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# ProDiet

Prostate and Diet Study

Protocol v 1.3

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CRUK/07/057

**Principal Investigators:**

JA Lane<sup>1</sup>

C Metcalfe<sup>1</sup>

FC Hamdy<sup>2</sup>

JL Donovan<sup>1</sup>

DE Neal<sup>3</sup>

**Trial Co-ordinator:**

JA Lane<sup>1</sup>

<sup>1</sup>Department of Social Medicine, University of Bristol, Bristol BS8 2PR Tel: 0117 9287335

<sup>2</sup>Nuffield Department of Surgery, University of Oxford, Oxford OX3 29DU Tel: 01865 221297

<sup>3</sup>Oncology Centre, Addenbrooke's Hospital, Cambridge, CB2 2QQ Tel: 01223 331940

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**Co-Investigators**

Professor George Davey-Smith, Dept of Social Medicine, University of Bristol, [zetkin@bristol.ac.uk](mailto:zetkin@bristol.ac.uk)

Professor Jeff Holly, Dept of Clinical Sciences at North Bristol, University of Bristol,  
[jeff.holly@bristol.ac.uk](mailto:jeff.holly@bristol.ac.uk)

Professor Richard Martin, Dept of Social Medicine, University of Bristol, [r.martin@bristol.ac.uk](mailto:r.martin@bristol.ac.uk)

**Clinical Coordinator**

Professor Freddie Hamdy, Nuffield Department of Surgery, University of Oxford, Oxford OX3 29DU  
Tel: 01865 221297, Fax: 01865 765063, email: [Freddie.hamdy@nds.ox.ac.uk](mailto:Freddie.hamdy@nds.ox.ac.uk)

**Study Coordinator**

Dr Athene Lane, Dept of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road,  
Bristol BS8 2PR Tel: 0117 9287335, Fax: 0117 9287292, email: [athene.lane@bristol.ac.uk](mailto:athene.lane@bristol.ac.uk)

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**Principal Statistician**

Dr Chris Metcalfe, Dept of Social Medicine , Bristol, Tel: 0117 9287326, email:  
[C.Metcalfe@bristol.ac.uk](mailto:C.Metcalfe@bristol.ac.uk)

**Data Manager**

Ms Liz Down, Dept. Social Medicine, Bristol Tel: 0117 9287275, email: [Liz.Down@bristol.ac.uk](mailto:Liz.Down@bristol.ac.uk)

**Qualitative Research**

Dr Kerry Avery, Dept. Social Medicine, Bristol Tel: 0117 9287272, email: [Kerry.Avery@bristol.ac.uk](mailto:Kerry.Avery@bristol.ac.uk)

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## Abbreviations

CC = Clinical Centre, SMed = Dept of Social Medicine, University of Bristol

## 1. Introduction

### 1.1 Background to study

Prostate cancer is a major public health issue. The natural ageing of the population, combined with the continued and widespread use of improved diagnostic tests such as serum prostate specific antigen (PSA), are resulting in an increase in the numbers of men diagnosed with localised prostate cancer. In England and Wales, it is the second most common malignancy in men, with 6,179 new cases registered in 1971, rising to 17,210 in 1993<sup>1</sup>. Screening to identify prostate cancer while it is confined to the gland has provoked much public and scientific attention and there is intense debate about its role in improving men's health. While there are strong advocates of screening, the findings from most reviews of the scientific evidence conclude that there is insufficient evidence to recommend population screening because of the lack of evidence that prostate cancer screening would improve the quantity and quality of men's lives<sup>2-5</sup>. Particular concerns relate to the lack of knowledge about the natural history of screen-detected disease, and the lack of evidence about the effectiveness of treatments.

