VIDEO: Vitamin D evaluation in osteoarthritis

A randomised, double-blind, placebo controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis

Eudract Number 2004-000169-37
ISRCTN94818153
Protocol Reference No VIDEO800

Protocol Version number 2.8
Protocol date 29/11/2010

Authorised by:
Name Dr Richard Keen Role Chief Investigator
Signature Date 07/01/2011
General Information
This document describes an Arthritis Research Campaign (arc) funded trial being conducted in collaboration with the Medical Research Council Clinical Trials Unit (MRC CTU), Royal National Orthopaedic Hospital, Royal Free and University College London. This protocol provides information about procedures for entering participants into the trial. The protocol should not be used as an aide-memoire or guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering participants for the first time are advised to contact the MRC Clinical Trials Unit, London to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant Principal Investigator.
This trial will be conducted in compliance with the protocol, MRC GCP, Data Protection Act (DPA number: G0027154) and other regulatory requirements, as appropriate.
Name of person authorised to sign final protocol amendments: Dr Richard Keen

Contact Details

Chief Investigator
Dr Richard Keen
Senior Lecturer and Consultant Rheumatologist
Royal National Orthopaedic Hospital
Brockley Hill, Stanmore, Middlesex, HA7 4LP,
Tel: 020 8909 5314
Fax: 020 8420 7487
Email: richard.keen@ucl.ac.uk

Principal Investigators
Professor Cyrus Cooper
Consultant Rheumatologist
Southampton University Hospital
Tel: 02380 777624
Fax: 02380 704021
Email: cc@mrc.soton.ac.uk

Professor Nigel Arden
Consultant Rheumatologist
Southampton University Hospital
Tel: 02380 777624
Fax: 02380 704021
Email: nka@mrc.soton.ac.uk

Dr Terry O’Neil
Consultant Rheumatologist
ARC Epidemiology Unit,
Stopford Building,
University of Manchester,
Oxford Road,
Manchester, M13 9PT
Tel: 0161 2755040 Fax 0161 275 5043
Email: Terry@fs1.ser.man.ac.uk

Professor Alex MacGregor
Consultant Rheumatologist
University of East Anglia
School of Health Policy and Practice
Norwich NR4 7TJ
Tel: 01603 593 570
Email: a.macgregor@uea.ac.uk

Dr Fraser Birrell
Consultant & Senior Lecturer in Rheumatology
University of Newcastle upon Tyne
Rheumatology, 4th Floor, Cookson Framlington Place
NE2 4HH
Tel: 0191 222 7541 Fax 0191 222 5455
Email: Fraser.Birrell@ncl.ac.uk
MRC Clinical Trials Unit
222 Euston Road
London
NW1 2DA
Tel: 020 7670 4700
Fax: 020 7670 4829

Trial Manager
Anna Bara
Trials Manager, ODG
Tel: 020 7670 4823
Email: aib@ctu.mrc.ac.uk

Data Manager
Lyndsey Castle
Data Manager, ODG
Tel: 020 7670 4838
E-mail: lac@ctu.mrc.ac.uk

Trial statistician
Caroline Doré
Senior Statistician, ODG
Tel: 020 7670 4725
Email: cd@ctu.mrc.ac.uk

Clinical laboratories
Routine clinical analyses will be done at NHS trust laboratories at the participating centres. Study specific analyses will be performed at the Centre for Integrated Genomic Medical Research (CIGMR) at the University of Manchester, the Wellcome Trust Sanger Institute in Cambridge, and any other laboratories selected as appropriate by the trial Sponsor.

Funding Body
Arthritis Research Campaign (arc)
Copeman House
St Mary's Court
St Mary's Gate
Chesterfield, Derbyshire S41 7TD
Tel: 01246 558033 Email: info@arc.org.uk

Sponsor
Royal National Orthopaedic Hospital
Brockley Hill, Stanmore, Middlesex, HA7 4LP

Emergency Contact
Dr Richard Keen
Senior Lecturer and Consultant Rheumatologist
Royal National Orthopaedic Hospital
Brockley Hill, Stanmore, Middlesex, HA7 4LP,
Tel: 020 8909 5314
020 8954 2300 (Hospital Switch Board)
07956 309461 (mobile)
Fax: 020 8420 7487
Email: richard.keen@ucl.ac.uk

RANDOMISATIONS
Tel: 020 7670 4711 (Mon - Fri, 09:00 – 17:00)
Fax: 020 7670 4829
CONTENTS

1. Summary ........................................................................................................... 8
   1.1 Lay summary .................................................................................................. 8
   1.2 Abstract and summary of trial design ........................................................... 8
   1.3 Flowchart .................................................................................................... 10

2. Background ........................................................................................................ 11
   2.1 Introduction ................................................................................................... 11
   2.2 Rationale and objectives ............................................................................. 11
   2.3 Relevant studies/trials .................................................................................. 11
   2.4 Risks and benefits ........................................................................................ 12

3. Selection of Centres/Clinicians .................................................................... 12
   3.1 Centre/Clinician eligibility criteria ............................................................... 12

4. Selection of Participants ................................................................................ 13
   4.1 Patient inclusion criteria ............................................................................. 13
   4.2 Patient exclusion criteria ............................................................................ 13
   4.3 Number and source of participants ............................................................... 13
   4.4 Screening Procedure .................................................................................... 14

5. Randomisation & Enrolment procedure .................................................. 14

6. Treatment of Participants ............................................................................. 15
   6.1 Trial treatment ............................................................................................. 15
   6.2 Trial product(s) ............................................................................................ 15
   6.3 Dispensing ................................................................................................... 16
   6.4 Randomisation codes/ Unblinding ................................................................. 16
   6.5 Modification of trial treatment ..................................................................... 16
   6.6 Accountability and unused drugs/devices .................................................... 16
   6.7 Measures of compliance/adherence ............................................................. 16
   6.8 Non-trial treatment ...................................................................................... 17
   6.9 Co-enrolment guidelines ............................................................................. 17

7. Assessments and Procedures ....................................................................... 17
   7.1 Schedule for follow-up ............................................................................... 18
   7.2 Procedures for assessing efficacy ................................................................. 19
   7.3 Procedures for assessing safety .................................................................... 19
   7.4 Trial closure ................................................................................................ 19

8. Withdrawal of Participants ............................................................................ 20
   8.1 Withdrawal from trial intervention ............................................................... 20
   8.2 Loss to follow-up ......................................................................................... 20

9. Statistical considerations ................................................................................. 21
   9.1 Method of Randomisation .......................................................................... 21
   9.2 Outcome Measures ...................................................................................... 21
   9.3 Revised sample size statement ..................................................................... 21
9.4 Interim Monitoring and Analyses ............................................................... 21
9.5 Outline Analysis Plan ............................................................................ 22

10. Data Verification and Site Monitoring .................................................. 23
10.1 Checks at CTU ................................................................................... 23
10.2 Clinical site monitoring ....................................................................... 23

11. Adverse EVENTS AND REACTIONS .................................................... 23
11.1 Adverse events and reactions ............................................................... 23
11.2 Serious adverse events (SAE) .............................................................. 25
11.3 Severity/grading of adverse events ....................................................... 26
11.4 Relationship to trial treatment ............................................................. 26
11.5 Follow-up after adverse events ............................................................. 26

12. Ancillary studies .................................................................................... 27
12.1 Genetic analysis .................................................................................. 28
12.2 Bone Mineral Density .......................................................................... 28
12.3 Magnetic Resonance Imaging (MRI) .................................................... 28
12.4 Muscle Strength ................................................................................... 28

13. Ethical considerations and approval .................................................... 28
13.1 Ethical considerations ......................................................................... 28
13.2 Ethical approval ................................................................................... 29

14. Regulatory Approval ............................................................................. 29

15. Indemnity .............................................................................................. 29

16. Finance .................................................................................................. 29

17. Trial Committees ................................................................................... 30
17.1 Trial Management Group (TMG) ......................................................... 30
17.2 Trial Steering Committee (TSC) ........................................................... 30
17.3 Independent Data Monitoring Committee (IDMC) ............................... 30

18. Publication ............................................................................................. 30

19. Protocol Amendments ........................................................................... 31

20. Sequence of responsibilities .................................................................. 32

21. References ............................................................................................ 33

22. Appendices ........................................................................................... 37
FIGURES

FIGURE 1: Flow chart - Trial entry, randomisation and treatment
FIGURE 2: AE Reporting Sequence
FIGURE 3: SAE Reporting Sequence

TABLES

TABLE 1: Flow chart - Schedule for follow-up
TABLE 2: Flow chart - Schedule for sub-studies

APPENDICES

APPENDIX 1: Patient Information Sheet ................................................................. 38
APPENDIX 2: Consent Form .................................................................................. 44
APPENDIX 3: Genetic Patient Information Sheet .................................................. 45
APPENDIX 4: Genetic Consent Form ..................................................................... 48
APPENDIX 5: GP Letter ......................................................................................... 49
APPENDIX 6: GP Recruitment Letter ..................................................................... 50
APPENDIX 7: Hospital Recruitment Letter ........................................................... 51
APPENDIX 8: Poster .............................................................................................. 52
APPENDIX 9: Bone Biochemistry Information ..................................................... 53
APPENDIX 10: Dietary Assessments ................................................................... 54
APPENDIX 11: Muscle Strength Assessment ........................................................ 55
APPENDIX 12: Bone Density Measurement ......................................................... 57
APPENDIX 13: Magnetic Resonance Imaging ...................................................... 58
APPENDIX 14: Musculoskeletal Function, Static and Dynamic Balance ............ 60
APPENDIX 15: Cognition ..................................................................................... 61
APPENDIX 16: Depression .................................................................................. 62
APPENDIX 17: Biochemical Analyses .................................................................. 63
APPENDIX 18: Womac Questionnaire ................................................................. 65
APPENDIX 19: WHOQOL Quality of life questionnaire ....................................... 69
APPENDIX 20: SAMPLE LABEL ......................................................................... 70
APPENDIX 21: Patient Card ................................................................................ 71
APPENDIX 22: Ultrasound Imaging ..................................................................... 72
APPENDIX 23: PASS-SF Questionnaire ............................................................... 73
APPENDIX 24: Biomechanics of the knee sub-study using the 'smart-tog' ......... 76

ABBREVIATIONS AND GLOSSARY

AE  Adverse Event
AR  Adverse Reaction
arc  Arthritis Research Campaign
BDI  Beck’s Depression Inventory
BMD  Bone Mineral Density
CF  Consent Form
CI  Chief Investigator
CRF  Case Report Form
CTA  Clinical Trial Authorisation
CTU  Clinical Trials Unit
DM  Data Manager
DMC  Data Monitoring Committee
DXA  Bone Density Scan or Dual Energy X-Ray Absorptiometry
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERC</td>
<td>Endpoint Review Committee</td>
</tr>
<tr>
<td>FFQ</td>
<td>Food Frequency Questionnaire</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>International standard randomised controlled trial number</td>
</tr>
<tr>
<td>IU</td>
<td>International Units</td>
</tr>
<tr>
<td>JSN</td>
<td>Joint space narrowing</td>
</tr>
<tr>
<td>JSW</td>
<td>Joint space width</td>
</tr>
<tr>
<td>k &amp; l</td>
<td>Kellgren &amp; Lawrence</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medical and Healthcare Devices Regulatory Authority</td>
</tr>
<tr>
<td>MPTT</td>
<td>Multi-Practitioner Triage Team</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MREC</td>
<td>Multi-Centre Research Ethics Committee</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSA</td>
<td>Muscle strength assessment</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>ONS</td>
<td>Office for National Statistics</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIS</td>
<td>Patient Information Sheet</td>
</tr>
<tr>
<td>PSP</td>
<td>Postural sway and proprioception</td>
</tr>
<tr>
<td>QL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RN</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SSAR</td>
<td>Serious Suspected Adverse Reaction</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Serious Unexpected Suspected Adverse Reaction</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TS</td>
<td>Trial Statistician</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>VAR</td>
<td>Variance</td>
</tr>
<tr>
<td>VIDEO</td>
<td>Vitamin D Evaluation in Osteoarthritis</td>
</tr>
<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Osteoarthritis Index</td>
</tr>
</tbody>
</table>
1. **SUMMARY**

1.1 **Lay summary**
Osteoarthritis (OA) is a painful condition affecting a large proportion of the elderly population. At present there are no treatments that can prevent this condition, and current treatments are aimed merely at controlling pain and trying to keep people active and mobile. There is a growing interest in the use of dietary supplements to prevent a wide range of diseases, and this study aims to assess whether adding vitamin D to the diet through a supplement can prevent the deterioration of osteoarthritis at the knee joint and reduce pain. Researchers based at University College London are planning to study 470 people with knee OA over 3 years to determine if vitamin D can prevent the destruction of cartilage (as assessed by changes on X-ray) and whether people experience less pain. As vitamin D is relatively safe and cheap to administer, the findings may have important implications to the general population and to the NHS.

1.2 **Abstract and summary of trial design**
Osteoarthritis is a common disorder, and at present there are no effective treatments that alter disease pathology. Management of OA is primarily aimed at symptom control with the aim to retain or improve joint function. Epidemiological data suggest that low dietary intake of vitamin D and low serum 25-hydroxyvitamin D$_3$ levels are associated with radiological progression in knee OA.

The study’s aim is, therefore, to determine whether vitamin D supplementation can reduce the rate of disease progression and improve symptoms in participants with knee OA. In total, 470 participants with knee OA will be studied in a 3 year, randomised, double blind, placebo-controlled trial of cholecalciferol 800 IU daily or placebo. The primary outcome measure will be radiological progression with secondary endpoints being symptoms and quality of life assessments. Sub-studies will examine the effect of vitamin D supplementation on subchondral bone assessed using dual energy x-ray absorptiometry and magnetic resonance imaging, muscle mass and strength, and ultrasound. Additional information will also be available on whether vitamin D has a beneficial treatment effect on hip OA. As Vitamin D supplementation is safe and cheap, any proven benefit in the management of OA will have important relevance to healthcare in the elderly.

