VIDEO Study

MRC Clinical Trials Unit

VIDEO: Vitamin D Evaluation in Osteoarthritis

Eudract Number 2004-000169-37
ISRCTN94818153

Statistical Analysis Plan

Version 1.3

MRC Clinical Trials Unit
Aviation House
125 Kingsway
London WC2B 6NH

Tel: +44 (0)20 7670 4823
Fax: +44 (0)20 7670 4829
Email: aib@ctu.mrc.ac.uk

Version date: 18 Mar 2013

Contacts
Anna Bara
Caroline Doré
Suzie Cro

This template and all preceding versions will be stored in the Statistical Analysis Master File for this trial held by Caroline Doré

---

1. Abstract – Background and Design 4
2. Outcome measures 5
2.1 Primary outcome measure 5
2.2 Secondary outcome measures 5
3. Data 6
3.1 CRFs and variables 6
3.2 Management of datasets 6
3.3 Data completion schedule 6
3.4 Data verification 6
3.5 Data coding 6
4. Abbreviations and Glossary 7
5. Sample Size Estimation 9
6. Analysis Principles 10
6.1 ITT or PP? 10
6.2 Significance levels of tests 10
6.3 Baseline comparability 10
6.4 Adjustment for design factors 10
6.5 Follow-up and losses to follow-up: missing data 10
6.6 Summarising models 11
7. Analysis Details 12
7.1 Recruitment and follow-up patterns 12
7.2 Baseline characteristics 12
7.3 Trial treatment 12
7.4 Trial events 12
7.5 Analysis methods 13
7.5.1 Primary Analysis 13
7.5.2 Sensitivity Analyses 14
7.5.3 Secondary Analyses 16
7.6 Toxicity/ Symptoms 19
7.7 Quality of life analysis 19
8. Additional Information in the Clinical paper 19
9. Signatures of Approval 20
10. References 21
11. Appendices 22
11.1 Appendix A – Dummy tables 22
11.1.1 Table 1. Baseline clinical characteristics 22
11.1.2 Table 2. Baseline radiographic characteristics 24
11.1.3 Table 3. Baseline biochemical variables 24
11.1.4 Table 4. Main Radiographic outcome measures 25
11.1.5 Table 5. Secondary outcome measures 25
11.1.6 Table 6. Subgroup analyses 26

1. Abstract – Background and Design

Aims and objectives: The Vitamin D Evaluation in knee Osteoarthritis (VIDEO) trial aims to assess whether adding vitamin D to the diet through a supplement can prevent destruction of cartilage and reduce pain in the knee.

Population studied: 474 ambulatory patients of both sexes aged over 50 years with knee pain on most days in the month prior to screening were recruited to the study.

Trial design: VIDEO is a phase III parallel group randomised controlled double blind study. Patients are randomised to receive a vitamin D supplement or placebo. The primary outcome measure is radiological progression of knee osteoarthritis (OA) in the medial joint compartment, as measured by joint space width (JSW) in the worst knee at baseline (smallest JSW) over three years.

Sample size: A total of 474 patients were recruited to the study, with equal allocation to vitamin D and placebo groups. This gives 80% power to detect a difference in the rate of joint space narrowing between treatment groups of 0.22mm assuming 32% of patients are not evaluable and a standard deviation of 0.7mm, using the two tailed 5% significance level.

Randomisation: Randomisation is stratified by study centre. There are no other factors in the study design to promote balance between treatment groups.

2. Outcome measures

The primary and secondary outcome measures are listed under the appropriate headings below.

2.1 Primary outcome measure

Radiological progression of knee OA in the medial joint compartment of the index knee, as measured by the rate of change in joint space width (in mm per year), where the index knee is defined as the most severely affected knee at baseline (knee with the smallest joint space width at baseline). X-rays will be measured blind to treatment and time.

2.2 Secondary outcome measures

- Radiological progression of knee OA in the lateral joint compartment (rate of change in joint space width in mm per year) of the index knee
- Radiological progression of knee OA in the medial and lateral joint compartments (rate of change in joint space width in mm per year) of the contra-lateral knee
- K&L grade (worst of medial and lateral K&L grade) in the index knee and contra-lateral knee
- Pain and functional disability (Knee effusion (index knee), Knee warmth (index knee), WOMAC scores, Timed Walk Test (time taken to walk 10m), Get up and go test (GUG), Grip strength (dominant hand), Quadriceps strength (index knee))
- Quality of life (WHOQOL-Bref scores)
- Depression and cognition status (BDI, MMSE)

3. Data

3.1 CRFs and variables

Full details of data collection and timing are described in the trial protocol (version 2.8, 29/11/10). A copy of the CRFs and Quality of Life (WHOQOL) questionnaires are included in the Trial Master File.