Finasteride reduces the risk of prostate cancer in the men with a low PSA and negative biopsy<sup>6</sup> but side effects made its use on a long term community basis unfeasible and it has not been widely prescribed for prostate cancer prevention. Dietary prevention could be an alternative, and promising candidates have been identified in the recent WCRF systematic review of observational studies<sup>7</sup>, with some of the strongest evidence emerging for lycopene. The only ongoing trials in this area are of Vitamin E and selenium (the SELECT trial)<sup>8</sup> in men with an initial PSA of less than 4.0ng/ml and a US trial of selenium with HGPIN patients.<sup>9</sup> Ideal dietary modification would inhibit both tumour initiation and growth of small cancer foci. Laboratory and observational studies indicate that lycopene and green tea may both possess this dual action but robust trial evidence is urgently required.<sup>10</sup>

Lycopene is a carotenoid constituent of tomatoes with potent cytostatic activity. Tomato consumption was associated with a 31% reduction in prostate cancer risk<sup>7</sup> and lycopene reduced *in vivo* DNA damage.<sup>10</sup> A recent small trial in high risk men in Tobago has shown lycopene supplementation to be acceptable and tolerable in that setting.<sup>11</sup> A recent review of lycopene concluded that 'further well-designed studies are necessary to establish the role of tomatoes and tomato products in the prevention and therapy of prostate cancer'.<sup>12</sup> Green tea contains active polyphenols including the catechins epigallocatechin-3-gallate (EGCG).<sup>13</sup> An effect of green tea in reducing prostate cancer risk is supported by some observational evidence.<sup>7</sup> A small trial of green tea in HGPIN patients showed good tolerability at 12 months.<sup>13</sup> Initial evidence suggests that these phytochemicals may modulate insulin-like growth factor (IGF-1 and IGFBP-3) levels which are associated with prostate cancer risk.<sup>14</sup>

