they can do and they can find out and they can cure it, it it's just like peace of mind that you haven't got that.

Similarly, there was a desire to avoid thinking about the potential implications of testing unless and until this became necessary:

> No I umm (2) I mean I'd looked at it but obviously thinking that err, you know, I had no concerns about going. I wasn't too worried about it. Never even considered it. Never thought, never even thought about it 'cause I thought well (1) it err, you know, wouldn't involve me.
>
> To me it makes sense that if there's likelihood or possibility of a problem, let's check it out and then worry about it later like sort of thing.

Knowledge about the uncertainties surrounding early detection and treatment, and knowledge that serious complications might result from treatment did not lead participants to question the advisability of PSA testing itself:

> Things like (.) an outside chance of an operation causing incontinence or err impotence – all these things were mentioned but eh (.) I'm still looking on the bright side [laugh].
>
> I had no doubts whatsoever. I mean, umm she gave me the form.… And you know I sort of posted it straight away. I thought … there's only benefits in it for me, err that's the way I looked at it.
>
> **Int: Could you imagine any situations in which perhaps it it it wouldn't be beneficial or were any possible reasons for not having tests raised at the clinic?**
>
> No, I don't think there (is) you know. I'd be quite honest with you, I wasn't interested in any disadvantages. Umm I couldn't well apart from I mean you know if you have it and then you have treatment you can (1) you can umm incontinence problems and this sort of thing, but I mean you know (3) you you've got to weigh one against the other haven't you? And I'm sure that if if there was any problem, and I go back and I do have to have treatment that the medical people will, and, you know, against what's best and what they can do and this sort of stuff.

There was an assumption that the available treatments would be successful and curative, and considerable faith in the medical profession was expressed:

> The fact that it could be treated and was usually successful and that if you hadn't got secondary developments it was almost certain to be successful.

(1) Of course I didn't know about the three methods of treatment, that was all explained to me at the blood test…

Int: What do you understand the implications for a person of having early stage prostate cancer to be?

Well, they're (a) going to have to have treatments, and some of the treatments sound a bit unpleasant, but (b) that they're likely to be cured.

I'd say you had to know what the treatments are before you could say, but err I suppose they're not going give you, do something which is not gonna be good for you … They're trying to do a job, they're trying to find out what's wrong with you so I'd go for anything.

The impact of the PSA test result

As indicated above, the majority of men expected to receive a negative PSA result. Most had a clear idea about when to expect to hear the result, and any delay in receiving this appeared to cause considerably raised anxiety. After some initial difficulties in predicting the timing of the return of results, all centres worked hard to ensure that results were not sent out later than expected.

The receipt of a raised PSA result provoked a number of different reactions in the men, but three clear patterns were seen:

A small number of men were extremely shocked by the result:

I was Mr happy-go-lucky, I made everybody else laugh, but all of a sudden I don't feel like laughing.

A larger group were concerned about the result, but were more positive:

I don't think I really worried about it, but I have **concerned** … It's a good thing that it has been done and it's come to the forefront.

A further group were very stoical in their response:

Oh well, they'll do some more tests … tomorrow's another day.

Experience of a negative biopsy

By chance, the majority of men interviewed turned out to have negative biopsy results. Most of these had a second PSA test in which levels had returned to normal, and these men were relieved that they did not have cancer but also aware that this did not necessarily mean that they would not have prostate cancer in the future. Some of the men continued to have raised PSA levels, and while most were not overly concerned that they might have prostate cancer, they wanted further information and explanation about what this meant and what sort of testing they should have in the future.

Int: Do you feel any more or less susceptible to getting prostate cancer in the future than you did before you took part in the study?

Well, seeing as they've found I haven't got nothing now, basically, I'm glad I took part actually… I would have it [PSA test] done [again] because I'm at that age like, you know, anything can happen …

This has now been clarified for the main trial, as men with evidence of a pre-cancerous lesion (high-grade PIN) will be offered immediate repeat biopsies. Those without high-grade PIN will have free/total PSA measured and if the ratio is greater than 0.12, they will be offered future PSA tests.

Experience of a positive diagnosis

The diagnosis of prostate cancer was given to the men by a urologist in a short 'eligibility' appointment. This appointment was intended to be short to allow the men to absorb the news about the diagnosis, to be informed about the recruitment trial, and randomised to return to see either a nurse or urologist for a longer 'information' appointment. The information appointment was much longer and focused on the details of the treatments, the need for a randomised trial, and recruitment to the trial.

Men who were asked to attend an eligibility appointment were not surprised to receive news of a positive diagnosis. They expected it because they thought that a negative result would be sent by letter:

And when (1) err you're finally finally told that yes you've got a a cancer of the err prostate that of course is quite umm shattering even although you have (.) fears or you suspect by this time that that might well be the case.