1.2.1 **Type of design**
Randomised, double-blind, placebo-controlled trial. The major measures to minimise bias in this trial are off-site, remote randomisation and blinding of treatment allocation. In addition, grading of all knee radiographs and their analysis will be conducted centrally and so blinded to patient treatment.

1.2.2 **Disease/patients studied**
Ambulatory patients aged over 50 years of both sexes with knee pain on most days in the month prior to screening will be invited to participate. For more details refer to section 4.

1.2.3 **Trial treatments – intervention and control**
Participants will be randomised to receive oral vitamin D 800 IU (as cholecalciferol) daily or matching placebo. Participants will receive treatment packs at 6 monthly intervals for a total of 3 years. For more details refer to section 6.

1.2.4 **Outcome measures**
Primary: Radiological progression of knee OA in medial joint compartment at 36 months.

Secondary: Radiological progression of knee OA in other joint compartments.
Reduction in pain and functional disability.  
Improvement in quality of life.

For more details refer to section 9.2

1.2.5 Duration
Participants will be reviewed at baseline, 3 months, 6 months and then at 6 monthly intervals for a total of 3 years.

For more details and the sequence of trial periods refer to section 7.

1.2.6 Data recording
Data will be recorded on case report forms (CRFs), the top copy/original should be sent to the MRC CTU for data entry and a copy kept at the local centre. The type of data to be recorded is detailed in the Assessments and Procedures section (Section 7).

1.2.7 Ancillary studies
An ancillary study to assess the role of genetic factors in OA is planned. Separate consent for this sub-study will be obtained from participants.

Additional investigations will be performed as sub-studies within the main trial. These will help determine how vitamin D may effect cartilage and bone.

For more details of ancillary studies refer to section 12.
1.3 Flowchart

Figure 1: Trial entry, randomisation and treatment

Pre-screening
Participant identified. Study explained by Research Nurse (RN) Questionnaire for suitability. PIS issued

Final Screening
Eligibility checked. Consent taken. Screening number issued by RN.

If Knee X-ray negative for OA

Abnormal blood

If knee X-ray positive for OA

Blood samples for routine haematology and biochemistry, 24 hour urine sample.

RANDOMISE
Tel: 020 7670 4711

Treatment A
Vitamin D 800 IU as cholecalciferol. 2 tablets per day

Treatment B
Placebo 2 tablets per day

GP informed

If Knee X-ray negative for OA

Referred to GP

Pre-screening

Participant identified. Study explained by Research Nurse (RN) Questionnaire for suitability. PIS issued

Final Screening
Eligibility checked. Consent taken. Screening number issued by RN.

If Knee X-ray negative for OA

Abnormal blood

Final Screening
Eligibility checked. Consent taken. Screening number issued by RN.

If Knee X-ray negative for OA

Abnormal blood

If knee X-ray positive for OA

Blood samples for routine haematology and biochemistry, 24 hour urine sample.

RANDOMISE
Tel: 020 7670 4711

Treatment A
Vitamin D 800 IU as cholecalciferol. 2 tablets per day

Treatment B
Placebo 2 tablets per day

GP informed

Screening to baseline within 100 days

Eligible, consenting participants

T=0 Baseline assessment
Medical history, clinical examination, ECG, symptom and QOL questionnaires, food diary, food frequency questionnaire (FFQ), blood samples, urine sample, sub-studies.

T= 3 months Assessment 1. Blood/urine samples

T= 6 months Assessment 2. Questionnaires, symptom and QOL questionnaires, urine samples, trial drug.

T= 12 months Assessment 3. Clinical examination, sub-studies, symptom and QOL questionnaires, blood/urine samples, trial drug, knee x-ray.

T= 18 months Assessment 4. Symptom and QOL questionnaires, FFQ, Trial drug.

T= 24 months Assessment 5. Clinical examination, sub-studies, symptom and QOL questionnaires, urine samples, trial drug.

T= 30 months Assessment 6. Questionnaires, trial drug.

T= 36 months Assessment 7. Clinical examination, Knee x-ray, Sub-studies, symptom and QOL, depression and cognition questionnaires, FFQ, blood/urine samples.
2. **BACKGROUND**

2.1 **Introduction**  
**Vitamin D and Osteoarthritis**  
Epidemiological data from the Framingham Study has specifically examined the relationship between vitamin D and disease progression at both the knee and hip over 8-10 years (McAlindon et al, 1996a; Lane et al, 1999). Low vitamin D intake, as assessed by both dietary intake and serum 25-hydroxyvitamin D₃ levels, was associated with a three to four-fold increased risk of progression at the two skeletal sites. The serum 25-hydroxyvitamin D₃ levels in participants within the lower 2 tertiles was <62.5nmol/l, and therefore not all these participants had vitamin D deficiency as defined by a clinical diagnostic cut-off of <25nmol/l. It is recommended that serum 25-hydroxyvitamin D₃ levels should be maintained above 75nmol/l and the authors conclude that randomised trials of vitamin D supplements should therefore be considered in OA management (Lane et al, 1999).

2.1.1 Population  
The population to be studied in this trial is older adults over 50 years with early osteoarthritis of the knee.

2.1.2 Investigational product/ intervention  
The investigational product is vitamin D as cholecalciferol. The supplier was Healthspan, Channel Islands, and the manufacturer Thompson & Capper. The investigational product will now be supplied directly by Thompson & Capper as Healthspan have changed their formulation.

2.2 **Rationale and objectives**  
Management of OA is primarily aimed at symptom control with the aim to retain or improve joint function. In cases where this is unsuccessful, surgery such as total joint replacement remains an effective option for the majority of patients. To date there are very limited therapeutic options that can alter the natural history of the disease process and delay OA progression. Research is therefore needed to identify agents that may prevent, retard or reverse the morphological changes of cartilage in OA, thereby reducing radiological progression. In addition, these agents may be found to have independent effects on patients’ symptoms, thereby improving quality of life.

Epidemiological data suggest that low dietary intake of vitamin D and low serum 25-hydroxyvitamin D₃ levels are associated with radiological progression in knee OA. The study’s aim is, therefore, to determine whether vitamin D supplementation can reduce the rate of disease progression and improve symptoms in patients with knee OA.

2.3 **Relevant studies/trials**  
**Vitamin D and cartilage metabolism**  
Vitamin D has been shown to stimulate synthesis of proteoglycan by mature articular cartilage in vitro, suggesting that vitamin D through its receptor may affect articular cartilage metabolism (Corvol et al, 1981). Growth plate cartilage is responsive to vitamin D, and hypertrophic adult articular cartilage chondrocytes redevelop receptors for vitamin D.

**Vitamin D and bone**  
There is growing evidence that OA may be associated with defects in subchondral bone. As normal bone metabolism is dependent on vitamin D, a relative deficiency results in adverse effects on calcium metabolism, osteoblastic activity, matrix ossification and bone density (Radin
et al, 1970). Studies have previously demonstrated that vitamin D supplementation increases bone mineral density (BMD) and reduces this fracture risk (Chapuy et al, 1992; Dawson-Hughes et al, 1997). Low tissue concentrations of vitamin D may therefore impair the ability of bone to respond adequately to pathophysiological processes in OA, predisposing to disease progression. Many studies have examined the association between osteoporosis and OA (Dequeker et al, 1996, Chapuy et al, 1994), and a recent study has observed that high BMD and BMD gain over 2 years decreased the risk of progression of radiographic knee OA (Zhang et al, 2000). This data has prompted preliminary studies of bisphosphonates in the management of knee OA.

Vitamin D and Inflammation
Vitamin D has effects on the immune system and altered vitamin D homeostasis may result in immunomodulation (Hewison, 1992). 1,25-dihydroxyvitamin D$_3$ has been shown to inhibit the mitogenic response of T lymphocytes and the production of IL-2 (Rigby et al, 1984), whereas the release of IL-1 was stimulated (Bhalla et al, 1986). This may be relevant, as low levels of inflammation have been associated with knee osteoarthritis (Spector et al, 1997).

Vitamin D and ageing
Vitamin D deficiency becomes increasingly apparent after the age of 65. In the Framingham Study, low serum 25-hydroxyvitamin D$_3$ concentrations were seen in 14% of women and 6% in men, with these figures increasing with age (McKenna, 1992). There are currently limited data on vitamin D status as assessed by 25-hydroxyvitamin D$_3$ levels in the UK population aged 40-64 years. In non-institutionalised people aged 65-74 years, between 51-65% had evidence of vitamin D insufficiency with serum 25-hydroxyvitamin D$_3$ below 60nmol/l (Department of Health 1998). Extrapolation of the epidemiological data would suggest that this vitamin D deficiency could be contributing significantly to risk of knee OA in the ageing population.

2.4 Risks and benefits
There may be a minor risk of redness, soreness or bruising at venepuncture sites necessary to obtain blood samples for analysis. Radiation exposure from knee radiographs is well within the maximum annual dose limits recommended in the Ionising Radiation Regulations (1999). In general, treatment with vitamin D is very well tolerated. Unless taken in excessive doses, side effects are rare but may include some of the following symptoms: loss of appetite, tiredness, nausea and vomiting, diarrhoea, weight loss, production of large volumes of urine, sweating, headache, thirst, and dizziness. Raised concentrations of calcium and phosphate can also occur in blood and urine.

3. SELECTION OF CENTRES/CLINICIANS
Following the favourable opinion of the REC, there will be a 2 day central training programme for investigators, research nurses and radiographers. There will then be further meetings/training to initiate the centres. Full training will be given in the completion of documents.

For further details on ethical approval, refer to section 13.

3.1 Centre/Clinician eligibility criteria
1. Proven research record
2. Clinical expertise in OA
3. Adequate resources and facilities to support recruitment within the specified time.
4. Adequate qualified staff to conduct the trial properly and safely.
4. SELECTION OF PARTICIPANTS

4.1 Patient inclusion criteria
1. Participants aged over 50 years
2. Male or female
3. Ambulatory (Not wheel chair bound)
4. Able and willing to attend or comply with treatment and follow-up.
5. Radiological evidence of early disease at medial tibio-femoral knee compartment
   (Modified Kellgren & Lawrence (k&l) score 2/3, JSW >1mm)
6. Pain in knee for most days of previous month.
7. Written informed consent

4.2 Patient exclusion criteria
2. History of inflammatory arthritis
3. Knee stiffness > 30 minutes duration
4. Current user of cod liver oil or vitamin supplementation with a total Vitamin D content
   greater than 200 IU
5. Current use of glucosamine or chondroitin for less than 3 months
6. History of hyperparathyroidism or osteomalacia
7. Current use of anti-epileptic medication
8. Current use of bisphosphonates or use within 2 years
9. History of hypercalcaemia or hypercalciuria
10. History of hyperthyroidism, sarcoidosis
11. History of renal stones
12. Previous intra-articular injection: steroid within 3 months, hyalgan within 6 months
13. Previous knee surgery or arthroscopy within 6 months
14. History of osteoporotic fracture
15. History of cancer within last 5 years, excluding skin cancer.
16. Serious psychiatric disorders including dementia.
17. Inability to understand the procedures
18. Inability to attend or comply with treatment or follow-up scheduling
19. Pregnancy

4.3 Number and source of participants
470 eligible participants will be recruited from three main sources.

(1) The community via primary care trusts (PCTs) and Multi-professional Trial Teams (MPTTs).
This will utilise General practitioner lists of participants aged over 50 years with a clinical
diagnosis of knee OA. Standard letters (Appendix 6) will be sent to the potential participants
from the relevant GP to invite them to participate in the VIDEO study and enclosing a PIS.
Those participants who respond will be telephoned in the first instance to establish suitability
and invited to attend the study site for an interview if appropriate.

(2) Secondary care. This will utilise lists of patients referred to District General and Teaching
Hospitals for knee pain. Standard letters (Appendix 7) will be sent to the potential participants
from the relevant consultant to invite them to participate in the VIDEO clinical trial and
enclosing a Patient Information Sheet (PIS). Those patients who respond will be telephoned
in the first instance to establish suitability and invited to attend the study site for an interview
if appropriate.
(3) From advertisement. Posters (Appendix 8) will be displayed in GP surgeries, physiotherapy and hospital waiting areas. Potential participants who respond will be telephoned in the first instance to establish suitability, a PIS will be sent and they will be invited to attend the study site for an interview if appropriate.

Advertisements of a similar format and wording may also be used in the local/national press to encourage recruitment.

### 4.4 Screening Procedure

**Pre-screening**

All potential participants should be pre-screened in person, by telephone interview or by mailed questionnaire regarding age, current medical condition, medical history, current and past medications and willingness to participate in a 3-year research study. Only those participants with a suitable history for participation in the study will be invited to attend for screening. Participants will be given the Patient Information Sheet to aid their decision regarding participation in the study.

**Final Screening**

All participants must provide written informed consent before any study specific procedures are performed. The investigator, or a person designated by the investigator, should discuss the trial with the potential participant and provide adequate opportunity for questions and answers. Once this is done and the potential participant has agreed to participate in the study, the informed consent form should be personally signed and dated by the participant, and by the person who conducted the informed consent discussion. The participant must then be provided with a copy of the signed informed consent. A copy of the consent form will also be placed in the medical notes and the original kept in the Trial site file.

After giving informed consent, the participants will be assigned a pre-defined site-specific screening number by the RN. This number will be entered into the Screening Log, which is a list of all participants at the site who signed the informed consent for this study. The Screening Log must show all of the participants who were pre-screened to participate in the study, whether or not any final screening procedures were subsequently conducted.

After informed consent has been obtained, participants will undergo knee radiography to determine the presence and severity of their knee OA. Participants with knee radiographs fulfilling the study entry criteria will then have routine blood samples taken to assess haematology and biochemistry. A 24 hr urine sample will also be obtained.

All X-ray results and laboratory test results will be reviewed by the Principal Investigator (local) prior to randomisation. Participants will have their randomisation and baseline assessment within 100 days of their screening visit.