3.2 Management of datasets

At the time of analysis:
A copy of each dataset will be made and moved to a designated area of CTU network (data frozen) by the CTU Database Programmer.
If necessary, new data can be entered on the main, unfrozen dataset.
If any outstanding data queries are resolved during the analysis that relate to data in the frozen dataset (e.g. problems that are found during analysis or amended CRFs that are returned to CTU), the main and the frozen datasets should both be changed under the oversight of the Trial Manager.
If any outstanding data queries are resolved while the analysis files are being prepared (i.e. when only a practice dataset has so far been copied), the changes need only be made to the main datasets and an updated, frozen copy made available on the CTU statisticians' area.

3.3 Data completion schedule

The last patient was enrolled for VIDEO in July 2008. All forms for 3-year follow up will therefore be available by August 2011, with leeway of 14 days for study visits.

3.4 Data verification

Data verification, consistency and range checks are performed at data entry by the MRC CTU, as well as checks for missing data (copies of these checks can be found in the Trial Master File). Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Any problems with trial data will be queried with the Trial Managers, Data Managers or statisticians, as appropriate. If possible, data queries will be resolved; although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. These will be minimised.

3.5 Data coding

Details of the variables, including variable coding list are presented in the metadata which forms part of the Trial Master File.

4. Abbreviations and Glossary

Term	Definition
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
ECG	Electrocardiogram
ERC	Endpoint Review Committee
FFQ	Food Frequency Questionnaire
GCP	Good Clinical Practice
GUG	Get-Up-And-Go Test; Clinical measure of balance, graded 1 to 6.
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
IU	International Units
JSN	Joint Space Narrowing
JSW	Joint Space Width
K&L	Kellgren and Lawrence
MAR	Missing at random
MHRA	Medical and Healthcare devices Regulatory Authority
MMSE	Mini-Mental State Exam
MPTT	Multi-Practitioner Triage Team
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic Resonance Imaging
MSA	Muscle Strength Assessment
NHS	National Health Service
OA	Osteoarthritis
ONS	Office for National Statistics
PI	Principle Investigator
PIS	Patient Information Sheet
PP	Per Protocol

PSP	Postural Sway and Proprioception
QL	Quality of Life
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Serious Suspected Adverse Reaction
SUSAR	Serious Unexpected Suspected Adverse Reaction
TMG	Trial Management Group
TS	Trial Statistician
TSC	Trial Steering Committee
Var	Variance
VIDEO	VItamin D Evaluation in Osteoarthritis
WHOQOL-Bref	World Health Organization Quality of Life assessment instrument
WOMAC	Western Ontario and MacMaster universities osteoarthritis index

5. Sample Size Estimation

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) at three years was 0.7 mm. VIDEO sample size estimation was based on the following assumptions:

Power	80%
Significance	5%
Clinically important mean difference	0.22mm
Standard deviation	0.7mm
Sample size	159 patients per group

Assuming that 32% of patients do not provide an evaluable final X-ray at the end of the study, the total sample size required is 470 patients. This is conservative because it does not take account of the nature of the analysis, so power should in fact be higher than the nominal 80%.

6. Analysis Principles

6.1 ITT or PP?

Some patients enrolled (n = 10) but were found to be ineligible or withdrew consent at the baseline visit so never received any treatment. Except for these patients – for whom no data are available – analyses will be by intention-to-treat, to retain the validity of the randomisation process.

6.2 Significance levels of tests

All statistical tests will use a 2-sided p-value of 0.05, unless otherwise specified. There will be no formal adjustment of p-values for any interim analyses performed. All confidence intervals presented will be 95% and two-sided.

6.3 Baseline comparability

Baseline characteristics will be summarised by randomised group. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

6.4 Adjustment for design factors

Since randomisation was stratified by centre, analyses of outcomes will always involve some form of adjustment for centre as a random or fixed effect (as recommended in ICH E9, section 5.7). Treatment effects are then estimated conditional on centre. The primary analysis model of the joint space narrowing in the medial compartment of the index knee will adjust for the baseline JSW in the medial compartment of the index knee. Secondary analysis models of the joint space narrowing in the contra-lateral knee and other joint compartments will adjust accordingly for the associated baseline JSW. The secondary analysis models of pain, functional disability, quality of life, depression and cognition status will adjust for the baseline K&L grade in the index knee (worst of medial and lateral K&L grade), which incorporates a measure of JSW.