This is not to say, however, that receipt of a positive diagnosis was not a 'shock'. Indeed, it was a serious shock and most indicated that they could not absorb much information at this point as they had to concentrate on the diagnosis itself:

It's just it is a bit hard to take on board straight away because as I said earlier (.) hhhh you think you're hard and death's not going to disturb you but when it's your own that's on the line it's that hardness sinks away and you become vulnerable like anyone else.

> Ah so and that was on a Monday and I saw (urologist) on the Thursday so I'd had Tuesday, Wednesday and Thursday, 72 hours to think about it and in the early stages one does **little** apart from think about it. Um being diagnosed with cancer for the first few days there is **nothing** else, it simply fills one's mind and then this gradually retreats.

These data support the retention of this two-stage process in the main trial.

Acceptability of treatment options

The majority of men understood that the ProtecT study was primarily about evaluating treatments. Among men at the point in the study when they have received a raised PSA result, but not had cancer confirmed, the majority indicated that they would like to avoid surgery if at all possible:

> I think if they can just monitor it and see how it goes on, I think it would be one of the best rather than having an operation or radiotherapy.

> If it's a life-saving thing, then you have to have [surgery] … If they could sort of control it without an operation (like they've controlled my blood pressure) I would rather go for that really.

Understandings of randomisation

The data in this section have been taken primarily from analyses of the paired transcripts of information appointments and subsequent interviews with the men.

Irrespective of whether they agreed or refused randomisation, the majority could recall the major principles of the study design.

Chance

The men used a number of lay terms to convey their understanding, including likening the study design to 'a lottery', 'premium bonds', 'balls in a bag', 'tossing a coin', 'straws', 'rolling a die' and 'out of a hat':

> I could have got anything. I mean it's a lottery really isn't it.

> They put it in a computer and all the computer is doing is like a one arm bandit.

Comparison

The majority were clear that randomisation permitted comparison between treatments, with a minority indicating that they also understood bias:

> To me they'll want so many to have the operation, so many to have the radiotherapy and so many to have the (monitoring) so that through the years they can find out what the best treatment has been.

> If people everyone in the survey simply chooses what treatment I can only **assume** that that doesn't give a **fair objective** sampling of the efficacy of A, B and C, something like that you know, the self selection maybe a certain type of person would choose that and that would somehow skew the objective findings of which happens or which turns out objectively to be the best for most people of this particular cancer.

Clinical equipoise

Clinical equipoise is generally taken to be the position that clinicians do not have evidence to decide which of two or more treatments will be the most effective and so are unsure which to recommend. Most men indicated that they understood this concept by stating that the study was being conducted because clinicians do not currently know the best treatment for localised prostate cancer:

> They [study clinical staff] **emphasised** frequently that they don't really know which is the best (treatment) option, what's the best for **me** or another patient.

> They're doing the study because they don't know which is the best way to go, which is the most satisfactory. So in order to check that out they would like to have as many people um randomly going in and saying well I don't mind which one I have.

It can be seen from the above that almost all the men interviewed were able to recall and understand the main principles of the randomised design. This did not automatically mean, however, that they found these principles acceptable. Many of the men had strong feelings that clinicians should have been able to decide on the best treatment based on clinical factors:

> I understood enough about it (random allocation) yea yeah. Not saying that I agree with it. Well, I agree with them having to, trying to get an equal number of people on each one but um I still feel that somewhere along the line (doctors) must have a little bit more preference for one (treatment) or the other.

In making their decision about whether or not to consent to randomisation, the men had to weigh up their understanding of the purposes of the study design with their own beliefs about how sensible it seemed:

> Well I think (random treatment allocation) is quite dodgy. You'd have thought that when you come down to a particular individual their particular circumstance like their age, like the extent of the cancer, like the degree of dispersion of the cancer,

> like the level of the PSA, I mean all those individual factors you'd have thought would have some impact on the decision over the treatment. How would you feel if you were told you've got I don't know breast cancer or something and we've got three random treatments wouldn't you try and identify want to identify **with** the doctor the best treatment for **you** as an individual? See what I mean? So that is a bit bit odd that but of course it's the state.
>
> He said if I couldn't make me mind up that they would put the three things or something into a computer and let that do it for us. Well I wasn't happy with that part of it like (N2). Well I, I didn't think it was right to decide what operation you were going to have you know. He has a mind of his own you know.
>
> Well the treatment basically what he said it was either the knife or the radiotherapy or this wait and see business which would be, if I would agree, by computer random choice and I said well yes because I've got int back of my mind that whoever's programmed that computer has got to have some kind of medical knowledge because obviously someone whose got a very large cancer, which could cause death straight away or within a few month, I can't imagine his name being down on a wait and see basis. What I'm trying to say, there's got to be a level somewhere where they can say yes we'll wait, no we can't wait, I'm hopin', I'm puttin' me faith in it.

Some found comfort in the idea that they would have time and opportunity to think about the allocation and decide freely whether or not to accept it:

> I did agree to (randomisation of treatment), on the understanding of course that I didn't have to accept the randomised choice … I was happy (with random treatment allocation) because I knew that I had an alternative to make my own decision if it wasn't what I wanted.