### 5. RANDOMISATION & ENROLMENT PROCEDURE

All inclusion and exclusion criteria must be satisfied prior to randomisation. Eligible participants will be randomised to treatment. Study drug will be dispensed only after completion of the baseline procedures and eligibility has been re-checked at this baseline visit.
Further details on the process of randomisation can be found in section 9.1

<table>
<thead>
<tr>
<th>RANDOMISATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel: 020 7670 4711 (Mon - Fri, 09:00 – 17:00)</td>
</tr>
<tr>
<td>Fax: 020 7670 4829</td>
</tr>
</tbody>
</table>

Following written consent and screening assessments from participants the research nurse will telephone a MRC Clinical Trials Unit Randomisation Line. Following telephone randomisation, the MRC Clinical Trials Unit will fax notification of receipt, study number confirmation and participant attendance diary to the centre. The screening form, randomisation form and fax notification will be placed in the CRF by the RN. The study number will be 5 digits: the first two will correspond to the centre number (01, 02, 03, 04 or 05) the following 3 digits will be sequential from 1 i.e. 001, 002. The Research Nurse will be responsible for enrolling participants into the trial. Randomisation will occur after eligibility has been confirmed and before issue of trial medication.

The baseline visit must take place within 100 days of the screening visit. All inclusion and exclusion criteria must be satisfied again prior to the baseline assessments. The study records must clearly reflect the participant's eligibility for the study and copies of all relevant tests, reports and examinations must be included in the participant records.

Participants will be asked to fast for 12 hours before their baseline visit (i.e., no food or beverages except water). See section 7 for details of assessments at baseline.

6. TREATMENT OF PARTICIPANTS

6.1 Trial treatment
Participants will be randomised to receive oral vitamin D (as cholecalciferol) 800 IU/day (20 µg/day) or matching placebo tablets. All participants will be given their supplies of medication at baseline, 6 months, 12 months, 18 months, 24 months and 30 months.

Data from clinical trials suggest that 800 IU/day cholecalciferol can produce significant increases in serum 25-hydroxyvitamin D₃ levels, and that these increases are evident within 1 month of starting treatment (Vieth 1999). The mean post-treatment levels from 10 studies using this dose was 77.5 nmol/l. Data from McAlindon et al (1996) and Lane et al, (1999), suggest that supplementation of 800 IU/day would be sufficient to raise serum levels above the threshold of 77 nmol/l to have a potential impact on OA progression. Refer to section 7 for the follow-up schedule.

6.2 Trial product(s)
The active treatment was supplied by Healthspan and manufactured by Thompson & Capper. Healthspan have changed their formulation, and so the active treatment will be supplied directly by Thompson & Capper, following the original formulation. The placebo will be supplied by Thompson & Capper.

The active treatment, placebo and randomisation list will be supplied to Bilcare Global Clinical Supplies (Europe) Ltd for packing and labelling. See Appendix 20 for sample label.
The blinded products will then be dispatched to each centre by Bilcare Global Clinical Supplies (Europe) Ltd.

The trial drug will be dispensed initially to the patient after randomisation, and then at 6 monthly intervals in standard closure containers in quantities of 2 x 200 tablets to allow for the potential delay in follow-up appointments or cancellation.

The active treatment refers to 2 x 10µg cholecalciferol = 800IU.
Each active tablet contains 10µg i.e. 400IU

6.3 Dispensing
Drugs will be stored in the pharmacy at each participating hospital. The dose being used is 20µg (800 IU) per day. Participants will be issued with 2 containers at months 0, 6, 12, 18, 24, 30. The participants will be instructed on the label to take two tablets once a day with food. This will be repeated verbally by the RN.

6.4 Randomisation codes/ Unblinding
Unblinding is generally discouraged during treatment. The reason for unblinding should be clearly stated (preferably in writing). In order to unblind a patient on grounds of safety the Chief or Principal Investigator should contact the Trial Statistician (with support from Computer Services).
All instances of unblinding should be recorded and reported to the IDMC.

6.5 Modification of trial treatment
Treatment with the study drug may be stopped if a participant has experienced a significant toxicity thought to be due to the study medication. It may be possible to rechallenge the protocol in order to evaluate the relationship of the study drug to the adverse event. However, such a rechallenge may only take place if:

- All of the following agree to the rechallenge - local Principal Investigator and Chief Investigator.
- The participant has provided informed consent for the rechallenge.

For further information see Appendix 9

6.6 Accountability and unused drugs/devices
Drug allocation registers, delivery receipts, prescription sheets, details of returns to hospital/site/pharmacy will be kept by the Research Nurse at each centre and will be reviewed by the Trial Manager. Unused drugs will be returned by the patient at each appointment and counted by the Research Nurse. The Research Nurse will keep documentary drug reconciliation records, working with the pharmacist.

6.7 Measures of compliance/adherence
Procedures for monitoring patient compliance will be employed. Blood sampling and questionnaires will be used to measure the serum 25-hydroxyvitamin D₃ and reported consumption of dietary or supplemental vitamin D.

The patient will be asked to return the container at the end of the 6 month period when attending for assessment and dispensing of further trial drug. The RN will count any
remaining tablets to assess whether the correct amount has been taken. This will allow the Research Nurse to counsel the patient about the importance of taking the correct amount of trial medication.

6.8 Non-trial treatment

6.8.1 Medications permitted
Stable dosages of NSAIDs or Cox II specific inhibitors.
Stable dosages of glucosamine or chondroitin
Analgesics at therapeutic doses
Hormone replacement therapy (HRT)
Selective oestrogen receptor modulators (SERMs)
Cod liver oil or other vitamin D supplements with a total daily dose of less than 200IU (5mcg)
Vitamin D1. (Utiger RD. 1998., Vieth R.1999)

6.8.2 Medications not permitted
The drugs listed below are also not permitted at baseline, and their use is strongly discouraged during the course of the study unless medically indicated:
- Anti-epileptic medications
- Bisphosphonates
- Steroids as intra-articular injection
- Hyalgan as intra-articular injection

If a participant is prescribed one of these concomitant medications, then they will be followed on an intention to treat basis. A decision regarding whether these participants may remain on study drug will be made by the Chief and Principal Investigators.

6.8.3 Data on concomitant medication
Details of all concomitant medications will be collected at each assessment and recorded in the CRF.

6.9 Co-enrolment guidelines
Participants should not enter any other clinical trial while participating in the VIDEO study.

7. ASSESSMENTS AND PROCEDURES

Follow-up visits will be scheduled 3, 6, 12, 18, 24, 30 and 36 months after the baseline visit. The first two follow-up visits (at 3 and 6 months) will take place within 14 days of the originally scheduled date. For subsequent visits (12, 18, 24, 30 and 36 months), these must also take place within 14 days of the originally scheduled date for the visit. Dates for follow-up visits will be calculated with reference to the date of randomisation and according to calendar months and a follow-up schedule issued at the time of randomisation. See table 1 for details. For the 18 and 30 month visits the participant may choose whether to attend the research site in person, or whether to be assessed over the telephone by the research nurse instead. This telephone assessment will include adverse event monitoring, and the study drug, symptom questionnaires (WOMAC and WHOQOL) and FFQ will be sent to the participant.
Recruitment to the study will continue for up to 3 years.

### 7.1 Schedule for follow-up

**TABLE 1 Flow chart/schedule for follow-up**

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>Pre-screen</th>
<th>Final screen</th>
<th>Baseline</th>
<th>3/12</th>
<th>6/12</th>
<th>12/12</th>
<th>18/12</th>
<th>24/12</th>
<th>30/12</th>
<th>36/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire for suitability</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Information Sheet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical exam including vital signs</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 lead ECG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee X-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-flexed - Tibio-femoral joint</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skyline - Patello-femoral joint</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom questionnaires (WOMAC, WHQOL)</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food diary (4 day)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food FFQ</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples (appendix 17)</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fasting, except at screening visit, for</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Routine haematology</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Biochemistry (includes glucose except at screening)</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Baseline glucose</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bone biochemistry (appendix 9)</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bone and cartilage biomarkers</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine sample (2nd void, fasting) for</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bone biomarkers</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hour urinary calcium sample</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis *</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Protein</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Glucose</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Blood</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense medication</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record AEs</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition and Depression (MMSE and BDI)</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication/Non-drug treatment</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* If the participants choose to have a telephone follow-up assessment at the 18 and 30 month visits instead of visiting the research site, then urinalysis will not be performed.

**TABLE 2 Flow chart/Schedule for sub-studies (site specific)**

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>Baseline</th>
<th>3/12</th>
<th>6/12</th>
<th>12/12</th>
<th>18/12</th>
<th>24/12</th>
<th>30/12</th>
<th>36/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent for genetic analysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample for DNA *</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee MRI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee Ultrasound</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lumbar spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Whole body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tibial/subchondral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle strength assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hand grip strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quadriceps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Get Up and Go Test and Timed 10m Walk</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* If 30 mls of blood is not taken at baseline as required, then additional blood to make up this amount may be taken at other visits at the follow-up appointments where it is permitted to take blood.

### 7.2 Procedures for assessing efficacy

Efficacy as measured by the primary outcome measure will be assessed by X-ray of the knee by measuring joint space narrowing. The Research Nurse will record results reported by the radiologist in the questionnaire in the CRF. Anonymised X-rays will be sent to MRC CTU for checking and reading.

Efficacy as measured by the secondary outcome measures will be assessed by recording symptoms at each 6 month assessment. The RN will record symptoms reported in the questionnaire in the CRF.

### 7.3 Procedures for assessing safety

Safety parameters and procedures will include the following assessments:
- Clinical examination
- SAE/SAR and AE reporting
- Laboratory evaluations

### 7.4 Trial closure

The official time of closure will be the time at which the last X-Ray is received by CTU. Assessments and procedures required when closing the trial will be:
- Clinical examination
- Knee X-ray
- Sub-study investigations
• QL, Cognition/Depression and symptom questionnaire
• FFQ
• Blood and urine analysis
• AEs
• Concomitant drug use and non-drug treatments

These will be recorded in the CRF and will be necessary whether the trial closure is planned or premature.

A final monitoring visit will be made to each centre by the TM or DM.

8. WITHDRAWAL OF PARTICIPANTS

In consenting to the trial, participants are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes. If the patient explicitly states their wish not to contribute further data to the study, the CTU should be informed in writing and a withdrawal form in the CRF completed.

8.1 Withdrawal from trial intervention

Participants may be withdrawn from their randomised treatment for the following indications:

• Serious Adverse Event that is believed related to study medication
• Hypercalcaemia which does not correct on temporary cessation of the trial medication and/or reduction of dose
• Hypercalciuria, judged to be clinically significant, which does not correct on temporary cessation of the trial medication and/or reduction of dose.
• Orthopaedic surgery to index knee joint. Participants will be asked to undergo the procedures listed for 36 months prior to their surgery.
• Inability to attend regularly for treatment or assessment
• Participant choice

Follow-up will continue on all randomised participants unless the patient explicitly also withdraws consent for follow-up.

Withdrawn participants will be invited to undergo the procedures listed for 36 months at the recruiting centre.
Withdrawn participants will not be replaced.

8.2 Loss to follow-up

It is anticipated that 30% of participants recruited into the study will fail to complete the 3 year treatment course. These estimates are based on recent observations from a study of glucosamine in knee OA, where 36% of participants in the active treatment group and 33% in the placebo group did not complete the 3 year treatment course (Reginster 2001).

The research nurse will make every effort to locate participants who are lost to follow-up, primarily using GP records and ONS.
9. STATISTICAL CONSIDERATIONS

9.1 Method of Randomisation
Participants will be randomised to treatment or placebo group using random permuted blocks. The randomisation will be performed separately for each participating centre.

9.2 Outcome Measures

Primary
Radiological progression of knee OA in medial joint compartment

Secondary
Radiological progression of knee OA in other joint compartments
Reduction in pain and functional disability
Quality of life
Changes in depression and cognition status

Sub-study Outcome Measures
BMD at spine, hip and whole body
Subchondral BMD
Body composition
Subchondral bone oedema
Cartilage volume
Muscle strength
Postural stability
Cognition
Depression index
Biochemical indices
Glucose/insulin metabolism

9.3 Revised sample size statement
Based on two recently published long term trials using semi-flexed X rays of the knee (Bingham 2006, Brandt 2005), the pooled estimate of the standard deviation of the rate of joint space narrowing (JSN) was 0.7 mm. A sample size of 159 patients per group would be sufficient to detect a difference in JSN of 0.22 mm between the Vitamin D and placebo groups, assuming a sd of 0.7 mm, using a power of 80% and significance level of 5%. A difference in JSN of 0.22 mm would be clinically important. Assuming that 32% of patients will not attend for their final X-ray at the end of the study, the total sample size required is 470 patients.

9.4 Interim Monitoring and Analyses
Any confidential interim analyses will be performed at the request of the IDMC.
9.5 Outline Analysis Plan

The statistical analysis will be based on participants randomised, irrespective of subsequent compliance with their randomised treatment (i.e. analysis will be on an intention-to-treat basis). The exception to this is that participants who have not been dispensed any medication will not be included in the intention-to-treat analysis. Every effort will be made to obtain follow up data on all randomised participants whether or not they continue to take their study medication. The primary outcome measure, the rate of JSN, will be estimated by the slope of the regression of JSW on time for each patient. For the rate of JSN summary measures, the effect of treatment will be obtained from a linear regression model, adjusting for baseline JSW, OA severity, gender, glucosamine use, and centre. The primary analysis will be based on the most severely affected knee (knee with the smallest joint space width at baseline).

For the secondary analysis, generalised estimating equation models will be used to incorporate information from both knees in participants with evidence of bilateral disease (Zhang et al, 1996). The effect of treatment on the proportion of participants with clinically significant progression (JSN>0.5 mm) at 3 years, will be obtained using a logistic regression model, adjusting for baseline JSW, and centre.

The area under the curve (AUC) for the total WOMAC score will be used as the main summary measure for symptom modification. Separate analyses will examine the AUC for WOMAC pain, physical function, and stiffness sub-scales. Continuous outcome measures, assessed on more than one occasion, will be summarised using AUC approach, and a two-sample t-test will be used to compare the randomised groups. If necessary, a log transformation will be used to achieve normality and equal variances. If a log transformation is not successful, then the groups will be compared using a non-parametric Mann-Whitney U test. Adverse event rates in the two groups will be compared using comparisons of two independent proportions.