6.5 Follow-up and losses to follow-up: missing data

Missing baseline covariates will be dealt with using mean imputation (White and Thompson 2004). Any missing values for a baseline covariate X will be replaced with the mean observed X. Mean imputation is an appropriate method because randomisation means baseline variables are independent of treatment group.

In a pragmatic clinical trial over a three-year time frame some patients are inevitably lost to follow-up. Sample size estimation assumed 32% of patients would not provide an evaluable 36 month x-ray. If this rate is observed, data for many patients will be only partially observed.

Since missing outcome values are likely to be missing at random, and to avoid loss of efficiency, missing outcome values (both primary and secondary) will be imputed using multiple imputation by chained equations (Van Buuren 1999). Details are provided in section 7.5.1. Reasons for missingness may be important and these will be investigated using logistic regression of covariates on an indicator of missingness.

For patients who have a total knee replacement during the trial we will include observed data before surgery in the analysis and assume data after surgery to be missing. Sensitivity analyses are planned to investigate the validity of the missing-at-random data assumption for patients who undergo total knee replacement of the index knee during the study in the primary outcome analysis. We will also perform sensitivity analyses to investigate the validity of the missing-at-random data assumption for all patients missing primary outcome data in the primary outcome analysis.

6.6 Summarising models

Estimates from linear regression models will be summarised by regression coefficients and 95% confidence intervals. Summary measures for continuous normally distributed outcome measures will be differences in means, and 95% confidence intervals for differences in means.

7. Analysis Details

The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

7.1 Recruitment and follow-up patterns

Recruitment will be presented by year and centre.

The number of CRFs completed – excluding patients who have been withdrawn from therapy and were unwilling to continue follow up – will be reported by treatment group.

The number of patients who were withdrawn from therapy, were unwilling to continue follow-up, had replacement surgery of the index knee or died while on study will be reported by treatment group.

7.2 Baseline characteristics

Baseline characteristics will be reported by treatment arm. Continuous variables will be reported as mean (SD) if normally distributed or median (IQR) if non-normal. Categorical variables will be presented as number/n (%). Variables to be reported at baseline are listed in the dummy tables 1 to 3 (appendix A).

7.3 Trial treatment

Patients who were randomised were issued with treatment at their baseline visit. Most of the time randomisation occurred at the baseline visit, however in some cases it was before the visit. This does not affect when treatment is received or when follow-up visits occur.

7.4 Trial events

As listed in section 2. the outcomes of interest are:

Primary: Radiological progression of knee OA in the medial joint compartment of the index knee (rate of change in joint space width in mm).

Secondary:

- Radiological progression of knee OA in the lateral joint compartment (rate of change in joint space width in mm) of the index knee
- Radiological progression of knee OA in the medial and lateral joint compartments (rate of change in joint space width in mm) of the contra-lateral knee
- K&L grade (worst of medial and lateral K&L grade) in the index knee and contra-lateral knee
- Pain and functional disability (Knee effusion (index knee), Knee warmth (index knee), WOMAC scores, Timed Walk Test (time taken to walk 10m), Get up and go test (GUG), Grip strength (dominant hand), Quadriceps strength (index knee)
- Quality of life (WHOQOL-Bref scores)
- Depression and cognition status (BDI, MMSE)

Exploratory Analysis:

Two pre-defined exploratory, hypothesis generating interaction analyses will be performed for the primary outcome. These are:

1. Treatment interaction with baseline JSW (Does vitamin D supplementation confer greater benefit for those patients with greater JSW at baseline?)
2. Treatment interaction with baseline 25-hydroxyvitamin D3 levels (Does vitamin D supplementation confer greater benefit for those patients with lower baseline 25-hydroxyvitamin D3 levels?)

An additional exploratory sub group analysis will be performed to determine:

3. Treatment interaction with use of HRT in postmenopausal women. (Does vitamin D supplementation confer greater benefit in patients using HRT?)

These analyses are exploratory in nature hence results should be interpreted cautiously.