One man very succinctly indicated that randomisation provided a way to make a treatment decision in the face of uncertainty:

> Didn't know which other way to go. I found it an **immensely** difficult decision to make.

The men struggled with competing views but eventually had to decide whether or not to participate in the trial. The difficulties inherent in participating in a randomised trial were encapsulated by S5:

> I understood that (treatments were equally effective), but I just find it difficult to deal with a random approach to anything. To feel that this very important decision, which is genuinely a decision about the possibility of life or death at some point in the future, being down to chance, I find that difficult to accept. I ought to be able to do better than that. I ought to work it out, the one that is most appropriate for me. I think well one of three is going to be better than the other two for me.

Recruitment to the treatment trials

The data from this section were taken primarily from the analysis by JD of a number of information appointment transcripts, examined in the context of the material from the in-depth interviews and the paired interviews and information appointments. The findings were used to change aspects of the conduct of the feasibility study and the content of the information given to patients by recruitment staff. This process happened particularly during the final 15 months of the feasibility study, and determined the final design of the main treatment trial.

Early findings from these analyses were discussed with one urologist (FCH), and FCH and JD discussed strategies to enhance recruitment which FCH then implemented in one centre. The findings and recommendations for changes to the content and presentation of information were reproduced in three short documents circulated to recruiters in June, October and November 2000. JD evaluated the impact of the documents by listening to subsequent information appointments and discussing findings from patient interviews conducted by NM, MS and LB. A training programme based on the findings was then developed and delivered to recruiters in two centres between August and November 2000. Consent to randomisation and acceptance of allocation were assessed regularly and separately. The focus in this section is on the impact of the qualitative research on changes to the information and patterns of delivery.

The recruitment rate to the treatment trials changed considerably over time (*Table 7*). The overall cumulative proportion consenting to randomisation increased from 49% in July 2000 to 51% in August, and reached 61% in January 2001, and 70% by the end of the feasibility study. The proportion accepting the random allocation remained around, or in excess of, 70%.

The rate of consent to randomisation changed over time as the findings from the qualitative research were introduced into the conduct of the trial through the circulation of documents and training. The findings from the qualitative research had an impact on the conduct of the feasibility study in four major ways:

TABLE 7 *Cumulative consent to randomisation to trials over time (cases with data available on final treatment decision)*

Date	Eligible	Consent to randomisation	Accept allocation*
October 1999 to May 2000	30	Range, 30–40%	Range 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%)
After training		80%	73%

* *Denominator is those consenting to randomisation*

- organisation of study information
- terminology used in study information
- specification and presentation of the non-radical arm
- presentation of randomisation and clinical equipoise.

Organisation of study information

The original study patient information was based on the results of the team's systematic review of the literature[1] and was written with the intention that treatments should be presented in a standard way with surgery first, radiotherapy second, and monitoring third. Recordings of the information appointments and subsequent patient interviews in the early part of the study showed clearly that the treatments were not presented or interpreted equally. The following extract from one information appointment indicates how surgery and radiotherapy were portrayed in detail as aggressive, curative treatments, and monitoring briefly and weakly as 'wait and see':

> Clinic staff 1: We believe that you are suitable for any of these three treatment possibilities … The first treatment is that of radical prostatectomy. Probably the simplest answer is to remove the prostate gland completely – that that gives you the opportunity of removing the whole of the cancer in its entirety. The problem is that radical prostatectomy is a major operation and there are risks … [26 lines of detail follow]
>
> … The second method is radiotherapy – you are trying to destroy the cancer cells by means of X-rays without removing the gland. In other words the X-ray beam destroys the cancer cells and the prostate gland remains *in situ*… [29 lines of detail follow]
>
> … The final treatment is what we call watchful waiting. The basis of this is that we don't know whether your tumour is going to progress or not, and we can simply just watch it carefully … [10 lines of detail follow]
>
> … We can do [randomisation] for the three treatments, that is surgery, radiotherapy or watchful waiting, or if you didn't want to consider watchful waiting, just to compare two treatments which actually try to cure the disease, either surgery or radiotherapy.

By July 2000, fewer patients accepted an allocation of, or expressed a preference for, monitoring compared with radical treatments. Recruiters were asked to present the treatments in the following order: 1) monitoring, 2) surgery and 3) radiotherapy and to describe in similar detail each of the different modes of management and side-effect profiles.

Terminology used in study information

We were aware that certain terms may be interpreted by patients differently from intended.[23,24] The word 'trial' was often confused with the monitoring treatment option and some recruiters assumed patients had refused randomisation when they had only rejected the monitoring arm. Included in the early patient information was a phrase intended to reflect evidence of good 10-year survival: 'the majority of men with prostate cancer will be alive 10 years later.' Patients interpreted this phrase as an (unexpected) suggestion that some might be dead in 10 years – an idea that shocked some in their 50s and 60s.