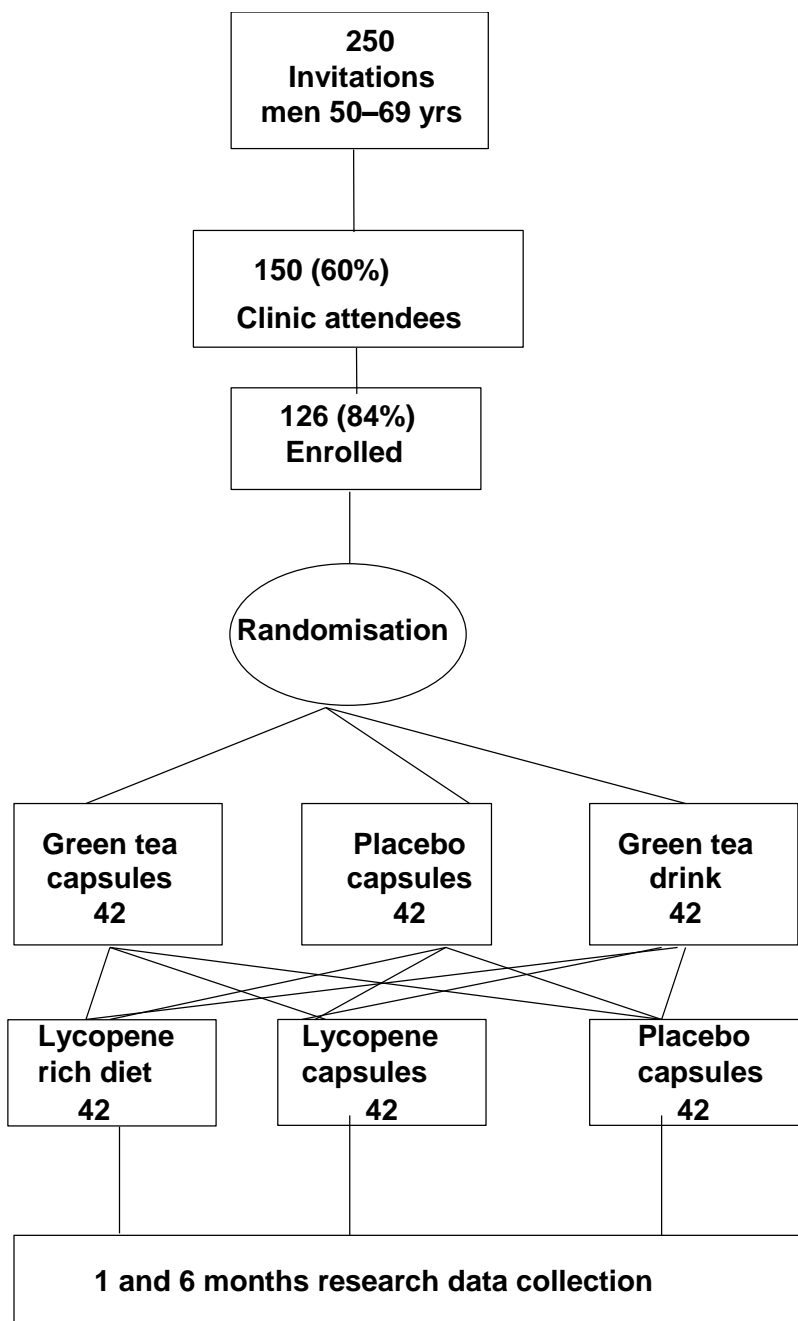
### 1.2 Benefits to the NHS

Prostate cancer is a major public health problem with significant mortality and morbidity. The opportunities for prevention currently are few, with the value of prostate cancer screening awaiting randomised trials including ProtecT (Prostate Testing for Cancer and Treatment), a multi-centre treatment trial preceded by community-based prostate specific antigen (PSA) testing with over 85,000 men enrolled. The ProtecT study also identifies men with PSA values just below the biopsy threshold (3.0 ng/ml) (c.2,400) and others with negative biopsies (c.4,300). These men have an

elevated risk of prostate cancer as they include those with precursor conditions (e.g. HGPIN) and small cancer foci undetected by biopsies.

Dietary prevention would be an important clinical development as there is no guidance currently available to reduce prostate cancer risk for these groups. There is an increasing rate of detection in the general population through opportunistic PSA screening. This represents an increasing burden on NHS resources, and is becoming a serious economic and ethical problem. While the need for randomised controlled trials of dietary prevention is not in doubt, difficulties in mounting such trials called for new methodological approaches which were employed in the ProtecT study – methods which incorporates more fully the participant’s perspective.

## 2. Trial design



### 3. Aims

This study aims to investigate the feasibility of recruiting men identified with an increased risk of prostate cancer from the ProtecT study into a randomised trial of dietary modification. The study also aims to investigate whether dietary modification or supplementation results in elevated serum levels of the biological active dietary agents.

### 4. Objectives

The primary objective is to assess serum lycopene and epigallocatechin-3-gallate (green tea) levels at six months following randomisation. The secondary objectives are to evaluate:

- trial recruitment and randomisation rates
- intervention tolerability
- compliance
- trial retention
- PSA values
- dietary compliance with recommendations
- weight and body mass index
- attitudes and views of men and their spouses about dietary modification and participation in long term

### 5. Study design

The study consists of two major components:

- 1) A 2x3 factorial design double blind RCT of dietary modification with green tea and lycopene
- 2) In-depth qualitative interviews which will investigate men's views about disease prevention, diet and prostate cancer, their willingness to modify diet or take supplements and attitudes towards participation in long-term trials of dietary modification.

### 6. Ethical aspects

#### 6.1 Ethics

The study will be conducted according to the Declaration of Helsinki 1964, as revised in Tokyo 1975, in Venice 1983 and by the 41st World Medical Assembly, Hong Kong, September 1989.

#### 6.2 Ethics Committee Approval (CC)

Approval has been obtained from Trent MREC for the study (08/H0405/61). The principal investigator at each clinical centre (CC) will submit the protocol for approval for research governance. The application for approval will include a copy of the participant consents, information sheets and other relevant materials.

#### 6.3 Participant Consent (CC)

Persons asked to participate in this research are entitled to choose whether or not to take part. Their decision will be voluntary and they will be competent to understand what is involved. Consent forms will be designed to assure the protection of their rights.

Participants will receive both written and verbal information. The written information has been approved by the medically qualified investigators. The verbal explanation to the participant will be performed by the research nurse under the supervision of the medically qualified investigators. The verbal explanation will cover all the elements specified in the written information provided for the participant. The participants will be informed of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail.

The participant will be given every opportunity to clarify any points he does not understand and if necessary ask for more information. At the end of the discussion the participant will be given time to reflect. The participant is at liberty to withdraw their consent to participate at any time, without prejudicing any future medical care.

The research nurse will then obtain the participants freely given written informed consent. Both investigators and participants retain copies of the signed consent forms.