7.5 Analysis methods

7.5.1 Primary Analysis

A linear mixed model will be used to analyse the rate of change in the joint space width in the medial compartment of the most severely affected knee, which is referred to as the index knee (knee with the smallest joint space width at baseline). Treatment and time (in years) will be modelled along with the interaction between them. This interaction will be the parameter of central interest. It is interpreted as the average difference in the rate of joint space narrowing per year for patients on vitamin D compared to those on placebo.

The model will include: random effects for centre (random intercept) and patient (random intercept and slope on time) to allow for between patient and centre differences at baseline and between patient differences in the rate of change over time, and fixed effects for baseline JSW, gender, glucosamine use, age and BMI. An unstructured covariance matrix will be used (Carpenter & Kenward 2008). The model makes assumptions about random effects distributions, correlation structure and residuals, which will all need investigation. Use of mixed modelling means that significance of random effects will always be based on likelihood ratio tests, while fixed effects will be assessed using Wald tests.

The linear mixed model of the joint space width, y_{ijk}, where i indexes the visit time (in years), j the individual and k the centre will hence be,

$$y_{ijk} = \beta_{0jk} + \beta_{1j}(time_{ijk}) + \beta_2(vitD_{jk}) + \beta_3(vitD_{jk}*time_{ijk}) + \beta_4(baseline\ JSW_{jk}) + \beta_5(gender_{jk}) + \beta_6(glucosamine_{jk}) + \beta_7(age_{jk}) + \beta_8(BMI_{jk})$$

Where

$$\beta_{0jk} = \beta_0 + v_{0k} + u_{0jk} + \varepsilon_{ijk}$$

$$\beta_{1j} = \beta_1 + u_{1jk} \qquad (1)$$

And the covariance matrix is unstructured. The model will be fitted using REML.

The main parameter of clinical interest is β_3 which represents the average difference in the rate of joint space narrowing between the treatment groups per year.

If the variation between the centres is low and the model fails to converge a fixed centre effect will be fitted instead. If the random patient specific slope on time is found not to be significant this term will be removed from the model.

To avoid bias and loss in efficiency, missing outcome values will be imputed using multiple imputation by chained equations (Van Buuren 1999) under the assumption that missing data values are likely to be missing-at-random (dependent on the values of the observed data, but not dependent on the values of the missing data).

50 imputed data sets will be drawn separately for each randomised group, replacing missing outcome values with simulated values using predictive mean matching from a set of imputation models containing all potential prognostic baseline covariates, (baseline JSW in medial joint compartment- index knee, centre, gender, glucosamine use, age and BMI) the primary outcome variable (JSW in medial joint compartment at 1 and 3 years- index knee), the secondary outcome variables (JSW in lateral joint compartment-index knee , JSW in medial and lateral compartment -contra lateral knee, K&L grade of index knee and contra-lateral knee, knee warmth and knee effusion of index and contra lateral knee, WOMAC scores, WHOQOL-Bref scores, timed walk test, get up and go test, grip strength (dominant hand), quadriceps strength (index knee), BDI and MMSE at all follow-up time points) and a binary knee replacement indicator (did the patient receive a knee replacement of the index knee at any time during follow up, yes/no). Missing values for continuous outcomes will be imputed from linear regression models, missing values for binary variables will be imputed from binary logistic models and missing values for ordinal variables will be imputed from ordinal logistic models. Model (1) will be fitted to each of the 50 imputed data sets and the results will be combined using Rubin's rules (Rubin, 1987). Intermediate pain outcomes and the knee replacement indicator are included in the imputation models to make the MAR assumption plausible for patients who experienced a knee replacement.

7.5.2 Sensitivity Analyses

Primary analysis assumes that the probability of missing data is not dependent on the values of the unobserved data themselves, conditional on the observed values of the variables included in the imputation model (MAR). Reasons for missingness may be important and

these will be investigated using logistic regression of covariates on an indicator of missingness.

To explore the validity of the missing-at random assumption for patients who undergo total knee replacement of the index knee during the study sensitivity analyses assuming missing not at random mechanisms will be undertaken for the primary outcome. Multiple imputation by chained equations will be used to impute missing JSW outcome values from the observed distribution of the data under the MAR assumption as outlined in section 7.5.1 and then in each case, each JSW imputation after knee replacement will be modified to reflect departures from the MAR assumption.