Changes to terminology were introduced in document 1 and reinforced in the training programme. Recruiters replaced 'trial' with 'study' and presented positive information about survival in terms of 'most men with prostate cancer live long lives even with the disease.'

Specification and presentation of the non-radical arm

It rapidly became clear that the non-radical treatment option caused difficulties for patients and recruiters. Initially, the arm was termed 'conservative monitoring' to emphasise the lack of radical intervention and regular review process. As the excerpt above shows, however, recruiters tended to portray monitoring as 'do-nothing' and often called it 'watchful waiting'. Patients made it clear that they interpreted this as 'no treatment' and 'watchful waiting' had the shocking

implication that clinicians would just 'watch while I die':

> Patient 1: Two [treatments] seem to be a way of getting rid of it and one seems to be 'we'll let you know when you're getting any worse' … I would imagine once you've got it, it just gets worse and worse and if you leave it too late, you-you've gone, you know, you've possibly had it."

In June 2000, the non-radical arm was re-named 'monitoring' and re-defined to involve regular PSA tests (3- or 6-monthly), with the potential for intervention if required or requested. Recruiters were asked to emphasise the generally slow-growing nature of most prostate cancers and present monitoring first in the list of treatments (see above). To balance the detail about treatment complications potentially arising from the radical treatments, men were more clearly informed that the risk with monitoring was that future radical treatment might not be possible because the tumour itself had progressed or the patient was no longer young or fit enough for it.

There was an immediate impact across the centres as patients accepted the monitoring allocation or expressed a preference for it. Continued scrutiny of information appointments showed that in two centres there was still a tendency to describe it weakly and to create distinctions between it and the radical 'active' treatments, such that patients could not accept monitoring (two separate excerpts below):

> Clinic staff 2: Watching it and treating it – it's not treatment immediately, it's, it's a different form of management: you're managing the disease rather than treating immediately, you're monitoring it and treating it if [it] shows signs of progression … if you monitor it, it may not cause problems for some time … if it does start to progress and cause problems you deal with them usually with hormone treatment.
>
> Patient: Well I suppose it's better for me to say now you know that I feel that I would rather have something done about it at this stage.
>
> Clinic staff 3: Monitoring – obviously older people they often choose that because they feel, you know, if they may not be around in ten years time and it may be a good bet to take
>
> Patient: Hmm
>
> Clinic staff 3: Some people your age still choose that treatment because it sort of balances things – you want a good quality life at the moment well we'll deal with the problem if and when it comes up.

Documents 2 and 3 re-stated what monitoring should involve, with the addition that test results should be presented graphically and the inclusion of anonymised examples of 'good' and 'not so good' information presentation. In the training programme, the non-radical arm was re-named 'active monitoring', with a strong emphasis on the close scrutiny of regular test results to ensure that radical treatments should remain an option for those who would want them if (but only if) their prostate cancer began to show evidence of progression. Recruiting staff expressed much greater confidence in this:

> Clinic staff 4: The first one would be to be monitored very closely and not to receive any active intervention and that would be by watching you every 3 months certainly for the first year, we will bring you back, we'll do the blood test we check the prostate and if the disease remains stable then there is obviously you know everybody's happy. **If** the blood test starts to change it is extremely sensitive and it would give us an indication that there may be more activity there, so then **all** the options are discussed again. So that's option number one.

Presentation of randomisation and clinical equipoise

Recruiters and patients also had difficulty with randomisation and clinical equipoise. Many men had misgivings about randomisation and had difficulty understanding why the best treatment was not known (see above). Each of the documents contained guidance on these aspects, and they are an integral part of the training programme.

In terms of equipoise, we found it necessary to emphasise that the recruiter must be genuinely uncertain about the best treatment and thus to believe the patient to be suitable for all three treatments. Even more important, they needed to be confident in this belief. We further emphasised that the aim of the information appointment was to describe the treatments in terms of probably having equivalent mortality outcomes but different complications and side-effects. Patients often expressed lay views that cancer needed to be surgically removed or knowledge of friends or relatives who had died of advanced disease or suffered treatment complications. Some brought information from newspapers or websites, which was often biased in favour of radical treatment. It was necessary to help recruiters feel comfortable about challenging views and information that was biased.

In terms of randomisation, it was necessary to convince recruiters that randomisation could offer a reasonable way of resolving the dilemma of treatment choice, so that they could then

pass on this belief and confidence to patients. They were encouraged to attempt randomisation before the end of the information appointment, as men who left without a random allocation tended to believe that they had to reach their own choice. Finally, it was made clear that patients should not necessarily have to accept or reject the allocation at the end of the appointment as some needed time to consider whether the allocated treatment was acceptable. It was also re-emphasised that patients must know that there was no compulsion whatever to accept the allocation and that they could opt for a different treatment at any time.

The gradual impact of the changes introduced by the documents on the randomisation rate is evident from *Table 7*, as is the substantial rise in consent to randomisation to 80% following the implementation of the training programme. At the same time, the proportion accepting the random allocation remained the same (around 70–75%).

