RANDOMISED PLACEBO – CONTROLLED TRIAL OF DAILY ORAL VITAMIN D AND CALCIUM FOR THE SECONDARY PREVENTION OF OSTEOPOROSIS RELATED FRACTURES IN THE ELDERLY

Known as RECORD (Randomised Evaluation of Calcium OR vitamin D)

This protocol describes a major UK trial to establish or refute the claimed benefits of vitamin D and calcium, alone or in combination, to prevent bone fractures in the elderly. The trial is designed to be as simple as possible both for those participating and for those involved in clinical care. Research nurses will provide local co-ordination in all clinical centres.

1. THE REASONS FOR THE TRIAL

1.1 The burden of the problem

It is well known that osteoporotic fractures in the elderly create a significant and increasing burden of ill health. An estimated 50,000 to 80,000 women in the United Kingdom will suffer a hip fracture each year by 2006[1]. The annual cost to the NHS is estimated at £258 million, and total public sector costs (including residential care) probably exceed £900 million[2].

1.2 The decision to test vitamin D and calcium

Of various putative strategies[3-8] for preventing fractures, the most promising is supplementation with a combination of vitamin D and calcium.

In an exhaustive systematic review of previous trials of vitamin D and calcium for fracture prevention[9], a total of 18 eligible randomised controlled trials were identified. (Most of the 42 studies excluded had no fracture outcome data.) Fifteen of the eighteen were explanatory type trials; each had less than 200 participants; most were conducted in institutional referral centres; and the principal outcomes were usually bone density or biochemical measurements. The three larger trials were pragmatic; they all had more than 500 participants, were community based, and focused on fractures. The results of these three trials appear contradictory.

The widely quoted French trial conducted by Chapuy and colleagues[10,11] suggested that the combination of vitamin D and calcium significantly reduced the risk of fractures amongst elderly women in sheltered housing. In contrast, the large trial conducted in the Netherlands by Lips and colleagues[12], suggested no reduction in fracture risk from vitamin D alone. (This was despite an apparent improvement in bone density, raising questions about the validity of such measurements as a surrogate for fracture prevention.) The third larger trial[13] suggested a benefit of calcitriol (a vitamin D analogue) in comparison with calcium. One of the studies excluded from this review is widely quoted as showing the effectiveness of a single dose of vitamin D in fracture prevention[14]. Quasi-random allocation to open vitamin D or no treatment was based on month of birth, and there is evidence of significant selection bias.

A more recently published trial[15] amongst about 400 people provided further evidence that vitamin D and calcium taken together reduce the risk of fracture. Current evidence therefore suggests that it is this combination, which is most likely to be effective. However, because of the relatively high cost of calcium, this is unlikely to be cost saving, especially for primary prevention (unless the price falls significantly). Vitamin D alone, on the other hand, is more attractive because of its low cost but evidence of its effectiveness is much less promising.

1.3 The questions which this protocol will address

The trial described in this protocol is therefore needed urgently because (a) the importance of calcium, alone or in combination with Vitamin D, must be clarified; (b) vitamin D alone should still be tested because if effective it could be very cost effective; (c) without this trial vitamin D and calcium use is likely to increase with major resource implications and (although very unlikely) possible hazards.

1.4 The advantages of a secondary prevention trial

The trial will be of secondary prevention in the setting of current NHS provision of fracture care. This has advantages. First, those who have sustained a fracture constitute a high-risk group for further fracture: 5-10 fold for another hip fracture after a first hip fracture, and about two-fold after other types of fracture[16,17].

Secondly, virtually all patients with new fractures are in contact with the health services, and this offers an efficient method of identification both for a trial, and for prevention should this trial demonstrate effectiveness. Thirdly, during a trial, provided that minimal demands are made on clinic staff, research staff may efficiently recruit participants. Fourthly, after a recent fracture, older people may be particularly receptive to prophylactic options.

2. TRIAL RECRUITMENT

2.1 Who will be considered for trial entry?

The trial will involve people aged 70 or over who have had a previous fracture:

(i) Those who have sustained a fracture (except cervical spine, skull or face) in a fall from no more than a standing height within the previous two years (while eligible patients may have sustained more than one fracture, those who have high energy transfer injury will not be eligible)

(ii) Those with a clinical vertebral fracture (defined as a definite clinical event with radiological evidence* of an incident vertebral fracture)

Potential participants will be identified by study nurses based in each clinical centre from amongst patients attending hospital as outpatients or inpatients. A log will be kept of patients meeting these criteria, describing the reasons if they are not subsequently recruited to the trial. (Depending on the numbers of people attending hospital who are recruited, additional patients may also be identified from medical records as having sustained an eligible fracture in the preceding two years.)