Naturally we will suppose that patients who have a knee replacement will have poorer response than predicted by MAR. If δ is defined as the mean percentage change in the rate of JSN per year between observed and unobserved individuals, adjusted for all other included covariates [so δ=0% is MAR] then the conditional mean for the first JSW response after knee replacement will be reduced accordingly by δ. If knee replacement was experienced prior to one year the conditional mean for the first response after knee replacement at one year will be reduced by δ and the second response after knee replacement at three years will be reduced by 3δ to maintain a linear change in the rate of decline. JSW can never be < 0, consequently if the change in the rate of decline results in an imputation <0mm, JSW will be set to 0mm.

The results of multiple imputations with values of 25%, 50%, 100%, 200% and 500% for $\boldsymbol{\delta}$ **(**percentage change in rate of JSN per year between unobserved and observed cases) will be compared to explore varying departures from the MAR assumption. Results will then be combined using Rubin's rules.

Further sensitivity analyses will assume $\boldsymbol{\delta}$ is not the same in each treatment arm. δ_1 will be defined as the mean percentage change in the rate of JSN per year between observed and unobserved individuals, adjusted for all other included covariates in the placebo arm and δ_2 as the mean percentage change in the rate of JSN per year between observed and unobserved individuals, adjusted for all other included covariates. We will explore the following sets of $\boldsymbol{\delta}$**;** (δ_1=500%, δ_2=25%), (δ_1=25%, δ_2=500%), (δ_1=200%, δ_2=25%), (δ_1=25%, δ_2=200%), (δ_1=100%, δ_2=25%), (δ_1=25%, δ_2=100%), (δ_1=50%, δ_2=25%), (δ_1=25%, δ_2=50%), (δ_1=50%, δ_2=100%), (δ_1=100%, δ_2=50%), (δ_1=200%, δ_2=100%), (δ_1=100%, δ_2=200%).

Additional sensitivity analyses will then assume that data is missing informatively only in the placebo arm, hence δ_2= 0%. Multiple imputation by chained equations will be used to impute missing measures from the observed distribution of the data under the MAR assumption. 50 imputed data sets will be created and in each case each imputation in the placebo arm will be modified by δ_1, for δ_1=25%, 50%, 100%, 200% and 500% to reflect departures from MAR and model (1) will be fitted. Results will be combined using Rubin's rules. The corresponding cases with the data assumed to be alternatively informatively missing only in the intervention arm (δ_1 = 0%) will subsequently be explored.

Two further sensitivity analyses will investigate the worst and best case scenarios. In the worst case scenario post knee replacement, JSW = 0. Multiple imputation by chained equations will be used to impute missing JSW outcome values from the observed distribution of the data

under the MAR assumption as outlined in section 7.5.1 and then in each knee replacement case, each JSW imputation after knee replacement will be set to 0 to reflect worst case scenario departure from the MAR assumption.

In the best case scenario post knee replacement JSW = patients last non-missing score (last observation carried forward – LOCF). Multiple imputation by chained equations will be used to impute missing JSW outcome values from the observed distribution of the data under the MAR assumption as outlined in section 7.5.1 and then in each knee replacement case, each JSW imputation after knee replacement will be set to patients last non-missing JSW to reflect best case scenario departure from the MAR assumption for the knee replacement cases.

Sensitivity analyses will also be conducted to explore the validity of the MAR assumption for all patients with missing outcome data (not just those with TKR of the index knee) using the same imputation procedure and ranges of δ as outlined above. In each imputed data set, the imputations for all cases with missing data at one and three years will be modified by the pre-specified δ's to reflect departures from MAR.

7.5.3 Secondary Analyses

Missing secondary outcome values will be imputed using the multiple imputation procedure already outlined in section 7.5.1 under the missing-at-random assumption. Consequently the models specified below will be fitted to each of the 50 imputed data sets and the results combined using Rubin's rules.

Continuous secondary outcome measures

The continuous secondary outcome measures of pain (WOMAC) and function (WHOQOL-Bref, BDI, Mini mental score, Quadriceps strength (index knee), Grip Strength (dominant hand) and 10m walk test) that are assessed on more than one occasion will be analysed using a linear mixed model. Treatment and time will be modelled along with the interaction between them. Random intercepts and slopes on time will be fitted for each patient along with a random centre effect (If the variation between the centres is low and the model fails to converge a fixed centre effect will instead be fitted). The models will be adjusted for baseline K&L grade of the index knee, gender, glucosamine use, age, BMI and the baseline value of the corresponding outcome.