Pilot of the treatment trial outcome measures

All men with confirmed localised prostate cancer were asked to consent to being followed-up under the ProtecT study, including all those randomised and expressing preferences. Procedures and paperwork have been developed that will allow full research and patient-based follow-up every year, with an interim first patient-based follow-up at 6 months. The following outcome measures were subjected to preliminary piloting and will be used in the main treatment trial.

Survival
All men involved in the study will be flagged with the Office of National Statistics so that details of deaths are sent to the research team and recorded. A small research group will be convened before each major analysis of survival to scrutinise death certificates and investigate/confirm the true cause of death.

Disease progression
This will be assessed using PSA, DRE, ultrasonography, biopsy and bone scans.

Treatment complications
Immediate and delayed treatment complications including blood loss, rectal/bowel injury, urethral stricture, incontinence, and concerns about living with an untreated cancer will be collected in clinical schedules.

General health status
This will be measured by the SF-12, a subset of the SF-36, and EuroQol EQ-5D in patient questionnaires.

Anxiety and depression
These will be measured by the HADS.[20]

Urinary symptoms and sexual function
These will be measured by the ICS*male*SF and ICS*sex* questionnaires.

Quality of life related to prostate cancer treatment
This will be measured using the FACT scale.

Chapter 4
Discussion

The ProtecT study shows that it is feasible to carry out an RCT of treatments for localised prostate cancer. The key to the success of the study was its innovative design, which included embedding the trial within a qualitative study[44] and preceding randomisation with a case-finding process in which men were clearly informed about the implications of PSA testing and the need for a randomised trial of treatments. Almost all men who attended prostate check clinics consented to have a PSA test. Qualitative research indicated that men appeared to recall and understand the potential implications of testing, but that their views about the power of preventative medicine and perceptions of the opportunities for early detection and treatment of prostate cancer and the likelihood that their test would be negative outweighed any concerns.

The programme of case-finding was successful, with 56% of those invited to prostate check clinics attending and a prostate cancer detection rate of 2.2% among tested clinic attendees. A total of 754 men underwent biopsy and 224 cases of prostate cancer were detected. The practices involved in the feasibility study were not selected with the aim of being representative of the general population and, as a consequence, were less ethnically diverse and of higher social status than the overall population. In the main trial, it will be necessary to include a greater social mix. It has been suggested that a comparison arm should be established in the form of a cluster randomised trial of practices allocated either to intensive case-finding in the ProtecT study or comparison arm with no intervention. Such a study would inform policy on prostate cancer screening.

The PSA threshold was changed to a level of ≥ 3.0 ng/ml for all men after 1 year of recruitment following publications indicating this to be a more efficient cut-off point.[35] The results for the PPVs according to various PSA thresholds provide a (retrospective) justification for this chosen cut-off point of 3 ng/ml for all men regardless of age. Men below the threshold of 3 ng/ml were not followed-up further as part of the study, and so no PPVs are available below this level. In turn, then, at this time it is not possible to calculate with any reliability (absolute) values for either the sensitivity or specificity for any of the cut-off points. Even in the long run, the fact that men who develop prostate cancer can and do remain undiagnosed means that true sensitivity (and hence specificity) will remain elusive. The PPVs that were obtained are similar to those found by Schröder and co-workers in the European trial of prostate cancer screening.[35] While levels around 25–30% may seem low, as the first PSA test is followed by a further test and many other investigations, expecting levels higher than this might be somewhat optimistic. In conclusion, then, even without reliable absolute estimates of sensitivity, in retrospect the chosen (non-age-related) cut-off point of 3 ng/ml would appear to be vindicated.

An examination of the impact of case-finding on levels of anxiety, depression and urinary symptoms suggested that the process was broadly acceptable, with even those attending for a biopsy with raised PSA results not showing increased levels of any of these aspects.

The two-stage process of presenting the diagnosis and then giving men 7–10 days before the 'information appointment' at which the treatments and study could be discussed at length was appreciated by the participants. Qualitative research showed that those with a positive diagnosis of cancer were not surprised to have cancer when they were asked to attend for an appointment, but that the shock of being given the diagnosis meant that they were not able to absorb much information at this stage. Many took the opportunity to bring partners to the information appointment and were grateful for the time given to them by the urologist or nurse.

The majority (90%) of men with confirmed localised prostate cancer consented to see either a nurse or urologist for the information appointment where they were given detailed information about the study and the treatments for prostate cancer, and asked to consent to randomisation in the treatment trials. By the end of the feasibility study, 70% of eligible men

were consenting to randomisation to either the three- or two-arm treatment trial. This had risen from around 30–40% in the earliest part of the feasibility study, with marked improvements as the findings of the qualitative research were implemented in the centres.[44] We expect these findings to be replicated in the new clinical centres required for the main trial and have devised a training programme for this purpose.