#### **6.4 Investigator responsibilities (CC)**

The principal clinical investigator at each centre will be responsible for the clinical conduct of the study staff. The clinical investigators will maintain a Trial Master File including a list and CVs of appropriately qualified persons to whom they have delegated significant trial-related duties. The investigator will be responsible that all such identified persons will be thoroughly familiar with the protocol and study procedures, as well as being aware of the principles of good clinical practice (GCP) (MRC Guidelines for Good Clinical Practice in Clinical Trials, MRC 1998). The research nurse shall have responsibility for the efficient operation of the study to GCP guidelines.

## **7. Study population**

Participants will be recruited through general practices that have participated in the ProtecT study of treatment for localised prostate cancer (ISRCTN20141297).

## **8. Inclusion and exclusion criteria**

### **Inclusion criteria**

- Age 50-69<sup>1</sup> years on the date of preparation of the list at the general practice of potential participants for the ProtecT study
- Male gender
- ProtecT participants with a PSA test between 2.0 to 2.95 ng/ml or a PSA level of at least 3.0 ng/ml with a negative biopsy (10 core procedure) from the ProtecT study
- Enrolled in the ProMPT study and willing to be contacted about further studies
- Able to give informed written consent to participate
- Registration with the participating general practice

### **Exclusion criteria**

This trial is of pragmatic design. Therefore, exclusion criteria will be kept to the minimum possible. All ProtecT participants are without major co-morbidities, other cancers or prior prostate malignancy. Participants will be excluded with:

- A PSA  $\geq 20$  ng/ml (indication of prostate cancer or prostatitis)
- History of allergic reactions to green tea or lycopene containing products (including guava, watermelon)



- Concurrent medication with finasteride or dutasteride (elevates PSA values)

## 9. Recruitment of participants

### 9.1 Information to general practices (CC and SMed)

Practices will be contacted by the trial coordinator and the GPs and practice manager will be briefed about the study and given the protocol. The study nurse will subsequently visit the practice to establish suitable accommodation for the study clinics and to liaise with practice staff.

### 9.2 Participant invitation procedures (CC and SMed)

A participant information sheet outlining the study will accompany the invitation letter (Information Sheet 1). All individuals invited to participate in the trial will be allocated a unique study number by SMed. Address labels will be generated and invitations to join the study sent to men in manageable batches. Letters are mailed out from the study office on the study notepaper.

The reply slips are returned to Social Medicine. The names and addresses of men indicating their willingness to join the study will be updated on the project database along with the date on which the reply slip was returned. Men who telephone and indicate either their willingness to participate or refusal are recorded in the same way as for letters. Those men who do not reply to the initial letter or who decline to participate on the reply slip will have no follow-up.

The study secretary will arrange appointments for these men and manage the clinic lists, including rearranging appointments where necessary. The dates and times of the clinics and attendees will also be entered into the study database. Persons who do not/can not attend their intended appointment will be contacted by telephone and a further appointment organised with details recorded on the database. Should they not attend on 2 occasions it will be assumed that they no longer wish to participate and this will be documented on the study database. The lists of appointments and place of the clinics will also be recorded on the database.

### 9.3 Participant visit schedule (CC)

- All individuals: enrolment visit
- If eligible for randomisation: research follow-up at one and six months after randomisation

## 10. Recruitment clinics (RC)

Recruitment will be performed mostly at the participating general practices, but also at the hospital. On attendance the research nurse (previously carefully instructed by the study team and working from a detailed script utilised in the training programmes) will provide verbal information on the study aims and design.

Prostate cancer risk and prevention will be discussed and it will be made clear that participation in the project is purely voluntary and the participant will be free to decline without prejudicing their future care. Participants will be given the opportunity to ask questions. Those who decline to participate will be free to leave and will be thanked for attending.

The research nurse will ensure that all men willing to participate in the trial are eligible to do so (using the eligibility criteria detailed earlier and in the RC schedule). Those ineligible to participate will have the reason for ineligibility explained to them and they will be thanked for their

attendance and support of the project. Men who wish to participate will be asked to give written, witnessed consent (Consent Form 1). A copy of all signed consent documents will be given to participants.