Binary secondary outcome measures

Binary outcome measures assessed on more than one occasion (knee warmth and effusion – index knee) will be analysed using a random slope logit mixed model. Treatment and time will be modelled along with the interaction between them. Random intercepts and slopes on time will be fitted for each patient along with a random centre effect. A fixed centre effect may alternatively be fitted if the observed variation at the centre level is low resulting in model instabilities. Models will be adjusted for the baseline value of the binary outcome along with baseline K&L grade of the index knee, gender, glucosamine use, age and BMI.

The probability of the binary outcome, $y_{ijk} = 1$ at time i for individual j at centre k is denoted as π_{ijk} and the logit mixed model for analysis will be,

$$\log\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) = \beta_{0jk} + \beta_{1j}(\text{time}_{ijk}) + \beta_2(\text{vitD}_{jk}) + \beta_3(\text{vitD}_{jk}*\text{time}_{ijk}) + \beta_4(\text{baseline index K\&L grade}_{jk}) + \beta_5(\text{gender}_{jk}) + \beta_6(\text{glucosamine}_{jk}) + \beta_7(\text{age}_{jk}) + \beta_8(\text{BMI}_{jk}) \quad (2)$$

Where $\beta_{0jk} = \beta_0 + u_{0jk} + v_{0k}$

And $\beta_{1j} = \beta_1 + u_{1jk}$

The logit mixed model has a nice interpretation; the exponents of the coefficients represent the associated conditional or subject-specific odds ratios. The interaction between vitamin D and time is of central interest; the exponent of β_3 represents the relative difference in the conditional odds of the binary outcome for a Vitamin D patient relative to a patient on placebo per year of exposure.

Ordinal secondary outcome measures

Ordinal outcome measures (K&L grade, get up and go test) assessed on more than one occasion will be analysed using a single-level ordinal logistic regression model. Robust Huber-White sandwich estimators of standard errors of the regression coefficients will be calculated to take account of the observed correlation between repeated assessments of the same patient.

Treatment and time will be modelled along with the interaction between them. Models will be adjusted for the baseline value of the ordinal outcome, centre, gender, glucosamine use, age and BMI. The probability of an ordinal response y_i for individual i, with 1,…C categories being category k or higher is defined as, $\Pr(y_i \geq k)$ and the ordinal logistic regression model for analysis will be,

$$\log\left(\frac{\Pr(y_i \geq k)}{\Pr(y_i < k)}\right) = \alpha_k + \beta_1(\text{time}) + \beta_2(\text{vitD}) + \beta_3(\text{vitD*time}) + \beta_4(\text{centre}) + \beta_5(\text{baseline K/L grade}) + \beta_6(\text{gender}) + \beta_6(\text{glucosamine}) + \beta_8(\text{age}) + \beta_9(\text{BMI}) \quad (3)$$

Where k = 1, ….C-1

The interaction between vitamin D and time is of central interest. The exponent of β_3 will represent the odds ratio of being in higher category of the ordinal outcome than a lower category for Vitamin D patients relative to patients on placebo per year.

The ordinal logistic regression model makes assumptions about proportional odds which must be checked. If the proportional odds assumption does not hold a multinomial logit model with Huber-White sandwich estimators of standard errors of the regression coefficients will be fitted.

Radiological progression of JSN in more than one joint

A secondary analysis of the radiological progression of OA in both knee joints will use a linear mixed model that is an extension of model 1 with the following additional fixed effects:

knee(index/contra-lateral indicator) main effect , knee x treatment interaction, knee x time interaction, and knee x treatment x time interaction.

Working correlation matrices will be unstructured, which is not unduly restrictive given that x-rays are only taken at three time points. The model for the analysis of the joint space width in both knees, y_{ijk} where i indexes the visit time (in years), j the knee (index/contra-lateral) and k the individual will hence be,

$$y_{ijk} = \beta_{0jk} + \beta_{1k}(time_{ijk}) + \beta_2(vitD_k) + \beta_3(vitD_k * time_{ijk}) + \beta_4(Knee_{jk}) + \beta_5(Knee_{jk} * vitD_k) + \beta_6(Knee_{jk} * vitD_k * time_{ijk}) + \beta_7(Knee_{jk} * time_{ijk}) + \beta_8(\text{baseline JSW}_{jk}) + \beta_9(gender_k) + \beta_{10}(glucosamine_k) + \beta_{11}(age_k) + \beta_{12}(BMI_k) + \beta_{13}(Centre_k) \quad (4)$$

Where $\beta_{0jk} = \beta_0 + v_{0k} + u_{0jk} + \varepsilon_{ijk}$

And $\beta_{1k} = \beta_1 + v_{1k}$

If the variation between the centres is low and the model fails to converge a fixed effect for centre will be fitted instead of the random effect. β_6 will quantify the difference in the treatment effect (rate of joint space narrowing, in mm per year) between the index and contra-lateral knee which is of main interest.