In terms of the effectiveness of nurses or urologists in obtaining consent to randomisation, the difference between them was neither large nor statistically significant ($p = 0.60$). The confidence limits were below the target difference specified in the power calculation for the trial of recruitment strategies. We were able to rule out nurses being substantially more effective than urologists. We took the decision that nurses would be the primary recruiters for the main trial on pragmatic and economic grounds. Further research is warranted to investigate differences between nurses and clinicians in recruitment.

Randomisation to the three-arm trial was significantly more common than to the two-arm trial ($p < 0.001$). In addition, the level of acceptance of the treatment allocation within the trials was high, and highest for the three-arm trial. Overall, 71% of those allocated within the three-arm trial accepted their allocation, compared with 65% in the two-arm trial (but this difference was not statistically significant).

It was essential that both consent to randomisation and acceptance of allocation remained high throughout the study. High levels of consent to randomisation were essential for the overall feasibility of the main trial. In addition, reasonably high levels of acceptance of allocation were required to ensure that primary analysis by intention-to-treat would provide a valuable estimate of the relative benefits of the treatments. Further, high levels of both aspects would suggest that patients were not coerced into consenting to randomisation.

The treatment preferences expressed by the men who did not consent to randomisation changed during the feasibility study. Initially, men favoured the radical treatments (particularly surgery), but by the end of the feasibility study, the most commonly preferred treatment was active monitoring, and the difference between the treatments was statistically significant ($p = 0.002$). However, when those who opted for the two-arm trial are also taken into account (they have rejected the active monitoring arm), treatment preferences were becoming more balanced across the arms.

Qualitative research in the feasibility study was used to explore the men's perceptions of prostate cancer and experiences of being in the ProtecT study. It was also used to investigate the interactions between recruitment staff and patients in the information appointments and men's subsequent views in interviews. This allowed the development of patient information and methods of presenting information that resulted in high rates of consent to randomisation while preserving informed consent and patient and clinic staff satisfaction. By the end of the feasibility study, 70% of men had consented to randomisation to the treatment trials.[44]

Qualitative methods are conventionally used to help the interpretation of quantitative results. Here we inverted the normal relationship between these methods, and embedded the randomised trial within the qualitative study. We have shown that the integration of qualitative research methods can aid understanding of the recruitment process and, further, elucidate the changes necessary to the content and delivery of information to maximise recruitment and ensure effective and efficient trial conduct.[44]

The qualitative research illuminated four ways in which the study information or presentation was having a negative impact on the study. Some of the issues raised might appear, in retrospect, to be simple, such as re-organising the order of presenting treatments, or avoiding terms such as 'trial' and 'watchful waiting', which had particular and unexpected meanings to patients. These 'simple' issues were, however, unknown at the commencement of the study and, although clearly plausible would probably never have become apparent without the qualitative research. A clear case in point is the term 'watchful waiting', which is in common use in urology and many other clinical specialties to describe, in shorthand, a non-interventionist treatment. In lay terms in the UK, this term conveys an impression of wilful neglect, in which a patient's disease is watched and everyone waits for death to arrive. It was only when the non-radical arm was re-defined as 'active monitoring' that patients and clinicians gained confidence in it as a non-neglectful option.[44]

Other issues that emerged were more complex. Studies that have investigated patients'

understanding of randomisation have concluded that the concept is difficult and that patients tend not to understand it.[22–24] In this study, most men were able to recall and describe randomisation but they found it difficult to accept. Clinical equipoise was particularly difficult and this has received remarkably little examination in the literature. Findings from this study relating to both these aspects will be presented in detail elsewhere, but it was clear that they were intertwined. We found it to be essential that recruiting staff themselves believed that each man was eligible for all three treatments, that they could not recommend any particular treatment because each had advantages and disadvantages and the most effective treatment was unknown, that a trial was urgently required, and that randomisation could provide a sensible and credible way of reaching a decision in the face of such uncertainty. If recruiters' manner, body language or use of terminology betrayed any indication that they were not committed to these aspects, patients were quick to pick this up and to question the study, often employing subtle and sophisticated reasoning that surprised some recruiters.[44]

Maximising recruitment and informed consent concurrently should be the aim of trials, but previous studies have suggested that improving patients' understanding of randomisation might lead to an increase in informed patients but a fall in recruitment rates.[22,23] The ProtecT feasibility study shows that this is not inevitable – indeed, recruitment and informed consent can be maximised together by the employment of these methods.[44] Differences in recruitment rates often develop between centres in multicentre trials. This was certainly the case in this study, but because of the flexibility of the qualitative research, we were able to investigate the causes of the disparities. Indeed, the differences between the centres focused our investigations and allowed us to examine the impact of changes and training.[44]

The desire to increase the rate of consent to randomisation could be interpreted by some as coercive and unethical. The proportion who accepted the treatment allocation remained at around 70–75% throughout. Indeed, it is likely that the study became more ethical over time as participants were increasingly likely to receive the optimal study information and thus to understand and be in a position to make an informed decision about whether to accept randomisation as a method of treatment choice. Many of those rejecting randomisation in the early part of the study did so because they had received unbalanced information open to misinterpretation.[44]