Summary measures for the baseline characteristics of each group will use means and standard deviations for continuous Normally distributed variables, medians and interquartile ranges for non-Normally distributed variables, and frequencies and proportions for categorical variables. Summary measures for linear regression models will be regression coefficients and 95% confidence intervals. Summary measures for continuous Normally distributed outcome measures will be means, standard errors and 95% confidence intervals for differences in means.

Sub-group analyses

Possible interactions with treatment effect will be investigated using multiple regression or logistic regression models for the following potential effect modifiers, but these will have limited power:

1) Use of HRT and/or SERMs in postmenopausal women
2) Baseline 25-hydroxyvitamin D₃ levels (to identify a potential threshold effect for the action of vitamin D supplementation on OA)

Proposed frequency of analyses

A final analysis plan will be prepared before the end of the trial. Any confidential interim analyses will be performed at the request of the Independent Data Monitoring Committee.
10. DATA VERIFICATION AND SITE MONITORING

10.1 Checks at CTU
Data stored at CTU will be checked by the data manager at MRC CTU for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by post or fax for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialed. The amended version should be returned to CTU and the site’s copy should also be amended. CTU will send reminders for any overdue and missing data.

10.2 Clinical site monitoring

Direct Access to Data
The investigator and participant will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents.

Confidentiality
Patient’s names and/or address will not be disclosed to the CTU. Patient’s data/specimens will be identified by trial number and/or initials or hospital number only. Individual participants will not be identified in the resulting publications and presentations from the trial. The CTU complies with the principles of the Data Protection Act.

Quality Control of Data
On site monitoring of operational techniques and source data verification, in line with ICH GCP guidelines, will be undertaken by the Trial Manager and Data Manager to verify that the requirements for quality of the trial related activities are fulfilled. 100% of SAEs and SARs will be monitored. A minimum of 10% of the records of randomised participants will be monitored. This may be amended by the Trial Statistician or the Trial Manager.

11. ADVERSE EVENTS AND REACTIONS

The MRC Clinical Trials Unit will undertake safety monitoring and reporting on behalf of the sponsor.

11.1 Adverse events and reactions
An Adverse Event (AE) is any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An Adverse Reaction (AR) is any untoward and any unintended response in a participant to an investigational product which is related to any dose administered to that participant.

An Unexpected Adverse Reaction (UAR) is an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question.
Reported adverse reactions of vitamin D include the following:

- Nausea
- Vomiting
- Anorexia
- Constipation
- Muscle weakness
- Weight loss
- Confusion
- Cardiac arrhythmia’s
- Increased urination
- Calcinosi
- Renal stones
- Hypercalciuria
- Hypercalcaemia
- Hyperparathyroidism

See figure 2 below for reporting sequence.

**FIGURE 2 AE Reporting Sequence**

1. AE, AR or UAR
2. RN/PI should complete AE log indicating causality and severity
   - RN notifies local Principal Investigator (PI) for review
   - Copy of AE log should be returned to Data Manager (DM) at MRC CTU for review
   - DM notifies Trial Manager (TM)
   - If event is an SAE then SAE reporting sequence should be followed
11.2 Serious adverse events (SAE)

A Serious Adverse Event (SAE) (Statutory Instrument 2004) is any adverse event, adverse reaction or unexpected adverse reaction, respectively, that –

a) results in death
b) is life-threatening
c) requires hospitalisation or prolongation of existing hospitalisation
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect
f) other medically important condition

These are classified as Serious Adverse Reaction (SAR), Unexpected Serious Adverse Reaction (USAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

FIGURE 3 SAE Reporting Sequence

- RN notifies PI immediately
- RN and PI complete SAE form in CRF
- RN faxes TM detailed report written by PI and supporting documents
- Phone to notify and FAX SAE form to MRC CTU
- TM notifies CI

Is it a SUSAR? (CI)
Based on:
- suspected causality
- unexpected for trial drug
- serious AR

- Yes
  - All PIs
    - Death or life threatening
      - Within 7 days
      - MHRA, RECs, sponsor
    - Other listed outcomes
      - Within 8 days

- No
  - quarterly
  - TM to report to IDMC, TSC Chair all suspected serious adverse reactions (SSARs)
  - Annually
    - List all SSARs and a report on the safety to MHRA and REC's

- Within 24 hours
- Within 7 days
- Immediately
- Within 15 days
- Annually
The following SUSARs **must** be rapidly reported to the relevant regulatory authorities by the following times from when the investigator is aware the case qualifies for rapid reporting (see Figure 3):

a) unexpected fatal or life-threatening SUSARs no later than 7 days for the first report plus a report and all additional relevant information no later than a further 8 days,

b) all other unexpected SUSARs no later than 15 days for the first report.

If an SAE occurs, the RN must notify the PI immediately. The RN will telephone to notify the TM and fax the completed SAE form of the CRF to the TM at the MRC Clinical Trials Unit within 24 hours. The TM will notify the CI immediately who will decide whether it is a SUSAR. A full report written by the PI at the centre where the SAE occurred will then be faxed to the TM within 7 days of the initial notification to the CTU. Appropriate anonymised supporting documents will be sent as soon as possible. These supporting documents should include post mortem reports and death certificates (where appropriate), discharge letters/summaries and results of investigations.

For death or a life-threatening SUSAR a written report from the CI must be sent to the regulatory authorities within 7 days of the first notification from the centre. This will be followed by all addition information within 8 days. For all other conditions listed as SUSARs a first report must be submitted not more than 15 days after the first notification of the event.

For SAEs where the CI has made the decision that it is not a SUSAR, the TM will report these to the IDMC and to the TSC chair quarterly. A list of all SSARs and a report on the safety of those participants will be sent to the MHRA and relevant RECs as soon as is practicable after the end of the reporting year. The reporting year is the year ending on the anniversary of the earliest date on which the trial was authorised.

### 11.3 Severity/grading of adverse events

Adverse events will be graded as mild, moderate or severe.

- **Mild:** trivial AE not causing any real problem to the subject
- **Moderate:** AE was a problem to the subject but did not interfere significantly with usual activities or clinical status
- **Severe:** AE interfered significantly with usual daily activities or clinical status

### 11.4 Relationship to trial treatment

The classification *definitely/ probably/ possibly/ unlikely/ not related* will be used to judge the relationship between the trial treatment and adverse events. This is to be recorded on the SAE CRF or the AE log.

### 11.5 Follow-up after adverse events

Participants experiencing SAEs will receive appropriate medical attention. After recovery and for those experiencing an AE, assessment will be made during the normal follow-ups. If, in the opinion of the attending doctor, further follow-up with regard to the event is necessary then the local Principal Investigator or the Emergency Medical Contact should be notified. The rechallenge protocol may be applied.

See Appendix 9 for the Rechallenge Protocol
12. ANCILLARY STUDIES

A number of optional sub-studies will be conducted in some centres (see section 3) as decided by the CI where the local PI demonstrates prior expertise and resources are available. These studies are:

12.1 Genetic analysis
In view of the unique nature of this cohort and the planned intervention, we will attempt to obtain samples for DNA analysis to assess the role which genetic factors may play in determining the natural history of OA and its response to treatment with vitamin D. Consent for this sub-study will be obtained from participants who will then donate an additional 30 ml blood for DNA extraction. DNA from these participants will be archived and made available to bone-fide investigators who wish to access the samples for academic research, participant to the approval of a biobank committee. 
(See Appendices 3 and 4)

12.2 Bone Mineral Density
BMD will be measured by dual energy x-ray absorptiometry (DXA) using a study approved densitometer (Hologic or Lunar). BMD measurements will be made at the lumbar spine (L1 to L4), hip and whole body. The latter measurement will include assessment of body composition. Proximal tibial BMD will also be measured to give information on subchondral bone changes. Measurements will be made at baseline, 1 and 3 years.

See Appendix 12.

12.3 Magnetic Resonance Imaging (MRI)
Imaging of the knees will be made using a study approved MRI machine. Baseline assessment will be made using T1 and T-2 weighted fat-saturated images to evaluate for presence of bone marrow oedema as previously described (Felson et al, 2001). Cartilage volume will also be measured. MRI data will be acquired at baseline and at the end of the study period.

See Appendix 13.

12.4 Muscle Strength
Hand grip and quadriceps muscle strength will be measured at baseline, 1 and 3 years. Hand grip strength will be measured in both right and left hands using a Jamar hand-held dynamometer (Promedics Ltd). Quadriceps muscle strength will also be assessed in each leg from the supine position, using a Lafayette Manual Muscle Test System (Lafayette Instrument Co.).

See Appendix 11.
12.5 Musculoskeletal Function, Static and Dynamic Balance
Musculoskeletal function, static and dynamic balance will be assessed using the Get Up and Go and Timed 10M Walk test at baseline, and then at 1 and 3 years. See Appendix 14.

12.6 Knee Ultrasound
Non-invasive assessment of joint structure and associated vascularity will be made using ultrasound and power Doppler at baseline, 1, 2 and 3 years. See Appendix 22.

13. ETHICAL CONSIDERATIONS AND APPROVAL

13.1 Ethical considerations
Consideration has been given to the following ethical aspects of this trial:

- Participants will be asked to make additional visits to hospital for follow-up assessments. Participants will be fully reimbursed for any additional travel costs. The participant will make a claim with receipts, where possible and payment by cheque or cash will be made by the RN or TM at MRC CTU. Where possible and within the appropriate time frame appointments will be made at a mutually convenient time and date.

- Additional tests i.e. scans, x-rays, blood tests, urine tests, questionnaire completion at various assessments will be required by the trial. The patient will receive a full explanation regarding these necessary tests. The risks to the patient from these tests are a small amount of discomfort and the possible risk of bruising from venepuncture. The patient will also have additional exposure to radiation. This however will remain within safe limits.

- Whole body DXA scans will be used at baseline. If any serious abnormalities are identified the potential participant will be excluded from the study. If the participant was referred by a consultant within the hospital performing the baseline assessments then referral to the appropriate specialist consultant will be made. If the potential participant was identified via a General Practitioner then the PI will contact that GP to recommend referral. Both methods will ensure that the participant receives the appropriate medical care. Contact with the GP or hospital specialist would only be with the permission of the study participant.

- Use of placebo. There are no proven treatments that delay the progression of OA, and therefore participants are not being denied any active and appropriate medication. Full explanation is given in the PIS see Appendix 1

- Cognitive decline in this age group is not usually of urgent concern. If participants are concerned about their memory they can be asked to contact their general practitioner. However, if incident cases of depression are detected, then referral to their GP is required (anyone with a Beck Depression Inventory (BDI) 18 or above). If participants have severe depression (score of greater than 30), then the RN should contact the Trial Manager or Principal Investigator for advice. Prompt clinical attention may be required.
13.2 Ethical approval

The protocol has received a favourable opinion of Main Research Ethics Committee (MREC) which must include site specific assessment by the Local Research Ethics Committee (LREC) before participants are entered from a new site. The Royal National Orthopaedic Hospital NHS Trust is the leading REC. The patient’s consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The patient information sheet and patient consent form are attached. A copy of the LREC approval from Main REC must be received by the CTU before randomising participants.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

14. REGULATORY APPROVAL

Application has been made for a Clinical Trial Authorisation (CTA) from the MHRA. The trial will not begin until a valid CTA is received. The trial has been registered with the EudraCT database.

15. INDEMNITY

If the patient is harmed by taking part in this study, there are no special compensation arrangements. If the patient has any cause to complain about any aspect of the way they have been approached or treated during the course of this study, the normal National Health Service complaint mechanisms are available to them.

All researchers will have full or honorary contracts with NHS organisations. These contracts will provide cover in the event of negligent harm via CNST.

This trial has been initiated by an employee of University College London. UCL holds insurance for compensation in respect of accidental injury of any participant, arising out of the trial, at all sites of this trial.

16. FINANCE

Payments will not be made to the patient. Three of the five centres were being paid for individual patient recruitment, but from 17th December 2007 all five centres will be paid for individual patient recruitment. Participants will however be reimbursed for travel to screening, baseline and follow-up assessment appointments.

All trial drugs and placebo will be supplied to participants free of charge. The drug and placebo had been purchased via Healthspan and manufactured by Thompson & Capper. Healthspan have recently changed their formulation, and so the drug and placebo will be purchased directly from Thompson & Capper, following the original formulation.
17. TRIAL COMMITTEES

17.1 Trial Management Group (TMG)
A Trial Management Group (TMG) will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

Dr Richard Keen, Chief Investigator, RNOH
Dr Nigel Arden, Principal Investigator, Southampton University Hospital
Ms Caroline Doré, Trial Statistician
Ms Anna Bara, Trial Manager

17.2 Trial Steering Committee (TSC)
The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

Professor Paul Dieppe (Chair), University of Bristol
Professor Michael Doherty (Vice-Chair), University of Nottingham Medical School, Nottingham
Dr Richard Keen (Chief Investigator), RNOH
Dr Nigel Arden (Principal Investigator) Southampton
Ms Caroline Doré (Trial Statistician), MRC CTU
Iva Hauptmannova (RNOH R&D Office)
Arthritis Care patient representative

17.3 Independent Data Monitoring Committee (IDMC)
The Arthritis Research Campaign will establish an Independent Data Monitoring Committee, which may advise the TSC, can address issues of ethics and safety and can recommend premature closure of the trial.
The IDMC will meet annually.

Dr Ade Adebajo (Chair), Rheumatologist, University of Sheffield
Dr Ernest Choy, Rheumatologist, King’s College Hospital
Dr Chris Roberts, Statistician, University of Manchester

Details of the interim analysis and monitoring are provided in the IDMC charter.

18. PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

No verbal or written report may be made without the approval of the Trial Steering Committee.
All publications shall include a list of participants, and if there are named authors, these should include the trial’s Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The Eudract number that has been allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

19. PROTOCOL AMENDMENTS

**Version 1.0 (17/05/2004)**
Original provisionally approved version.

**Version 1.1 (14/06/2004)**
Revisions recommended by Ethics Committee in provisional opinion of protocol 1.0.

**Versions 1.1 & 1.2 (14/06/04 & 21/07/2004)**
Flowchart changes.
Schedule for follow-up changes.
Secondary outcome measures changes.
Non-substantial amendments.

**Versions 1.2 & 1.3 (21/07/04 & 04/10/2004)**
Change of sample label.

**Version 1.4 (25/04/05)**
Change of investigator site (UEA/Norfolk and Norwich Hospital).
Change of post of PI (Prof Alex McGregor).
Addition of GUGOT and TWT.
Change from 7-day to 4-day food diary.
Change of re-pack organisation to SMPU, Cardiff.
Change to IMP label.
ISRCTN added to protocol.

**Version 1.5 (02/09/05)**
Additional of new site and investigator (Dr Fraser Birrell, Newcastle).
Use of WHOQOL questionnaire to replace SF36.
Addition of two references.

**Version 1.6 (07/09/06)**
Change of re-pack organization.
Change of vitamin D dose exclusion criteria.
Newsletter.
Addition of PASS-SF questionnaire.
Addition of ultrasound imaging of knee.
MRI increase to 3 Tesla (Newcastle only).
New label format for re-pack.

**Version 1.7 (22/01/07)**
Add additional one year knee x-ray and DXA scans.
Typographical corrections.

**Version 1.8 (23/04/07)**
Reduction in number of blood and urine tests being performed.
Typographical corrections.
**Version 1.9 (06/06/07)**
Recalculation of sample size from 800 to 600 participants.
Correction of error in last substantial amendment re blood and urine changes.
Typographical corrections.

**Version 2.0 (30/01/08)**
Recalculation of sample size from 600 to 450 participants.
Discontinue random glucose testing at screening visit.
Add additional one and two year MRI scans.
Change in drug ordering mechanism.
Change in payment methods to sites.

**Version 2.1 (07/02/08)**
New trading name of re-packers.
Hypercalciuría withdrawal change status.
Biomechanics of the knee sub-study.

**Version 2.2 (26/02/08)**
Clarification on number of knees scanned using MRI.
Clarification in protocol stating 4-day food diary is administered.
Placebo shelf life change information.
Correction of inconsistency in protocol re type of food diary used.

**Version 2.3 (03/04/08)**
18 and 30 month visits may be assessed by telephone if the participant prefers this.
Permission to contact participants after end of study.
Update of Genetic Patient Information Sheet.

**Version 2.4 (19/05/08)**
Recalculation of sample size from 450 to 470 participants.
Addition of hip questionnaire.
Time between screening and baseline visits changed from within 60 days to within 100 days.
Allow randomisation to be performed before baseline visit.
Statistical analysis change (exclude from intention-to-treat analysis participants never dispensed any medication).
Typographical corrections.

**Version 2.5 (14/10/2008)**
Non-substantial amendments, including typographical corrections.

**Version 2.6 (12/01/2009)**
Non-substantial amendments, including typographical corrections.

**Version 2.7 (06/03/2009)**
Add additional one and two year ultrasound scans.
Update of Patient Information Sheet.
Non-substantial amendments, including typographical corrections.

---

**20. SEQUENCE OF RESPONSIBILITIES**

The MRC Clinical Trials Unit accepts 3 main areas of responsibility on behalf of the Sponsor for the following trial activities:

- Trial Management
- Quality Control
- Data Handling
- Record Keeping
- Obtaining Research Ethics Committee and MHRA approval (with CI and local PIs)
- Pharmacovigilance
• Monitoring
• Preparation of Trial reports as required by regulatory agencies (with CI)

21. REFERENCES


Beck AT, Steer RA and Barbin MG. Psychometric properties of the BECK Depression Inventory: Twenty five years of evaluation. Clinical Psychology Review 1988; 877: 100


Buckland-Wright C. Imaging procedures for OA. Ballieres Clinical Rheumatology 1997; 11: 727-748.


Zhang Y, Glynn J, Felson DT. Musculoskeletal disease research: should we analyze the joint or the person. J Rheumatol 1996; 23: 1130-1134.


22. APPENDICES

APPENDIX 1: Patient Information Sheet.................................................................38
APPENDIX 2: Consent Form..................................................................................44
APPENDIX 3: Genetic Patient Information Sheet..................................................45
APPENDIX 4: Genetic Consent Form..................................................................48
APPENDIX 5: GP Letter.......................................................................................49
APPENDIX 6: GP Recruitment Letter.................................................................50
APPENDIX 7: Hospital Recruitment Letter.......................................................51
APPENDIX 8: Poster.........................................................................................52
APPENDIX 9: Bone Biochemistry Information......................................................53
APPENDIX 10: Dietary Assessments .................................................................54
APPENDIX 11: Muscle Strength Assessment.....................................................55
APPENDIX 12: Bone Density Measurements....................................................57
APPENDIX 13: Magnetic Resonance Imaging.....................................................58
APPENDIX 14: Musculoskeletal Function, Static and Dynamic Balance.............60
APPENDIX 15: Cognition....................................................................................61
APPENDIX 16: Depression...................................................................................62
APPENDIX 17: Biochemical Analyses ...............................................................63
APPENDIX 18: Womac Questionnaire...............................................................65
APPENDIX 19: WHOQOL Quality of life questionnaire......................................69
APPENDIX 20: SAMPLE LABEL .....................................................................70
APPENDIX 21: Patient Card...............................................................................71
APPENDIX 22: Ultrasound Imaging .................................................................72
APPENDIX 23: PASS-SF Questionnaire.............................................................74
APPENDIX 24: Biomechanics of the knee sub-study using the ‘smart-tog’...........76
APPENDIX 1: PATIENT INFORMATION SHEET

(To be presented on local headed paper)
Centre Number

VIDEO STUDY
EUDRACT No 2004-000169-37

A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis (The VIDEO Study)

We would like to invite you to take part in a research study. The purpose of this study is to examine whether treatment with 2 tablets of vitamin D (800IU daily) can slow or stop the progression of knee osteoarthritis and also reduce knee pain and disability. In addition, we hope that this study will provide useful information about the natural history of knee arthritis in the general population.

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information leaflet carefully and discuss it with relatives, friends, and the doctors and nurses involved in your care. Ask the study doctor or nurse if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The UK Clinical Research Collaboration (UKCRC) publish a booklet and a leaflet entitled “Understanding Clinical Trials” and “Clinical Trials: What they are and what they’re not”. These give more information about clinical trials and looks at some questions you may wish to ask. You can get a copy of these from the website http://www.ukcrc.org/publications/informationbooklets.aspx or from the study’s research nurse.

You can also contact Arthritis Care for more information on arthritis research on 020 7380 4500.

What is the purpose of the study?
In this study we are testing vitamin D, which is currently available for the treatment and prevention of osteoporosis and osteomalacia (rickets). The aim of this study is to assess whether vitamin D may also play a role in the management of knee osteoarthritis (OA). The study will look at the effectiveness and safety of vitamin D in the management of OA. It is hoped that vitamin D may prevent cartilage breakdown and that this will slow down the progression of the disease. It is also hoped that the treatment may reduce the level of knee pain.

The study will be undertaken in at least 5 centres throughout the UK. These include University College London Hospitals, The Royal National Orthopaedic Hospital in Stanmore, Hope Hospital Manchester, Southampton University Hospital, The Royal Victoria Infirmary in Newcastle and the Norfolk and Norwich Hospital.
Why have I been invited?
You have been chosen because you have OA in at least one knee. We plan to involve about 470 people who have knee OA throughout the UK. Participation in the study would last for a treatment period of 3 years. It is possible that the study may be extended, to last for a total of 5 years. If this happens you would be informed and asked again for your consent.

Do I have to take part?
No. Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your medical care. However, if you have received study treatment it is very important that you attend a post-treatment visit.

What will happen to me if I take part?
If you decide you would like to participate in this study, then you will be asked to sign a Study Consent Form (version 1.1 03/04/2008) that will give your consent to take part in the study. You would be given a copy of your signed consent form and you may also keep this information sheet.

At your first visit you would be seen by a qualified research nurse who would ask you questions regarding your age, gender, medical history, current and previous medication use, dietary information, and aspects of your lifestyle related to your joints and bones. Radiographs (x-rays) of your knees would also be taken to confirm the presence of osteoarthritis and to determine your suitability to enter the study. You will be asked to provide a routine blood sample of approximately 30 ml (six teaspoons).

If you are eligible to participate in the study, your treatment will be chosen randomly by a computer. Half of the participants will be selected to receive 2 vitamin D tablets daily (800IU total) and the other half will be selected to receive 2 matching placebo tablets (no active vitamin D) daily. Neither you nor the local researchers (your doctor and the research study nurse) will know if you are taking placebo or the vitamin D. If however a problem arises then the doctor in charge of this research at the hospital you attend will quickly be able to find out whether you have been taking the vitamin D or placebo tablets. After the end of the study you will be told which type of tablets you received.

If you are eligible you will be asked to return for a baseline visit where you will undergo a general physical examination including a specific assessment of your knees. You would also be asked to complete some questionnaires giving details on your quality of life and your usual diet to estimate intake of calcium and vitamin D. You will also be asked to provide a fasting blood sample, a urine sample, and to complete a 24 hour urine collection.

The following additional tests may also be undertaken: a magnetic resonance imaging (MRI) scan of your knees, a bone density scan (or DXA scan) of your lower spine, hip, lower leg and whole body, an electrocardiogram (ECG), measurement of your thigh muscle strength, ultrasound of your knees, your balance and walking speed assessment. Where possible these tests will be performed during your research appointments. You can expect to be at the hospital for approximately 1 to 3 hours at each of the 8 research appointments.

You would then be asked to visit the clinic after 3 and 6 months, and then every 6 months. You will be interviewed by the research nurse and asked to complete some further questionnaires at these visits. You are free to decline to answer any of the questions at any time without giving a reason. If you choose to withdraw then any data and samples collected
while you were taking part in the study will be analysed unless you request that they are destroyed. You can tell the study research nurse if you would like these destroyed.

Urine and blood tests will be repeated at some of the follow-up visits. All the blood and urine tests that you will have are summarised in the following table:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fasting blood tests</td>
<td>First visit</td>
</tr>
<tr>
<td>Fasting blood tests</td>
<td>Baseline, 3-month 12-month &amp; final follow-up visits</td>
</tr>
<tr>
<td>24 hour urine collection</td>
<td>Baseline, 3-month, 12-month, 24-month &amp; final follow-up visits</td>
</tr>
<tr>
<td>Fasting urine sample</td>
<td>Baseline, 3-month, 6-month, 12-month &amp; final follow-up visits</td>
</tr>
<tr>
<td>Urine tests</td>
<td>Baseline and follow-up visits</td>
</tr>
</tbody>
</table>

For the 18 and 30 month visits you may choose to have a telephone assessment instead of attending the research site in person. If you choose the telephone assessment the study drug will be sent out to you. The nurse will telephone you, and some of the study questionnaires will be posted to you for completion at home.

You will be asked to not eat or drink anything apart from water for 12 hours (overnight) before the fasting blood tests and fasting urine sample. At each annual visit a general physical examination will be performed. At the annual visits the following procedures may be repeated: measurement of thigh muscle strength, balance and walking speed assessments, MRI scans. At the 1 year and final 3 year visits repeat x-rays of your knees will be undertaken, as may the DXA scans. Ultrasound of your knees may also be undertaken at the 1 year, 2 year and final 3 year visits.

You may also have the movement of your knee assessed in your home environment by a lightweight device, similar to a knee sleeve. You will have to wear this on your knee for short periods of time on a few occasions.

During the study you will be asked to report any medical events or side-effects that you have experienced. The doctor or research nurse will ask you about any medication or supplements that you are taking.

You will be given a small card, about the same size as a credit card to keep for duration of the study. You should show this to the doctor/nurse/healthcare professional at any visit to your GP, hospital or clinic.

Staff involved with the study who are based at our Southampton site may contact you after the end of the study to ask about any continuing symptoms or new joint replacements. You will be asked separately on the Consent Form if you agree to this on-going assessment.

At no time will anything you do or say be video recorded.

**What is the drug or procedure that is being tested?**
The study will evaluate a daily dose of vitamin D (cholecalciferol) against a matching placebo. The active treatment will consist of a total daily vitamin D dose of 800 International Units (IU) in 2 tablets.
What are the alternatives for diagnosis or treatment?
If you decide not to take part, the study doctor would explain what alternative treatment options are available to treat your arthritis. These might include medications to relieve the pain and inflammation or in severe cases surgery may be necessary.

What are the side-effects of any treatment received when taking part?
In general, treatment with vitamin D is very well tolerated. Unless taken in excessive doses, side effects are rare but may include some of the following symptoms: loss of appetite, tiredness, nausea and vomiting, diarrhoea, weight loss, production of large volumes of urine, sweating, headache, thirst, and dizziness. Raised concentrations of calcium and phosphate can also occur in blood and urine. It is therefore recommended that while you are taking part in this study, that you do not use additional cod liver oil, vitamin D or multivitamin or mineral tablets that include Vitamin D. If you are taking supplements containing vitamin D, you should mention it to the Research nurse at your screening appointment. You should not restrict or limit your normal diet.

What are the possible disadvantages and risks of taking part?
You might experience some brief discomfort that would not last long when you give blood. In addition there can sometimes be redness or bruising at the site where the blood was taken.

The study does involve exposure to x-rays. The total amount of radiation you will get from all of the x-rays (knee and DXA scans) is low. It is approximately the same level as you might receive from spending 3 days in the summer sunshine in South West England. You should not, however, have an x-ray if you are, or think you might be, pregnant.

What are the possible benefits of taking part?
We hope that the results from this study will show that vitamin D can prevent the deterioration of knee arthritis, although this cannot be guaranteed. The information we get from this study may help us to provide better treatment in the future for patients with osteoarthritis.