## 10.1 Initial data collection at the Recruitment Clinic (RC)

### A. Research nurse

1. Discusses study information, and requests consent to participate in the ProDiet study (Consent 1).
  - Consent form 1 is for consent to enter the study and take blood for the PSA test
  - Consent 1 (one copy) are given to participant
  - A cross is placed in boxes of sections the participant does not consent to, initialled by the participant
2. Completes the S1 Schedule for Recruitment Clinic containing:
  - baseline socio-demographic data; age, socio-economic status, ethnicity
  - exclusion criteria checklist
  - a checklist to discuss with participants describing the ProDiet study
  - any recent PSA test results subsequent to the ProtecT study tests
3. Completes a single page version of the data entry form (RC Proforma) about the attendance at the clinic and outcome. The RC Proforma is entered onto the study computer at the earliest opportunity by the study secretary, including any other comments regarding the man or the appointment.
  4. Records on the RC Schedule the weight, height, blood pressure and pulse as well as the study instrument number of the scales and blood pressure monitor. If the blood pressure is above a hypertensive level agreed with the current practice (identified by the lead nurse in initial visits) the participant will be advised to have the blood pressure checked again by the practice nurse and the practice will be informed of the reading.
  5. Takes a baseline PSA test. Result sent by post to participant and GP, depending on normal result (PSA letter\_normal and letter\_normal GP) or raised PSA (PSA letter\_raised and PSA letter\_raised GP).

### B. Participants

1. Men complete a study questionnaire (FTQ1) on urinary symptoms (ICSmaleSF questionnaire<sup>16</sup>), general health status [Hospital Anxiety and Depression scale<sup>17</sup> (HAD) and Profile of Moods States]<sup>18</sup> which they may return in the post if necessary, using a freepost envelope.
2. Men also complete a questionnaire (FTQ1a) about their current diet [Food Frequency Questionnaire]

## 11. Randomisation (CC)

The main purpose is to provide the participant with sufficient information to allow him to decide whether or not he is willing to be randomised to the dietary interventions. The study nurse emphasises the need for a trial, describes the advantages and disadvantages of each of the dietary options and explains the purposes of randomisation. The information content and delivery builds on methodology gained from the ProtecT study and the nurse will work to a detailed but flexible

script. Men should not undergo randomisation unless they are willing to receive any of the dietary options, including placebo, and at that stage randomisation should then proceed.

Once the participant has agreed to be randomised, the nurse will telephone SMed to log the man's details. The nurse will open the next numbered sealed treatment pack. Treatment packs will contain a randomly allocated dietary intervention described in section 11.2. The treatment packs will be prepared by SMed (overseen by the principal study statistician) with the research nurse blind to the treatment pack contents.

### 11.1 Stratification variable

ProtecT RC PSA test (two strata: <3.0 ng/ml and 3.0 - 19.99 ng/ml)

### 11.2 Dietary interventions

The nurse will randomise men between **two** factors with three levels:

#### 1. Lycopene:

- a) dietary advice regarding a daily portion of cooked tomatoes (rich in lycopene) plus matched placebo capsules (deleted)
- b) tomato-derived lycopene supplement capsules daily with control dietary advice recommending five daily portions of fruit and vegetables ('healthy diet')(deleted)
- c) healthy dietary advice plus (deleted) matched placebo capsules (control)

#### 2. Green tea:

- d) green tea capsules at 800 mg daily
- e) matched placebo supplement capsules (control)
- f) dietary advice regarding green tea drinking

## 12. Research data collection (CC and SMed)

### 12.1 Evaluation of recruitment and attrition in follow-up (CC and SMed)

Records will be kept of the response rates at all stage of the study and those not completing follow-up where the research nurse will try to obtain a reason for the loss to follow-up.

### 12.2 Adverse events (CC)

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this treatment.

Adverse events resulting from any of the dietary interventions will be recorded by the nurse on the follow-up research schedule and by participants on an adverse events checklist at the time of the occurrence and returned in a prepaid-envelope to the study office.