The controversial nature of the study and the extreme differences between the treatment arms might be suggested to limit the generalisability of the findings to other randomised trials. However, it could be argued that it is controversial trials attempting to tackle difficult (some might say impossible) issues that are the very studies that need to benefit from the qualitative evaluation employed here. In many ways, the extreme nature of the treatment choices helped to illuminate the issues that were most difficult, and encouraged patients to be explicit about, for example, the way they interpreted terms. The plausibility of these findings suggest that such a qualitative evaluation of recruitment might be useful in all trials to make them more efficient and ethical.[44] However, this remains to be tested in other trials.

The findings here also support the suggestion that the conduct of trials is not as straightforward as the textbooks suggest. The concepts inherent in trials, particularly randomisation and clinical equipoise, are complex and difficult and place particular demands on participants and recruiters. Better training and information for these groups may help, but we would contend that the employment of qualitative methods is required to really understand what is happening within any trial.[44]

Health services research is still a developing tradition in which very different disciplines and paradigms are brought together to tackle particular health-related questions. Combining different approaches can be difficult, but in the ProtecT feasibility study we brought together under the general umbrella of health services research, the qualitative traditions of sociology and anthropology, the epidemiological and statistical disciplines informing randomised trial design, and academic urology and nursing. The methodology of the study contravened conventional approaches by being driven, not by the randomised trial design, but by the qualitative evaluation. Effectively, the ProtecT feasibility study embedded the randomised trial within the qualitative study and followed a sociological iterative approach.[44]

We have now been funded by the NHS R&D HTA Programme to extend the ProtecT feasibility study into a main trial including six further centres. The main study will require a 5-year programme of

case-finding and include a randomised trial of active monitoring, radical prostatectomy and radical conformal radiotherapy. The aim is to investigate the comparative effectiveness and cost-effectiveness of the three main treatments for localised prostate cancer with the primary outcome of survival at 10 years. A wide range of clinical and patient-based data will be collected to allow the evaluation of the short- and medium-term impact of each treatment on quality of life.

Acknowledgements

Research team

Primary grant holders

Jenny Donovan, Professor of Social Medicine, University of Bristol.

Freddie Hamdy, Professor of Urology, University of Sheffield.

David Neal, Professor of Surgery, University of Newcastle.

Tim Peters, Professor of Primary Care Health Services Research, University of Bristol.

David Jewell, Editor, Journal of General Practice/Senior Lecturer in Primary Care, University of Bristol.

Philip Powell, Consultant Urologist, Newcastle.

David Gillatt, Consultant Urologist, Bristol.

Steering group members

Steven Oliver, Lecturer in Epidemiology and Public Health, University of Bristol.

Hing Leung, Consultant Senior Lecturer in Urology, University of Newcastle.

John Anderson, Consultant Urologist, Sheffield.

Stephen Frankel, Professor of Epidemiology and Public Health, University of Bristol.

Peter Kirkbride, Consultant Radiotherapist, Sheffield.

Ian Pedley, Consultant Oncologist, Newcastle.

John Graham, Consultant Oncologist, Bristol.

Joanna Coast, Senior Lecturer in Health Economics, University of Bristol.

David Gunnell, Senior Lecturer in Epidemiology and Public Health, University of Bristol.

Funded research staff

Research

Lucy Brindle, Daniel Dedman, Mark Sidaway.

Nursing

Miranda Benney, Sally Burton, Ingrid Emmerson, Louise Goodwin, Christine Hardy, Peter Holding, Clare Kennedy, Sue Kilner, Teresa Mewes, Andrew Robinson, Liz Salter, Lyn Wilkinson.

Clerical

Helen Harris, Barbara Hattrick, Carol Torrington, Andrea Wilson.

Additional research staff supported by MRC HSRC

Nicola Mills, Monica Smith.

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Sian Noble.

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Public Health Directorate,
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Mrs Kathlyn Slack,
Professional Support,
Diagnostic Imaging & Radiation Protection Team,
Department of Health,
London

Mr Tony Tester,
Chief Officer,
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Dr Andrew Walker,
Senior Lecturer in Health Economics,
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Professor Martin J Whittle,
Head of Division of Reproductive & Child Health,
University of Birmingham

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Oxford Radcliffe Hospital

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Professor Iain T Cameron,
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University of Southampton

Mr Peter Cardy,
Chief Executive,
Macmillan Cancer Relief,
London

Dr Christopher Cates,
GP & Cochrane Editor,
Bushey Health Centre,
Bushey, Herts

Dr Karen A Fitzgerald,
Pharmaceutical Adviser,
Bro Taf Health Authority,
Cardiff

Dr Felicity J Gabbay,
Managing Director,
Transcrip Ltd,
Milford-on-Sea, Hants

Mr Peter Golightly,
Director, Trent Medicines Information Services,
Leicester Royal Infirmary