What if new information becomes available?
Sometimes during the course of a research project new information comes available about the treatment and/or the disease that is being studied. If this happens your doctor will tell you about it and discuss with you whether or not you wish to continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

What happens when the research study stops?
At the end of the study, your doctor will recommend appropriate treatment to you according to standard medical practices.

The study or your participation in it, may be stopped early by the study doctor or at the request of the Trial Steering Committee (TSC) without your consent. The TSC is an independent group of highly trained professionals and patient representatives, in place to ensure that the study is performed to necessarily high standards of clinical and research practice. Reasons for stopping might include the development of a disease that may put you at risk if you were to continue, if you fail to follow instructions provided to you by the research team which could place you at risk, or if there are concerns about the safety and efficacy of the trial medication. In such an event, you will be asked to return for an exit visit.
and your doctor will ask if you would be prepared to undergo some of the procedures listed for the final 36 month visit. 

You may be contacted by the study doctor after you have completed your study participation, to provide you with new information or to ask questions about your current health status especially regarding your knee arthritis.

**What if something goes wrong?**

If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been treated during the course of this study, the normal Health Service Complaints mechanisms may be available to you.

**Will my taking part in this study be kept confidential?**

All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Participation in this study will in no way affect your legal rights.

Personal data, which may be sensitive, (e.g. name, date of birth) will be collected and processed but only for research purposes in connection with this study. All data will remain confidential, and no personal details will be made available to any third parties or transferred outside the European Union. Details about you will be stored on a computer during this research project. Trial related information on you, your clinical history and biological samples will be coded so that these are all anonymous. The data will be stored at the local research centre, although anonymous data will be transferred to the co-ordinating centre at the MRC Clinical Trials Unit. Access to this data will be controlled by the Trial Steering Committee. The data will only be used for research purposes into osteoarthritis, and no other use of this data will be undertaken without seeking your prior consent.

With your consent, we would normally inform your general practitioner that you are participating in this study.

**Will my life or private medical insurance be affected if I take part?**

We do not anticipate that your participation in this study will affect any life or private medical insurance that you may have. We do recommend, however, that you check with your insurance company before you agree to take part.

**What will happen to the results of the research study?**

The results of this study may be published in medical and other scientific literature. Details of the study may also be presented at medical and scientific meetings. You would not be identified by name in any report or publication. We will send you results of the study if you wish through your study doctor.

**Who is organising and funding the research?**

This study is being funded by a charitable grant from the Arthritis Research Campaign (arc). A team based at University College London, the Royal National Orthopaedic Hospital and the MRC Clinical Trials Unit is responsible for the day-to-day management of the study. However, this hospital is one of several taking part in the UK and your doctor is part of the collaborating team.
Who has reviewed the study?
This research project has been reviewed and received the favourable opinion of The Scottish Main Research Ethics Committee, which is an independent panel which includes doctors, nurses and non-medical people.

Contact for Further Information
If you have any questions or concerns now or at any time about the study, your safety or your rights, please ask the doctor or a member of the research team.

Please note that neither you nor the doctor gets paid for taking part in this research. You will, however, be offered travel expenses for attendance for additional visits.

Contact details:
Dr Richard Keen
Metabolic Bone Disease Unit
Royal National Orthopaedic Hospital
Brockley Hill
Stanmore
Middx HA7 4LP
Tel: 020 8909 5314 (secretary)
     020 8954 2300 (Hospital switchboard),
Fax: 020 8420 7487
Email: richard.keen@ucl.ac.uk

Miss Anna Bara
Video Study Office
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: 020 7670 4823
Fax: 020 7670 4829
Email: aib@ctu.mrc.ac.uk

Thank you for taking time to read this document.

Please keep a copy of this information leaflet for future reference

THIS STUDY IS FUNDED BY ARTHRITIS RESEARCH CAMPAIGN
THE SPONSOR IS THE ROYAL NATIONAL ORTHOPAEDIC HOSPITAL NHS TRUST
APPENDIX 2: CONSENT FORM

(To be presented on local headed paper)

Consent Form
Centre Number

Date and version: 03/04/2008 Version 1.1

VIDEO A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis.

Eudract Number 2004-000169-37
Name of Researcher:

Please initial box to agree

1. I confirm that I have read and understand the information sheet dated ........................................ (version ............ ) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the trial or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to my blood and urine being analysed for the purposes given in the Patient Information Sheet.

5. I agree to my General Practitioner being notified of my participation in this study.

6. I agree to take part in the above study.

7. I agree that my contact details may be transferred to staff at Southampton University, and agree to take part in the long term follow-up of the VIDEO trial.

__________________________ ________________ _________ ___________
Name of Patient Date Signature

_________________________ ________________ ________ ____________
Name of Person taking consent Date Signature
(if different from researcher)

__________________________ ________________ _________ ___________
Researcher Date Signature
APPENDIX 3: GENETIC PATIENT INFORMATION SHEET (SUBSTUDY)

3 copies: 1 for patient, 1 for researcher, 1 to be kept with hospital notes
(To be presented on local headed paper)
Centre Number

Date and version: 14/10/2008 Version 1.2

VIDEO STUDY
Eudract Number 2004-000169-37

Patient information sheet for genotyping and additional research sub-study to:
A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis (The VIDEO Study)

An optional part of the main study that you have agreed to participate in involves the analysis of how genes or DNA relate to the development of osteoarthritis and its potential treatment with vitamin D. Consent for additional research is completely voluntary and is separate to the informed consent taken for participation in the main treatment study (Information Sheet version 2.4 date 29/11/2010, and consent form version 1.1 date 03/04/2008). You do not need to provide any additional informed consent to participate in the main treatment study.

Before taking part in this additional research, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information leaflet carefully and discuss it with relatives, friends, and the doctors and nurses involved in your care. Ask the study doctor or nurse if there is anything that is not clear or if you would like more information.

Why have I been invited?
You are being asked to donate a blood sample to be used for the analysis of your genes, or DNA, and other components of your blood. Your information together with that of many other participants will be used for research on how genes relate to the development and progression of osteoarthritis and whether they influence the treatment response to vitamin D.

Do I have to provide a sample?
No. Your agreement to provide the additional blood sample is entirely voluntary. You will receive the same treatment and care under the main study whether or not you agree to provide this blood sample. If you decide not to provide your blood or if you withdraw your consent later, you will not lose any benefits, medical treatment or legal rights to which you were otherwise entitled.

What will happen if I decide to take part?
If you decide you would like to provide this additional sample, then you would be asked to sign a Study Consent Form (version 1.1 date 14/10/2008) that will give your consent. You will be given a copy of your signed consent form and you may also keep this information sheet.
You would then provide a 30ml (6 teaspoons) sample of blood. This would be taken at the same time as other samples that are required for the main study, so there will not usually be an extra needle-stick.

**What are the possible disadvantages or risks of taking part?**
You might experience some brief discomfort that would not last long when you give blood. In addition there can sometimes be redness or bruising at the site where the blood was taken.

**What are the possible benefits of taking part?**
There is no direct benefit to you in donating the sample or having the genetic analyses performed. However, the knowledge we gain may help others in the future.

**What about confidentiality?**
Your information and samples would be given a study number, and samples will not be labelled with your name. All information in this study will remain strictly confidential.

**How long will samples be stored for?**
Storage of the genetic samples will be for up to 25 years. Then the sample will be destroyed.

**Can I take my sample out of storage?**
Yes. If you would wish for your DNA sample to be withdrawn from the study, then please contact the research staff. They will ensure that your sample is destroyed.

**Will my sample be used for genetic research into other diseases?**
The aim of this study is to evaluate genetic aspects of osteoarthritis. In the future, however, your sample might be used for analysis of other diseases, **BUT this will only be done if you give your permission** and sign a further consent form.

**Will my life or private medical insurance be affected if I take part?**
Providing this sample and participation in this study does not constitute a “genetic test” as defined by insurance companies.

**What will happen to the results of the research study?**
The results of this study may be published in medical and other scientific literature. Details of the study may also be presented at medical and scientific meetings. You would not be identified by name in any report or publication. We will be able to send you generalised results it will not be possible to send individual results. We will send you results of the study if you wish.

**Who has reviewed this study?**
This research project has received a favourable opinion of the __________________ independent Research Ethics Committee.

**Where can I get more information?**
If you have any questions or concerns now or at any time about the study, your safety or your rights, please ask the doctor or a member of the research team.
Contact details:  
Dr Richard Keen  
Metabolic Bone Disease Unit  
Royal National Orthopaedic Hospital  
Stanmore  
Middx  HA7 4LP

Tel:    020 8909 5314  
Fax:    020 8420 7487  
Email:  richard.keen@ucl.ac.uk

Thank you for taking time to read this document.  
Please keep a copy of this information leaflet for future reference

THIS STUDY IS FUNDED BY ARTHRITIS RESEARCH CAMPAIGN

THE SPONSOR IS THE ROYAL NATIONAL ORTHOPAEDIC HOSPITAL NHS TRUST
APPENDIX 4: GENETIC CONSENT FORM

(To be presented on local headed paper)

Consent Form

Centre Number

Date and version: 14/10/2008 Version 1.1

VIDEO Genotyping and additional research sub-study
A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis.

ISRCTN94818153

Name of Researcher:

Please initial box to agree

1. I confirm that I have read and understand the information sheet dated ........................................ (version ............ ) for the above study and have had the opportunity to ask questions.  

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree to my blood being analysed for genetic purposes.

4. I agree to take part in the above study.

_______________________ ________________ __________ __________
Name of Patient Date Signature

_________________________ ________________ ________ ____________
Name of Person taking consent Date Signature
(if different from researcher)

_________________________ ________________ ________ ____________
Researcher Date Signature

3 copies: 1 for patient, 1 for researcher, 1 to be kept with hospital notes
APPENDIX 5: GP LETTER

GP Letter

(To be presented on local headed paper)

Centre Number

Date and version: 19/05/2008 Version 1.2

VIDEO A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis.

ISRCTN:

Dear Dr _____________

Your patient, ________________ (date of birth dd/mm/yyyy), has been entered to the above trial.

Epidemiological data suggests that low dietary intake of vitamin D and low serum 25-hydroxyvitamin D$_3$ levels are associated with radiological progression in knee OA.

The study’s hypothesis is, therefore, to determine whether vitamin D supplementation can reduce the rate of disease progression and improve symptoms in participants with knee OA. In total, 470 participants with knee OA will be studied in a 3 year, randomised, double-blind, placebo-controlled trial of cholecalciferol 800 IU daily or placebo.

Please find enclosed a copy of the patient information sheet for this trial.

You will be kept up to date with your patient’s progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____________________________ at _____________________________(Hospital)
Tel: _____________________________

Kind regards,

Name

Position
APPENDIX 6: GP RECRUITMENT LETTER

Date and version: 17/05/2004 Version 1.0

To be on surgery headed note paper

Date

Name of participant
Address
Address
Address

Dear (Name)

This surgery is taking part in a comparative research study looking at a treatment (Vitamin D) for arthritis of the knee.

Your medical records have shown that you suffer from arthritis of the knee and so I am writing to you to find out if you might be interested in hearing more about the study.

To do this we need to compare how arthritis of the knee changes over time in patients who do and do not receive vitamin D.

The study will last for approximately 3 years and will involve you visiting (study site hospital) 8 times over that period.

If you are interested and would like to find out more about the study, please contact .................................................. on telephone number .................................................., who will be able to provide further information and discuss whether you would be eligible to take part in the research.

Please be assured that taking part in this study is entirely voluntary and declining to do so will not affect your medical care at the surgery in any way.

Many thanks

Yours sincerely

Dr..........................................................
APPENDIX 7: HOSPITAL RECRUITMENT LETTER

Date and version: 17/05/2004 Version 1.0

Dear

You recently attended Clinic for arthritis of your knee(s).

We are currently participating in a large clinical trial, which will evaluate whether Vitamin D reduces the progression of this disease.

Your medical records have shown that you suffer from arthritis of the knee and so I am writing to you to find out if you might be interested in hearing more about the study.

To do this we need to compare how arthritis of the knee changes over time in patients who do and do not receive vitamin D.

The study will last for approximately 3 years and will involve you visiting (study site hospital) 8 times over that period.

If you are interested and would like to find out more about the study, please contact ........................................... on telephone number ......................................................, who will be able to provide further information and discuss whether you would be eligible to take part in the research.

Please be assured that taking part in this study is entirely voluntary and declining to do so will not affect your medical care at the surgery in any way.

I have enclosed an Information Sheet about participating in this clinical trial.

There is, of course, no obligation to take part.

Yours sincerely

Dr

Consultant
APPENDIX 8: RECRUITMENT POSTER/ADVERT
The same layout and text will be used in a size reduced format for press advertisements

VIDEO TRIAL

**VI**tamin **D** E**valuation** in **O**steoarthritis

Do you have osteoarthritis of the knee?

We are currently looking for men and women over 50 years to help us with a clinical research trial for a treatment for osteoarthritis of the knee.

The treatment being studied is Vitamin D and would involve you visiting ..................hospital approximately 8 times over a 3 year period.

If you would like to know more then please contact

.................................................
on
................................................

Royal National Orthopaedic Hospital

NHS

arc

0870 850 0000
www.arc.org.uk

Committed to curing arthritis

MRC
Clinical Trials Unit
APPENDIX 9: BONE BIOCHEMISTRY (Sub-study)

GUIDELINES FOR MONITORING OF BONE BIOCHEMISTRY

**Mild increase in serum calcium (ULN to 2.75 mmol/l)**
Repeat tests should be undertaken within 3-7 days. If raised levels are confirmed, study medication should be discontinued. Biochemical tests should be repeated weekly until they resolve.

**Moderate increase in serum calcium ( > 2.75 mmol/l but < 3.00 mmol/l)**
Study medication should be discontinued. Repeat tests should be undertaken within 3-7 days. If raised levels are confirmed, they should be repeated weekly until they resolve.

**Marked increase in serum calcium (> 3.00 mmol/l)**
Study medication should be discontinued. These tests should be repeated within 48 hrs. Specific treatment should be initiated if the participant becomes symptomatic. Test should be repeated at 3-7 day intervals until they resolve.