Serious AE are defined by the MRC GCP guidelines:

Serious adverse events includes any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity

All serious adverse events (SAE) should be notified within 48 hours of occurrence to Professor Hamdy and the study co-ordinator. Death notification should occur within 24 hours of the study team learning of the event. SAE probably related to participation in the trial are reported to the MREC within 15 days on the COREC SAE proforma. There may be a requirement from the local R&D office to report SAE, and this should be established by a centre.

Adverse events reported from literature for lycopene and green tea, although causality was frequently not established due to the non-randomised study designs.

Adverse event	Lycopene extract	Green tea (extract and drink)
Nausea	Yes	Yes
Heartburn	No	Yes
Diarrhoea	Yes	Yes
Muscle cramps	No	Yes
Nocturia	No	Yes
Dyspnea	No	Yes
Headache	No	Yes
Hypertension	No	Yes
Insomnia	No	Yes
Fatigue	No	Yes

### 12.3 Participant data collection in follow-up (SMed and CC)

Participants will be given the ProDiet study telephone number for any questions or advice following randomisation. Research data collection for the participants will be at one and six months after the date of randomisation. Men will be invited to follow-up clinics with the study nurse by letter and telephone. Men will be asked to complete the questionnaire with the instruments used at baseline on anxiety and depression and urinary symptoms and dietary measures. There will be additional questions on compliance and satisfaction with the intervention, as well as any other dietary or vitamin supplementation be utilised by the participants. The nurse will also repeat the anthropometry and blood samples taken at recruitment. The nurse will take details of any prostate cancer related clinical information of relevance, e.g. additional PSA tests or biopsies conducted since randomisation. A ProDiet website will give details of the study including methods for the preparation of the lycopene-rich foods. Men unable to attend follow-up appointments will be followed-up by telephone where possible. Men can also provide email and/or mobile phone numbers to the study team. These contacts will be used for appointment and questionnaire reminders and to assist intervention adherence by the study team in between appointments.. Participants will receive a small token, e.g. a pen or a fridge magnet for contributing to the study.

If the participants do not attend the follow-up clinics, the questionnaire will be posted to participants after any changes of address or contact status are reviewed on the database by the clinical centres. A reminder is sent out 3 weeks after non-return of the questionnaire. The nurse will attempt to identify any PSA tests as part of clinical care if the participant does not attend follow-up clinics and any evidence of serious adverse events.

## 13. Outcome measures

### 13.1 Primary outcome

The primary outcome will assess serum lycopene and epigallocatechin-3-gallate (green tea) levels at six months following randomisation.

### 13.2 Secondary outcomes

The secondary outcomes will assess:

- trial recruitment and randomisation rates (measured at each stage of the study flowchart)
- intervention tolerability (adverse event reporting during the six months of follow-up)
- compliance (returned tablet counts and self reported counts at six months)
- trial retention (participants completing the six month follow-up and the questionnaires)
- PSA values (measured at baseline and six months)
- dietary compliance with recommendations (dietary questionnaire completed at six months and participant data reporting dietary change)
- weight and body mass index (measured at one and six months) to assess whether the interventions have beneficial or deleterious effects on weight
- blood pressure (measured at one and six months) to assess whether there are any overall health benefits to the healthy diets
- attitudes and views of men and their spouses about dietary modification and participation in long term (qualitative interviews conducted throughout the study)
- Anxiety, depression and psychological state - measured by the Hospital Anxiety and Depression Scale<sup>17</sup> and the Profile of Moods States<sup>18</sup>
- Urinary symptoms - measured by the ICSmaleSF questionnaire<sup>17</sup>, which includes voiding and incontinence scores, nocturia, frequency and urinary-specific quality of life care data sources.

## 14. Qualitative research (SMed)

In-depth qualitative interviews will investigate men's views about disease prevention, diet and prostate cancer, their willingness to modify diet or take supplements and attitudes towards participation in long-term trials of dietary modification, including undergoing prostate biopsies (a potential main trial outcome). Purposive theoretical sampling will select trial participants and refusers as well as compliant and noncompliant individuals. Men's spouses/partners and clinicians will also be interviewed as they may influence men's attitudes towards dietary prevention. Interviews will be fully transcribed and subjected to thematic analysis using specialist software (ATLAS-ti) to identify barriers to a successful dietary intervention and opportunities to overcome them. This research will be conducted and analysed by Dr Kerry Avery who is highly experienced

in this methodology and holds a DoH fellowship to investigate dietary change in prostate cancer patients (tel: 0117 9287272). Dr Jeremy Horwood, an experienced qualitative researcher will also contribute to the qualitative research component.