Dr Alastair Gray,
Director, Health Economics Research Centre,
Institute of Health Sciences,
University of Oxford

Mrs Sharon Hart,
Managing Editor, *Drug & Therapeutics Bulletin*,
London

Dr Christine Hine,
Consultant in Public Health Medicine,
Bristol South & West Primary Care Trust

Mrs Jeannette Howe,
Deputy Chief Pharmacist,
Department of Health,
London

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Dr Frances Rotblat,
CPMP Delegate,
Medicines Control Agency,
London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St James's University Hospital, Leeds

Mrs Katrina Simister,
New Products Manager,
National Prescribing Centre,
Liverpool

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Professor of Child Health,
University of Nottingham

Dr Richard Tiner,
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London

Professor Jenifer Wilson-Barnett,
Head of Florence Nightingale School of Nursing & Midwifery,
King's College,
London

Therapeutic Procedures Panel

Members

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Professor Bruce Campbell,
Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor John Bond,
Professor of Health Services Research, Centre for Health Services Research, University of Newcastle-upon-Tyne

Ms Judith Brodie,
Head of Cancer Support Service, Cancer BACUP, London

Ms Tracy Bury,
Head of Research & Development, Chartered Society of Physiotherapy, London

Mr Michael Clancy,
Consultant in A & E Medicine, Southampton General Hospital

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham

Dr Carl E Counsell,
Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd,
Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Gene Feder,
Professor of Primary Care R&D, St Bartholomew's & the London, Queen Mary's School of Medicine & Dentistry, University of London

Professor Richard Johanson,
Consultant & Senior Lecturer, North Staffordshire Infirmary NHS Trust, Stoke-on-Trent (deceased Feb 2002)

Dr Duncan Keeley,
General Practitioner, Thame, Oxon

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester

Professor Rajan Madhok,
Medical Director & Director of Public Health, North & East Yorkshire & Northern Lincolnshire Strategic Health Authority, York

Dr Mike McGovern,
Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford,
Consultant Physician, Frenchay Healthcare Trust, Bristol

Professor Mark Sculpher,
Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr Ken Stein,
Senior Lecturer in Public Health, Peninsular Technology Assessment Group, University of Exeter

continued

Expert Advisory Network

Members

Mr Gordon Aylward,
Chief Executive,
Association of British
Health-Care Industries,
London

Mr Shaun Brogan,
Chief Executive,
Ridgeway Primary Care Group,
Aylesbury, Bucks

Mr John A Cairns,
Reader in Health Economics,
Health Economics
Research Unit,
University of Aberdeen

Professor Nicky Cullum,
Director of Centre for
Evidence-Based Nursing,
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Dr Katherine Darton,
Information Unit,
MIND – The Mental
Health Charity, London

Professor Carol Dezateux,
Professor of
Paediatric Epidemiology,
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Dean of Faculty of Medicine
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& Primary Care,
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Mr Leonard R Fenwick,
Chief Executive,
Freeman Hospital,
Newcastle-upon-Tyne

Professor David Field,
Professor of
Neonatal Medicine,
The Leicester Royal
Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher &
Tutor & President,
National Childbirth
Trust, Henfield,
West Sussex

Ms Grace Gibbs,
Deputy Chief Executive
Director for Nursing,
Midwifery & Clinical
Support Services,
West Middlesex
University Hospital,
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Dr Neville Goodman,
Consultant Anaesthetist,
Southmead Hospital, Bristol

Professor Robert E Hawkins,
CRC Professor & Director
of Medical Oncology,
Christie Hospital NHS Trust,
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Professor F D Richard Hobbs,
Professor of Primary Care
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Professor Allen Hutchinson,
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Professor David Mant,
Professor of General Practice,
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Professor Alexander Markham,
Director,
Molecular Medicine Unit,
St James's University Hospital,
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Dr Chris McCall,
General Practitioner,
The Hadleigh Practice,
Corfe Mullen, Dorset

Professor Alistair McGuire,
Professor of Health Economics,
London School of Economics,
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Dr Peter Moore,
Freelance Science Writer,
Ashtead, Surrey

Dr Andrew Mortimore,
Consultant in Public
Health Medicine,
Southampton City Primary
Care Trust

Dr Sue Moss,
Associate Director,
Cancer Screening
Evaluation Unit,
Institute of Cancer Research,
Sutton, Surrey

Mrs Julietta Patnick,
National Coordinator,
NHS Cancer
Screening Programmes,
Sheffield

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe,
Stoke Poges, Berks

Ms Marianne Rigge,
Director, College of Health,
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Dr William Rosenberg,
Senior Lecturer &
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Professor Ala Szczepura,
Director, Centre for
Health Services Studies,
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Dr Ross Taylor,
Senior Lecturer,
Department of General
Practice & Primary Care,
University of Aberdeen

Mrs Joan Webster,
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Advisory Network

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We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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