**Hypercalciuria**
Local reference ranges will be used.

**Development of renal stones**
Study medication should be discontinued. Blood samples and urine samples should be obtained to identify hypercalcaemia and/or hypercalciuria. Results of any stone analysis and radiographic investigations should be obtained.

**Rechallenge protocol**
Participants may restart study medication (two tablets daily), provided agreement has been obtained from the local and Principal Investigators and verbal consent has been obtained from the participant.

Repeat biochemical assessments should be made 4 weeks after rechallenge and then at the discretion of the local investigator. If the biochemical abnormality has recurred, then the study medication should be discontinued and the participant monitored until the abnormalities have resolved again. At this point a 2nd rechallenge can be undertaken, with only one tablet of study medication daily. If the biochemical abnormalities occur at this lower dose, then study medication should be discontinued. Participants will remain, however, under follow-up within the study protocol.
APPENDIX 10: DIETARY ASSESSMENTS

At baseline, all participants will complete a validated food frequency questionnaire and an estimated 4-day food diary (Bingham et al, 1997). The questionnaire will be repeated at 18 and 36 months to monitor for any changes in dietary intake. In addition, the 18 month assessment will take account of any seasonal variation.

Training for research nurses will be provided at the outset of the study to enable them to instruct participants how to complete the diary in as much detail as possible. This training will be supervised by Dorothy Pattison from the arc Epidemiology Unit in Manchester.

Food diaries
At baseline, all participants will be asked to complete a 4-day ‘estimated’ food diary in which to record everything they eat and drink over a 4-day period. Participants will be instructed on how to estimate the quantities of food and drink consumed using household measures e.g. cups, bowls and spoons, and the food portion photographs provided in the diary. We will also collect details of any dietary supplements taken during the study period. A section is provided at the back of the diary for this purpose. At the initial assessment, “Day 1” of the diary will be completed by the research nurse along with the participant, using the 24-hour recall method of dietary assessment. The aim of this process is to give participants a good example of how to record their food intake. Experience from the EPIC study found this process to take 20-25 minutes.

Participants will be given a stamped addressed envelope in which to return the completed diary to the relevant study centre.

Food frequency questionnaires
The information collected in the baseline diaries will be used to validate the food frequency questionnaires (FFQ) that will be used in each of the participating centres at baseline, and at the 18 and 36 month assessments.

The validation process is essential to verify that the FFQ is picking up the main dietary sources of all nutrients that may have potential impact on OA, i.e. vitamin D and calcium in particular but also other antioxidants vitamin E, vitamin C, β-carotene and other carotenoids, if nutrient data becomes available. It is necessary to do this in each centre as the original FFQ was validated for the Norfolk population, whose dietary habits are likely to differ substantially from that of other regions in UK. Also, the FFQ was validated in the late 1980’s, so new foods and products will not be included and consequently important sources of some nutrients may be missed.

At the 18 month and 36 month stages the validated FFQs will be given to participants at their review with the research nurse. As the FFQ takes 20-30 minutes to complete a SAE will be supplied in order for the questionnaire to be returned.
APPENDIX 11: MUSCLE STRENGTH ASSESSMENT

Vitamin D deficiency is associated with myopathy and muscle weakness, and these symptoms improve with supplementation. Muscle strength will therefore be assessed at baseline, and then at annual intervals throughout the study period.

**Grip Strength**
This will be measured in both right and left hands using a Jamar hand-held dynamometer (Promedics Ltd). The protocol for this is detailed below:

1. Record hand dominance – right, left or ambidextrous (true ambidextrous relates to participants who can genuinely write with both hands).
2. Sit the participant comfortably in a standard chair with legs (not wheels), back support and fixed arms. Use the same chair for every measurement.
3. Ask the participant to rest their forearms on the arms of the chair with their wrist just over the end of the arm of the chair – wrist in a neutral position, thumb facing upwards.
4. Demonstrate how to use the dynamometer to show that gripping very tightly registers the best score.
5. Start with the right hand.
6. Position the hand so that the thumb is round one side of the handle and the four fingers are around the other side. The instrument should feel comfortable in the hand: alter the position of the handle if necessary. One can usually observe if the participant is comfortable.
7. The observer should rest the base of the dynamometer on the palm of their hand as the participant holds the dynamometer. The aim of this is to support the weight of the dynamometer, but be careful not to restrict the movement of the machine.
8. Encourage the participant to squeeze as long and as tightly as possible or until the needle stops rising. Once the needle stops rising you can instruct the participant to relax their grip.
9. The observer should read from the outside of the dial which gives grip strength measured in kilograms (kg). Record the result to the nearest 1 kg on the CRF.
10. Repeat measurement in the left hand.
11. Do 2 further measurements in each hand, alternating sides to give 3 readings in total for each side.
12. For analysis purposes the best grip strength from each hand will be used, so participants should be encouraged to achieve the highest score possible.

**Quadriceps Strength**
Quadriceps muscle strength will be assessed in the supine position, using a Lafayette Manual Muscle Test System (Lafayette Instrument Co.). Details are listed below:

1. Check with participants that they are happy to lay flat.
2. Participants should lay supine (i.e. flat on a couch with no pillow support for head). The arms should be resting on their stomach/chest or behind their head, whichever is more comfortable. If the arms are placed behind the head, the observer must monitor the participant more closely to ensure that they do not use the head for leverage.
3. The leg length should be measured on each side. Total leg length will be measured from the anterior superior iliac spine to the lower end of the medial malleolus. Lower leg length is measured from the base of the patella down to the distal tibia. The distal tibia can be located by palpating down the tibia and finding where the bone ends, or it can be seen as the crease between the top of the foot and the end of the leg.

4. Apply the bolster under the knee of the tested leg (start with the right leg). The malleoli of the tested leg should be at the edge of the couch. The bolster ensures that the hip and knee are not locked and the knee remains flexed to approximately 35 degrees.

5. The opposite leg should be flexed at the hip and knee so that the foot is flat on the couch and the participant is comfortable. This position will stabilise the pelvis.

6. Participants should be instructed to try and straighten the test leg. They must not try and lift their leg, hip or buttocks off the couch (i.e. the knee should remain in contact with the bolster). Raising the knee, hip or buttocks off the couch suggests that the participant is trying to use other muscle groups and this should be avoided.

7. The head must also remain on the table in order to ensure that other muscle groups are not used during the testing process.

8. In normal, healthy adults the dynamometer should be set to “H” for the high range.

9. The large pad should be connected to the hand held dynamometer (HHD) and turned on. The HHD should be set to measure peak force within 5 seconds (this can be programmed according to the manual instructions).

10. The observer should position themselves standing above the participant with arms in a locked position (as if performing CPR).

11. Apply the HHD just proximal to the medial malleolus. The observer should not push down on the participant’s leg, but should oppose the force the participant produces.

12. Ask the participant to try and straighten their leg using the correct technique as stated earlier. The participant should be told to push against the pad. On hearing the first bleep of the HHD the observer should encourage the participant to push maximally against the HHD.

13. Measure each side twice, alternating between the right and left leg.

14. Record the peak force in kilograms, and also the time the peak force was achieved.

15. Enter results into CRF.
APPENDIX 12: BONE DENSITY MEASURMENTS

Vitamin D is known to have positive effects on bone metabolism, and in combination with calcium has been demonstrated to reduce the risk of osteoporotic fractures. There is growing interest in the relationship between osteoporosis and OA, and changes in subchondral bone may influence the progression of OA.

Bone mineral density will therefore be measured using dual energy X-Ray absorptiometry (DXA) at lumbar spine (L1-4), hip, whole body and proximal tibia/subchondral region.
APPENDIX 13: MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging provides the ability to image all the relevant components of osteoarthritis within a given joint, including subchondral bone abnormalities. The commonest abnormality described in osteoarthritis is termed bone marrow oedema. This represents micro-trabecular fracture and repair. This feature is only identified with MRI. Bone marrow oedema has been associated with both osteoarthritic joint pain and structural progression within the ipsilateral compartment of the knee. Given the strong association of bone marrow oedema with structural progression in osteoarthritis, it is important to evaluate the effect of any possible bone modifying therapy such as vitamin D supplementation.

We plan to perform MRI of the knees at the baseline and annual visits. The MRI scans will be performed by 1.5T magnet. Participants will lie supine and MRI does not involve any ionising radiation, and claustrophobic reactions are uncommon when scanning the knee as the patient's head lies outside the MRI machine. The following sequences will be performed:

A sagittal T1 and 3D proset,
Coronal T1 and STIR
Axial T2 fat suppressed.

The MRI scans will be scored according to the method of Peterfy et al (Peterfy CG et al, Osteoarthritis cartilage 2004,12:177-190).

Sub-Study Variation (To use 3 Tesla) Magnet, to be carried out at on patients attending Royal Victoria Infirmary, Newcastle.

METHOD
MRI (3T to replace 1.5T)
The sequences will include 3 Tesla sagittal, coronal and axial images, including T1, T2, 3D and fat suppressed. Where appropriate, for example where differentiation between synovitis and effusion is difficult, gadolinium enhancement will be used.
Appropriate selected patients (for example, with large effusions) would also undergo MRS: this will entail a short extra acquisition time, but no additional ionising radiation. Total acquisition time will not usually exceed 30 minutes.

JUSTIFICATION
1.5 Tesla Magnetic Resonance Imaging (MRI) has been considered as a promising modality for the non-invasive investigation of knee osteoarthritis (KOA). There is a validated semi-quantitative scoring system- the Whole Organ MRI score (WORMS), work demonstrating that bone oedema lesions can predict progression and one study suggesting that cartilage loss on 1.5T MRI is more sensitive to change than radiographs. However, there are limitations, both with the time and expense of acquiring appropriate sequences and with the precision of serial femoral cartilage volumes being inadequate to supplant radiographs as the gold standard for the assessment of KOA. One further small study of 43 patients with KOA over a mean 18 months of follow up suggested that the site of cartilage lesions on 1.5T MRI can predict progression and might be an appropriate measure to stratify subjects in trials of disease modifying OA agents.
3 Tesla MRI scanning offers potential for shorter acquisition times and/or higher spatial resolution, with consequent improvement in discrimination and also likely improved precision. A larger longitudinal study using state of the art MRI can also address the question of whether localised MRI cartilage or bone oedema lesions, or both, best predict progression or even response to disease modifying agents.
APPENDIX 14: MUSCULOSKELETAL FUNCTION, STATIC AND DYNAMIC BALANCE

Get up and go test (GUGOT)
The GUGOT is a composite test of lower limb musculoskeletal function, static and dynamic balance. The test is carried out by asking the patient to stand up from a chair without using their arms, walk several paces, turning and returning to the chair and sitting down. The 3 minute timed get up and go test is becoming the more favoured test in that it is simple to perform in any given clinical setting and secondly it composes of both a static and dynamic assessment of balance and gait (Podsiadlo ET AL, Marthias ET AL)

Various grades of function define severity of limitation:
- Grade 1 (normal): able to rise from a chair easily, walk unaided, turn without dizziness or stumbling. Faster than 8 seconds.
- Grade 2 (normal): able to rise from the chair without arms, walk unaided, turn without dizziness or stumbling. Between 9-15 seconds.
- Grade 3 (borderline): Difficulty on rising from the chair, walk aided or unaided, turn without dizziness or stumbling. Between 16-24 seconds.
- Grade 4 (abnormal): Difficulty on rising from the chair, walk aided or unaided, turn without dizziness or stumbling. Between 25-40 seconds.
- Grade 5 (abnormal): Difficulty on rising from the chair, needs walking aid, unconfident or dizzy on turning or takes over 40 seconds.
- Grade 6 (abnormal): Unable to rise from the chair, walk or turn without help.

Simpler definitions are
- Normal: 15 seconds or less.
- Abnormal: more than 15 seconds.

Timed Walk Test
The test is carried out by asking the patient walk a marked 10 meter distance on two occasions. Both times (secs) are recorded.
APPENDIX 15: COGNITION

Mini-mental State Examination

The mini-mental State Examination (MMSE) is the most widely used short test of cognitive ability and is extensively used in research and clinical settings (Folstein et al, 1975). The participant is asked 2 items related to orientation (time and place), a brief test of memory encoding and short term recall (2 items), a measure of attention (1 item), 4 items related to language and one item related to both language and visuo-spatial ability. The test has good psychometric properties (MacKenzie et al, 1996; Tierney et al, 2000). In particular, the MMSE can be used to detect changes in cognitive functioning over time. The research nurses will be fully trained to administer and score the MMSE. The MMSE takes approximately 15 minutes to complete.
APPENDIX 16: DEPRESSION

Beck Depression Inventory

The Beck depression Inventory (BDI) is a 21 item self-report measure of depression severity (Beck et al, 1988). Individuals are instructed to circle the item which best describes how they have been feeling in the past few days, including the day the BDI is administered. Participants rate the severity of each item on a 4-point scale, which is scored 0 to 3. The total score is obtained by summing together scores from the 21 items (range 0 – 63). Traditionally the following cut off scores are used: <10 none or minimal depression, 11–19 mild to moderate depression, 19-29 moderate to severe depression, 30-63 severe depression. The BDI takes approximately 5 minutes to complete.
APPENDIX 17: BIOCHEMICAL ANALYSES

Fasting early morning samples of blood and urine to be collected from participants at time points detailed in the protocol’s Schedule of Procedures.