Clinically significant progression of JSN

The effect of treatment on the proportion of patients with clinically significant progression (JSN>0.5mm in the index knee) at 3 years will be obtained using a logistic regression model that adjusts for baseline index JSW, gender, glucosamine use, age, BMI and centre. For patients who have a total knee replacement during the trial we will assume JSN>0.5mm (clinically significant progression).

Serious adverse event rates

The percentages of patients experiencing any SAE's in the two groups will be compared using comparisons of two independent proportions.

Exploratory Analysis

Possible interactions with the treatment effect (β_3) in the primary analysis will be investigated for the following potential effect modifiers, but these will have limited power:

1) Baseline JSW (Does vitamin D supplementation confer greater benefit for those patients with greater JSW at baseline?)
2) Baseline 25-hydroxyvitamin D_3 levels (Does vitamin D supplementation confer greater benefit for those patients with lower baseline 25-hydroxyvitamin D_3 levels?)

Model 1 will be extended to include the appropriate additional main effects, lower order interaction terms and three-way interaction terms required for the two tests (treatment x time x baseline JSW and treatment x time x Baseline 25-hydroxyvitamin D_3 levels).

Sub Group Analysis

A sub-group analysis of postmenopausal women will be undertaken. The primary analysis model (1) will be extended to include use of HRT and the three way interaction of treatment x time x use of HRT (along with required lower order interaction terms) to investigate whether use of HRT in postmenopausal women is a treatment effect modifier; does vitamin D supplementation confer greater benefit in patients using HRT? This analysis is also exploratory and hypothesis generating as will have limited power.

7.6 Toxicity/ Symptoms

Since vitamin D is a licensed, available-over-the-counter drug, toxicity is unlikely. The most probable adverse events are hypercalcaemia and hypercalciuria. Counts of these adverse events will be compared across randomised groups using an appropriate count model (probably zero-inflated poisson or negative-binomial).

7.7 Quality of life analysis

WHOQOL-Bref scores collect information on quality of life. These will be analysed using the approach outlined in section 7.5.3 for continuous secondary outcomes.

8. Additional Information in the Clinical paper

No interim analyses are planned for the primary outcome measure as this will not become available until the end of the trial.

9. Signatures of Approval

Date: 18.03.2013
Version: VIDEO SAP v1.3

Signatures

Name	Trial Role	Signature	Date
Caroline Doré	Senior Statistician		
Suzie Cro	Designated Statistician		

Acknowledgement

This Statistical Analysis Template is constructed with the aid of an original document by Matthew Sydes.

10. References

Bingham J et al., 2006, Risedronate Decreases Biochemical Markers of Cartilage Degradation but Does Not Decrease Symptoms or Slow Radiographic Progression in Patients with Medial Compartment Osteoarthritis of the Knee, *Arthritis and Rheumatism,* 54(11), pp3494-3507.

Brandt KD et al., 2005, Effects of Doxycycline on Progression of Osteoarthritis, *Arthritis and Rheumatism,* 52(7), pp2015-2025.

Carpenter J and Kenward M, 2008, Missing data in randomised controlled trials - a practical guide, Birmingham: National Institute for Health Research, Publication RM03/JH17/MK. Available at: http://www.pcpoh.bham.ac.uk/publichealth/methodology/projects/RM03_JH17_MK.shtml

Rubin DB, 1987, *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley and Sons.

Van Buuren S et al., 1999, Multiple Imputation of Missing Blood Pressure Covariates in Survival Analysis. *Statistics in Medicine*, 18: 681-694.

White I and Thompson SG, 2004, Adjusting for partially missing baseline measurements in randomized trials, *Statistics in Medicine,* 24: 993 – 1007.