### **Non-responders**

**All non-responders would receive an explanatory letter with the short questionnaire which would also invite them to a telephone interview by returning a reply slip in a reply paid envelope to the study office. An experienced qualitative researcher would then contact those men agreeing to an interview and conduct interviews by telephone or in person, as men prefer. Interviews would utilise a shortened version of the main study topic guide. We would not send reminder letters regarding return of the questionnaire or interviews**

## **15. Data management and security**

A unique file identified by the study number will be maintained for participants. All data recorded on paper relating to the participant will be located in these files. A list will be maintained at each centre of staff authorised to make alteration to the study records, including the study database.

Data obtained on paper will also be entered onto and maintained on a 'Microsoft Access' database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to ProDiet study staff. Data from computerised sources will be converted to 'Access' databases and hard copies will be maintained in the relevant participants file in locked filing cabinets. Information capable of identifying participants will not be removed from SMed or clinical centres or made available in any form to those outside the study. All data held in SMed will conform to the Department Data Security Policy and Department Compliance with the Data Protection Act policies.

## **16. Management and ethical considerations and study organisation**

A Trial Steering Committee will oversee the trial. Written records will be taken of each meeting and copies held by the study coordinator. A Data Monitoring and Safety Committee will not be convened as there are no planned interim analysis and the primary endpoints are not clinical. Serious Adverse Events would be reported to MREC. Some tolerability data has already published on these dietary agents.

### **16.1 Trial Steering Committee**

The TSC will have an independent Chairman, Dr Steven Oliver, Senior Lecturer in Population Health at the University of York whose research interests include dietary prevention and prostate cancer. The TSC will comprise the Co-PIs, Dr Merran Toerran, an independent qualitative researcher with clinical trials experience from the University of York and a urologist, Mr Derek Rosario from the University of Sheffield. The final composition will be determined by the TSC Chairman. The TSC will meet every six months.

### **16.2 Publication policy**

Reports will be produced as requested by CRUK. Papers will be prepared for publication in general and urological peer-reviewed journals. The findings will also be presented at national and

international conferences. All publications using study data must be approved by the PIs prior to submission of the publication and they retain the decision to publish or communicate study results

### 16.3 Departures from protocol

It is important to keep participant withdrawals from the trial to a minimum but;

- a participant may be withdrawn from the study by their general practitioner or the study team at any time should it be considered detrimental to the participant to continue.
- a participant may withdraw from the study at any time without prejudice to his subsequent treatment.

Participants who fail to attend appointments will be contacted by telephone and letter, to encourage them to attend, to arrange alternative appointments and to determine reasons for withdrawal. Reasons for withdrawal will be fully documented on the study database and adverse event forms completed if applicable. If participants switch to different interventions post-randomisation this will be analysed by a per protocol secondary analyses. If data is missing on participants, a sensitivity analyses will be conducted, but this is less powerful than having the data.

### 16.4 Organisation of study documentation

All clinical centres will have an investigators' Trial Master File which will include all relevant information and documentation for the trial. This will include the protocol, MREC approval, financial agreements, CVs of all staff involved in the trial, and any correspondence or emails received pertaining to the study. It will be the responsibility of the research nurse at each site to maintain this file.

## 17. Project milestones

On commencement of funding:

Staff appointments

Two months:

Qualitative research commences

Three months:

Recruitment for two months

Four months:

One month follow up PSA tests

Compliance assessments

Nine months:

Six month follow-up participant visits commence

EGCG (green tea) and lycopene serum samples taken and analysed

Participant follow-up questionnaire

Twelve months:

Follow-up completed, including compliance assessments

Data cleaning

Fifteen months:

Qualitative research analysis completed

Analysis of primary and secondary outcomes

Eighteen months:

Final report to CRUK

Draft publication for peer reviewed journal



## 29. References

1. Majeed A, Babb P, Jones J, Quinn M. *BJU Int* 2000;85:1058-1062.
2. Wasson JH, Sushman CC, Bruskewitz RC, et al. *Arch Fam. Med* 1993;2:487-93.
3. Editorial. UK experts advise against prostate cancer screening. *Lancet* 1997;349 (9050):1-2.
4. Woolf SH. *BMJ* 1997;314:989-90.
5. Neal DE, Donovan JL. *Lancet Oncology* 2001: 17-24.
6. Thompson IM, Goodman PJ, Tangen CM, Lucia PHM, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ & Coltman Jr CA *New England Journal of Medicine* 2003: 349 215-224.
7. WCRF/AICR Food, nutrition, physical activity and the prevention of cancer: a global perspective. Washington DC: AICR. 2007.
8. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson Jr. IM, Kristal AR, Santella RM, Probstfield JL, Moinpour CM, Albanes D, Taylor PR, Minsian LM, Hoque A, Moody Thomas S, Crowley JJ, Gaziano, Stanford JL, Cook ED, Fleshner NE, Lieber MM, Walther PJ, Khuri FR, Karp DD, Schwartz GG, Ford LG & Coltman CA. *JNCI* 2005 97(2) 94-102.
9. Marshall JR, Sakr W, Wood D, Berry D, Tangen C, Parker F, Thompson I, Lippman SM, Lieberman R, Alberts D, Jarrard D, Coltman C, Greenwald P, Minasian, Crawford ED *Cancer Epidemiol Biomarkers Prev* 2006 15(8):1479-84.
10. Syed D. Khan N, Afaq, Mukhtar H. *Cancer Epi Biomarkers Prev* 2007; 16: 2193.
11. Bunker CH, McDonald AC, Evans RW, de la Rosa N, Boumshleh JM & Patrick AL. *Nutrition and Cancer* 2007 57(2):130-137.
12. Neill MG & Fleshner NE *Curr Opin Urol* 2006: ; 16:132-137.
13. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G & Corti A. *Cancer Res* 2006 66(2) 1234-40.
15. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM & Egger M *Lancet* 2006: 363:1346-53.
16. Donovan JL, Peters TJ, Abrams P, Brookes ST, De La Rosette JJ, Schafer W. *J Urol* 2000;164:1948-55.
17. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scan* 1983; 67:361.
18. Horowitz M, Wilner N, Alvarez W. *Psychomatic Medicine* 1979,41:209-218.

## **APPENDIX 1: Sample size calculations and statistical analyses**

### **Sample size**

Around 250 men will be invited to take part until 126 men agree to enrol - this would give an acceptance rate of 50% with a 95% confidence interval of 44% to 56%. If 126 men are enrolled, the study will have 90% power (5% significance) to detect a 67% increase in serum values of lycopene and EGCG between the control and intervention groups (including accommodation for the skewed distribution of measures).

### **Analyses plan**

The analyses will be conducted at the end of the study, i.e. the completion of the six month data collection and analyses of serum measures. The analysis of the primary outcomes, serum lycopene and EGCG, will compare mean levels between the three levels of the corresponding dietary factor (lycopene and green tea interventions respectively) with appropriate accommodation of positively skewed distributions using bootstrap methods. The analysis will be repeated for one month and six month follow-up assessments. For secondary outcomes, overall trial recruitment and randomisation rates will be calculated with 95% confidence intervals. Comparison of tablet counts between groups receiving active supplementation and the placebo groups for each factor in turn will indicate whether tolerability is affecting adherence. PSA levels will be investigated in the same manner as the primary outcomes but with the first PSA level measured during diagnosis being included as a covariate, with a potential improvement in statistical power. Interaction between the two factors will be investigated for each outcome, as the factorial design will be an efficient approach if there is none apparent and both dietary factors are carried over to the main trial. There is no existing evidence of biological interaction between the two dietary factors and investigation of this is required. There may be an interaction for measures of compliance, as individuals intolerant of one dietary factor may stop increasing their intake of both.

### **Subgroup analyses**

Recruitment and randomisation rates as well as the effects of supplementation on the primary and secondary outcome will be compared between the two groups of men recruited, i.e. those with a PSA of between 2.5-2.9 ng/ml and those with a PSA  $\geq$  3.0ng/ml and a negative biopsy.