The following clinical laboratory test will be measured locally:

**Haematology**
- Haemoglobin
- White blood cell count plus differential
- Platelet count
- Erythrocyte sedimentation rate (ESR)

**Serum Biochemistry**
- Sodium
- Potassium
- Creatinine
- Urea
- Glucose
- Total serum albumin
- Total serum protein
- Total bilirubin
- Aminotransaminases
- Calcium
- Phosphate

**Urine analyses**
- Urinalysis (protein, glucose, blood)
- 24 hr urinary calcium

Additional aliquots from these samples will be stored at –70 ° locally. These will then be transported on dry ice to laboratories selected by the trial Sponsor where the specialised investigations will be undertaken, which will include the following:

**Serum biochemistry**
- 1,25-dihydroxyvitamin D₃
- 25-hydroxyvitamin D₃
- Bone-specific alkaline phosphatase
- Growth hormone
- Insulin
- Insulin-like growth factor 1 (IGF-1)
- Osteocalcin
- Parathyroid hormone
- Procollagen peptide of Type 1 collagen (P1NP)
- Serum cartilage oligomeric protein (COMP)
- Serum CTx
- Serum type II collagen cross-links (CartiLaps)
- Vitamin D binding protein

**Inflammatory markers**
- C-reactive protein (CRP)
Urine biochemistry
• Urinary collagen cross-links
APPENDIX 18: WOMAC QUESTIONNAIRE

(WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX)

In sections A, B and C, questions are asked in the following order. You should give your answers by putting an 'X' on the horizontal line.

EXAMPLES

1. If you put your 'X' at the left of the line as shown below, then you are indicating that you have no pain.

   No Pain |X|Extreme pain

2. If you put your 'X' at the right of the line as shown below, then you indicating that your pain is extreme.

   No Pain |Extreme pain

3. Please note:
   a. that the further to the right you place your ‘X’, the more pain you are experiencing.
   b. that the further to the left you place your ‘X’, the less pain you are experiencing.
   c. Please do not place your ‘X’ past the end of the line

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced during the last 48 hours.

You should think about your knee (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness or physical disability that you feel is caused by arthritis in your knee (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which is your study joint, please ask before completing the questionnaire.
Section A

PAIN

Think about the pain you felt in your knee (study joint) due to your arthritis in the last 48 hours.

QUESTION: How much pain do you have..?

1. Walking on a flat surface.
   No Pain |---------------------------------------------------------------------|

2. Going up or down stairs.
   No Pain |-------------------------------------------------------------|Extreme pain

3. At night while in bed.
   No Pain |-------------------------------------------------------------|Extreme pain

4. Sitting or lying.
   No Pain |-------------------------------------------------------------|Extreme pain

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your knee (study joint) due to your arthritis in the last 48 hours.

5. How severe is your stiffness after first awakening in the morning?
   No Pain /------------------------------------------------------------------|Extreme pain

6. How severe is your stiffness after sitting, lying or resting later in the day?
   No Pain /------------------------------------------------------------------|Extreme pain
Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily activities due to arthritis in your knee (study joint) during the last 48 hours. By this, we mean your ability to move around and to look after yourself.

**QUESTION:** What degree of difficulty do you have?

<table>
<thead>
<tr>
<th>No.</th>
<th>Activity</th>
<th>Pain Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>Descending stairs</td>
<td>No Pain</td>
</tr>
<tr>
<td>8.</td>
<td>Ascending stairs</td>
<td>No Pain</td>
</tr>
<tr>
<td>9.</td>
<td>Rising from sitting</td>
<td>No Pain</td>
</tr>
<tr>
<td>10.</td>
<td>Standing</td>
<td>No Pain</td>
</tr>
<tr>
<td>11.</td>
<td>Bending to the floor</td>
<td>No Pain</td>
</tr>
<tr>
<td>12.</td>
<td>Walking on a flat surface</td>
<td>No Pain</td>
</tr>
<tr>
<td>13.</td>
<td>Getting in or out of a car, or getting on or off a bus.</td>
<td>No Pain</td>
</tr>
<tr>
<td>14.</td>
<td>Going shopping</td>
<td>No Pain</td>
</tr>
<tr>
<td>15.</td>
<td>Putting on your socks or tights</td>
<td>No Pain</td>
</tr>
<tr>
<td>16.</td>
<td>Rising from bed</td>
<td>No Pain</td>
</tr>
<tr>
<td>17.</td>
<td>Taking off your socks or tights</td>
<td>No Pain</td>
</tr>
</tbody>
</table>
No Pain /-----------------------------------------------|Extreme pain

18.  Lying in bed

No Pain /-----------------------------------------------|Extreme pain

19.  Getting in or out of the bath.

No Pain /-----------------------------------------------|Extreme pain

20.  Sitting

No Pain /-----------------------------------------------|Extreme pain

21.  Getting on or off the toilet.

No Pain /-----------------------------------------------|Extreme pain

22.  Performing heavy domestic duties.

No Pain /-----------------------------------------------|Extreme pain

23.  Performing light domestic duties.

No Pain /-----------------------------------------------|Extreme pain
APPENDIX 19: WHOQOL
QUALITY OF LIFE QUESTIONNAIRE
APPENDIX 20: SAMPLE LABEL

VIDEO TRIAL

Study Code: VIDEO 900  Randomisation Number: V
200 Placebo or Vitamin D 10 microgram tablets

Directions: Take TWO tablets ONCE a day with food

Patient Name: ____________________  Date: ________________

Chief Investigator: Dr Richard Keen  Tel: 020 8909 5314
For Clinical Trial Use Only  Store below 25°C
Keep out of the reach of children

Batch No: V  Use before: V
Sponsor: Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex  HA7 4LP

v001
APPENDIX 21: PATIENT CARD

FRONT OF CARD

VIDEO Study

You should keep this card with you at all times. Show it to the doctor/nurse/healthcare professional at all doctor or hospital appointments (including A&E)

This patient is taking part in the VIDEO Clinical Trial
Vitamin D Evaluation in Osteoarthritis

He or she may be taking 80µg Vitamin D daily

BACK OF CARD

If you have any queries, please contact:

Dr Richard Keen
Senior Lecturer & Consultant Rheumatologist
Royal National Orthopaedic Hospital
Brockley Hill, Stanmore,
Middlesex, HA7 4LP
Tel: 020 8909 5314
Fax: 020 8420 7487
APPENDIX 22: ULTRASOUND IMAGING

ULTRASOUND
(Tarhan S 2003, Backhaus M. 2001)

METHOD
Ultrasound assessment (using a 5-12 mhz high frequency linear array transducer; Toshiba Applio 70, Toshiba medical systems Europe, Netherlands)
Scans will include:
- transverse & longitudinal scans through the suprapatellar recess (knee flexed at 20 degrees and maximally flexed for assessment of articular cartilage and inflammation of synovium and capsular tissues)
- longitudinal scans laterally and medially to the patella and along the joint space (pt supine with extended knees)
- thickness, clarity and sharpness of the articular cartilage on medial and lateral condyles measured (McCune WJ 1990)
- compression test for differentiation of fluid and synovium; with a qualitative assessment of fluid & synovial thickness
- power Doppler assessment for vascularity of synovium and capsular tissues

Scans will be performed every 12 months, or where subjects have had a baseline assessment and not been scanned 12 months later, as soon as practicable afterwards. Scans will not normally be repeated at an interval of less than 12 months, although some or all of the subjects may have repeated acquisition of certain views by the same and or another researcher on a single visit to establish the reliability of ultrasound examination at the centre.

JUSTIFICATION
Ultrasound represents a further modality with considerable promise in the non-invasive assessment of KOA: similarly avoiding exposure to ionising radiation, but with advantages for both cost and portability. A cross-sectional comparison of 1.5T MRI and ultrasound has been performed, suggesting that ultrasound may be a suitable tool for initial evaluation of KOA (Tarhan S 2003), but this was a small study, including only 58 patients with KOA, the previous generation of imaging equipment was used (for example power Doppler assessment of synovium and capsular tissues was not included) and there was no follow up of subjects to assess whether either modality was predictive of outcome. High interobserver reliability has been demonstrated in expert ultrasound assessment of the knee (kappa=1.0) (Scheel AK 2005) and ultrasound findings in a multicentre cross-sectional study of 600 patients with KOA showed moderately good association with radiographic grade and signs of a clinical flare (D’Agostino MA 2005).
APPENDIX 23: PASS-SF QUESTIONNAIRE

Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities. Circle any number from 0 (NEVER) to 5 (ALWAYS) for each item.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>NEVER</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I think that if my pain gets too severe, it will never decrease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>When I feel pain I am afraid that something terrible will happen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>I go immediately to bed when I feel severe pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>I begin trembling when engaged in activity that increases pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>I can't think straight when I am in pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>I will stop any activity as soon as I sense pain coming on</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Pain seems to cause my heart to pound or race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>As soon as pain comes on I take medication to reduce it</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>When I feel pain I think that I may be seriously ill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>During painful episodes it is difficult for me to think of anything else besides the pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>I avoid important activities when I hurt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>When I sense pain I feel dizzy or faint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Pain sensations are terrifying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>When I hurt I think about the pain constantly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Pain makes me nauseous (feel sick)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>When pain comes on strong I think I might become paralyzed or more disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>I find it hard to concentrate when I hurt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>I find it difficult to calm my body down after periods of pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>I worry when I am in pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>I try to avoid activities that cause pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
JUSTIFICATION
PAIN ANXIETY AND FUNCTION IN EARLY KNEE OSTEOARTHRITIS:

Background
That there are individual differences in pain report is now widely accepted. A number of factors related to individual differences in pain experience have been explored, but the consistent psychological factors associated with increased pain, psychological distress and physical illness are catastrophising thoughts about pain, fear and helplessness and pain-related anxiety (Keefe, Rumble et al. 2004) – all anxiety-related constructs. Pain-related anxiety and fear is currently receiving more research attention and the correlates of pain anxiety are now better understood. Patients scoring highly on pain anxiety report higher attention to pain sensations (Crombez, Vlaeyen et al. 1999) and overpredict amount of pain they will experience in a physical examination (McCracken, Gross et al. 1993). They also report more depression and disability (McCracken, Zayfert et al. 1992), and more pain behaviour and help-seeking (McCracken, Gross et al. 1996). Taken together, these studies help to describe the high pain anxious group, however more research is needed into the effects of pain-specific anxiety. Research is particularly lacking in musculoskeletal disease other than low back pain.

The cognitive model of fear of pain (Vlaeyen, Kole-Snijders et al. 1995) postulates that negative appraisals about pain and its consequences, such as catastrophic thinking, are considered a potential precursor of pain-related fear. Fear (of any stimulus) is characterised by escape and avoidance behaviours so that daily activities (expected to produce pain) are not carried out. Avoidance behaviours occur as a response to the fear about pain and in anticipation of pain rather than as a response to pain itself, these behaviours continue because there are few opportunities to correct the expectancies and beliefs about pain as a signal of threat (the reinforcement process in the behavioural model). Persistent avoidance and resultant physical inactivity causes deterioration in musculoskeletal and cardiovascular function leading to the disuse or deconditioning syndrome which in turn can amplify pain perception through neuroplastic adaptions in the brain. Pain-related fear is predicted also to interfere with cognitive functioning so that patients become hypervigilant to pain stimuli and increased attention towards pain-related information reduces attention towards daily activities. In addition, avoidance also means the withdrawal from previous self-efficacy reinforcers thereby increasing mood disturbances such as irritability, frustration and depression, and there is much research showing the associations between these states and increased pain perception.

Aim
In summary, previous research shows that there are differences in the way that people adjust to a chronic pain condition. Recently, anxiety about pain has been identified as having a role in pain experience and cognitive behavioural models suggest that it is responses to this pain anxiety that may predispose some people to become more disabled than those that are not as fearful of experiencing pain. Most research in this area has been conducted with chronic back pain patients. The current study aims to report how much pain anxiety people with knee pain experience and how this pain-specific anxiety relates to physical function status over time.

Methods
Sample
We aim to administer a self-report pain anxiety questionnaire to participants recruited by the Norwich site of the VIDEO trial. The recruitment target is between 100 and 200.
**Pain anxiety**
The PASS-20 (Pain Anxiety Symptoms Scale) (McCracken, Zayfert, and Gross 1992) is a revised instrument that includes 20 items in 4 domains: cognitive anxiety responses, escape and avoidance, fearful appraisals, and physiologic anxiety responses (see appendix for all 20 items). The PASS-20 has been validated against the full PASS and other measures (McCracken and Dhingra 2002). It has been widely used in chronic pain samples.

**Function**
We will apply for the final assessment (36-month assessment) WOMAC data for the Norwich cohort following conclusion of the VIDEO study. It will also be necessary to control for radiological progression of disease.

**Procedure**
We propose giving potential participants in the Norwich VIDEO study the PASS-SF at their screening rather than baseline assessment in order not to add to the number of questionnaires being completed at that assessment.
APPENDIX 24: BIOMECHANICS OF THE KNEE SUB-STUDY USING THE ‘SMART-TOG’

JUSTIFICATION

The aim of this sub-study is to assess the dynamic biomechanics of the knee in patients with knee osteoarthritis, and to determine its association with function, pain and response to vitamin D over time.

It is known from previous small studies that altered biomechanics can affect pain and disease progression. However, these studies rely on static x-rays or dynamic assessments in a restricted biomechanics laboratory setting. The device we wish to use in this sub-study is the ‘Smart-Tog’, which is lightweight and wireless, and will be used in the patients’ normal environment to assess knee biomechanics. The Smart-Tog or Tog is a novel measurement system, and is currently undergoing development and evaluation by the University of Southampton in a collaborative project between the Schools of Electronics and Computer Science and Health Profession and Rehabilitation Sciences. The device enables real-time data to be acquired during the performance of everyday tasks to identify patterns of movement and muscle activity.

The system comprises a wearable component, or Tog, for the knee, which extends from mid thigh to mid calf. Together with force sensors in the shoes, they will capture the principal features of knee control movement. To be practical for patients to use, the Tog is made of light stretchy fabric that ensures close contact with the skin, and it is easy to put on and take off. There are no known side effects.

The Tog is embedded with off the shelf sensors attached to a flexible material component which exploits wireless technology to minimise the risks associated with tethered systems. The sensors will continuously monitor and record a functional task such as standing from sitting, walking or turning. Data acquired by the sensors is processed off-line to provide quantitative information about movement, forces and muscle activity. These can then be related to other patient data such as pain and deformity.

We will instruct subjects on the use of the Tog during their routine hospital visit, and they will then wear it for three 10 minutes walks in their home environment and for walking up a flight of stairs on three occasions. The Tog will then be collected.