11. Appendices

11.1 Appendix A – Dummy tables

11.1.1 Table 1. Baseline clinical characteristics

	Vitamin D	Placebo
Centre: RNOH		
Southampton		
Manchester		
Norwich		
Newcastle		
Age (yrs)		
Sex: female		
Index knee: right		
Standing height (m)		
Sitting height (m)		
Weight (kg)		
Birth weight (kg)		
BMI (kg/m^2)		
Temperature (^{o}C)		
Systolic blood pressure (mm/Hg)		
Diastolic blood pressure (mm/Hg)		
Pulse (bpm)		
Waist (cm)		
Age at first period if female (yrs)		
Age at menopause if female (yrs)		
Hysterectomy if female		
Any ovaries removed if female		
HRT if female		
Oral contraceptive if female		

Number of children if female
Family history of knee or hip OA
Alcohol consumption (units/wk)
Smoking status: Current
Ex
Never
Heberdens nodes
Bouchards nodes
CMC joint OA
% Bilateral knee OA
% taking glucosamine
% taking cod liver oil
% taking analgesic
Total visits to any practitioner in last 6 months
WOMAC pain score
WOMAC function score
WOMAC stiffness score
WHOQOL-Bref physical
WHOQOL-Bref psychological
WHOQOL-Bref social
WHOQOL-Bref environment

Becks Depression Inventory
Mini Mental Score
Number of physical activities (Q21)
% index knee varus
% index knee valus
% index knee fixed flexion
% warmth index knee
% effusion index knee
% crepitus index knee
Quadriceps strength (index knee)
Grip strength (dominant hand)
Timed Walk test (time to complete 10m walk – seconds)
Get up and Go Test

11.1.2 Table 2. Baseline radiographic characteristics

		Vitamin D	Placebo
Worst K&L grade (of medial/lateral)			
Index knee:	1		
	2		
	3		
	4		
	5		
Worst K&L grade (of medial/lateral)			
Contra-lateral knee:	1		
	2		
	3		
	4		
	5		
Medial JSW index knee (mm)			
Lateral JSW index knee (mm)			
Medial JSW Contra-lateral knee (mm)			
Lateral JSW Contra-lateral knee (mm)			

11.1.3 Table 3. Baseline biochemical variables

	Vitamin D	Placebo
Serum vitamin D		
Sodium (mmol/L)		
Potassium (mmol/L)		
Urea (mmol/L)		
Creatinine (μmol/L)		
Calcium (mmol/L)		
Bilirubin (μmol/L)		
Aminotransaminases (IU)		
Albumin (g/L)		
Protein (g/L)		
Phosphate (mmol/L)		
Alkaline phosphatase (IU/L)		
24 urine calcium (mmol/day)		
Haemoglobin (g/dL)		
White blood cell count ($x10^9$/L)		
Platelet count ($x10^9$/L)		
ESR (mm/hour)		
Glucose (mmol/L)		

11.1.4 Table 4. Main Radiographic outcome measures

	Vitamin D	Placebo	Difference (95% c.i.)
Primary outcome - Joint space loss medial compartment index knee (mm/year)			
Joint space loss lateral compartment index knee (mm/year)			
Joint space loss medial compartment contra-lateral knee (mm/year)			
Joint space loss lateral compartment contra-lateral knee (mm/year)			
Odds of higher K/L grade versus less severe K/L per year index knee			
Odds of higher K/L grade versus less severe K/L per year contra-lateral knee			

11.1.5 Table 5. Secondary outcome measures

	Vitamin D	Placebo	Difference (95% c.i.)
Rate of change in WOMAC pain			
Rate of change in WOMAC stiffness			
Rate of change in WOMAC function			
Rate of change in WHOQOL-Bref physical			
Rate of change in WHOQOL-Bref psychological			
Rate of change in WHOQOL-Bref social			
Rate of change in WHOQOL-Bref environment			
Rate of change in quadriceps strength (index knee)			
Rate of change in grip strength (dominant hand)			
Rate of change in serum vitamin D concentration			
Rate of change in Timed Walk Test (time taken to walk 10m)			
Rate of change in Get up and go test			
Rate of change in Becks Depression Inventory			
Rate of change in Mini mental State Exam			
Odds of knee warmth per year (index knee)			
Odds of knee effusion per year (index knee)			

*Rate of change is expressed per year.

11.1.6 Table 6. Exploratory analyses

	Associated rate of change in JSW per year		
	Vitamin D	Placebo	Interaction test
Baseline JSW (mm)			
Use of HRT			
No use of HRT			
Baseline 25-hydroxyvitamin D_3			