2.2 Informing potential participants about the trial

The nurse will describe the study to potentially eligible people backing oral information with the standard study information leaflet (Appendix 1). Those approached may choose to involve an accompanying person.

* lateral x-ray shows at least a 20% reduction in anterior, middle or posterior height of any vertebra and a 10% reduction of the projected vertebral area

2.3 Ruling out uncommon reasons for exclusion

Amongst those who indicate that they are likely to participate, the nurse, using a combination of questions and casenote review, will then check that none of the following exclusion criteria apply:

- Bed or chair bound prior to index fracture
- Unlikely to be able to comply with the protocol (e.g. abbreviated mental test score[18] of six or lower)
- Suffering from a cancer likely to metastasise to bone (e.g. breast, kidney, lung, thyroid, and prostate)
- Fracture associated with pre-existing local bone abnormality
- Known hypercalcaemia or active renal stone disease (documented in last 10 years)
- Current daily treatment with >200 IU vitamin D or >500mg calcium; had fluoride, bisphosphonates, calcitonin, tibolone hormone replacement therapy, selective estrogen receptor modulators or any vitamin D metabolite (such as calcitriol), in the last 5 years; vitamin D by injection in last year
- Unlikely to complete the study (e.g. known to be leaving the UK to reside abroad, or life expectancy less than six months)

2.4 Consent to participate

Once eligibility has been confirmed, the nurse will ask if the potential participant is ready to decide whether or not to join the trial. If so, she will give the participant a consent form (Appendix 2). (If not, she will arrange to make contact again about a week later.) After she has checked that the consent form is understood, the nurse will invite the participant to sign the form, add her own name and countersign it. (Consent will only be sought from in-patients with hip fractures after the second post-operative day at the earliest.) One copy of the consent form will be given to the participant, another will be filed in the hospital case notes, and the third will be posted to the Trial Office.

2.5 Information collected at trial entry

Once a participant has agreed to join the trial, the research nurse will record on a standard form (Appendix 3):

1. Identifying and contact information

- Full name, address, telephone number
- Date of birth, age on recruitment day, sex
- NHS, hospital number and CHI number (if available)
- Marital status, woman's maiden name
- Name of a 'best contact', such as a friend or relative, with contact details
- General Practitioner's and Hospital Consultant's (if in long term inpatient care) contact details

2. Descriptive information

- Ethnic origin, and place of birth including county
- Type (and date) of 'enrolling' fracture, and whether any previous fractures (since aged 50)
- (Current or recalled) weight, whether smoker, whether could walk out of doors prior to the recent fracture, and history of maternal hip fracture
- Type of current place of residence
- Whether diabetic, on oral hypoglycaemics and / or insulin.
- Current use of thiazides, thyroxine, prednisolone 7.5mg / d or more
- Dietary calcium and vitamin D intake and exposure

This information will be sent to the Trial Office.

2.6 Instructions about what is involved

The nurse will then give a standardised description of participation. This will include an information sheet about precautions against falls and exercise as possible means of fracture prevention (Appendix 4). The nurse will explain the arrangements for supplying the tablets (see below), and how they should be taken. The hospital case notes will be labelled at this time with a request to send to the local clinical co-ordinator copies of discharge summaries and letters if the patient has any further contact with the hospital.

3. TRIAL INTERVENTIONS

3.1 Two tablets taken each day

Participants will be asked to take two tablets every day with or after food.

Those allocated vitamin D will have a daily supplement of 800 IU (D_3).

Those allocated calcium will have a daily supplement equivalent to 1g elemental calcium.

Those allocated vitamin D and calcium in combination will have a daily supplement of 800 IU (D_3) and 1g elemental calcium.

3.2 The trial's 'factorial' design

The trial will use a 2 by 2 factorial design to test not only whether vitamin D and calcium on their own are effective, but also whether there is extra effectiveness from the combination. For this reason allocation will be to one of four groups:

	Calcium supplement (1g daily)	**No calcium supplement**
Vitamin D supplement (800 IU D_3 daily)	(a) Combined vitamin D and Calcium tablets	(b) Vitamin D tablets
No vitamin D supplement	(c) Calcium tablets	(d) Placebo tablets

3.3 Treatment allocation

The trial allocation will be computer-generated in the Trial Office. After stratification by trial centre, balance in respect of other key prognostic variables – age (under 80 or 80 and over), sex, time since fracture (previous three months or longer) and type of enrolling fracture (proximal femur, distal forearm, clinical vertebral and other) – will be ensured by a process of minimisation.

3.4 Tablet supplies and delivery

The allocated trial tablets will be supplied in screw top containers labelled with the participant's name, date of supply and batch number, with a unique study number, allowing rapid unblinding if later deemed necessary. Tablets sufficient for four months will be packaged together for dispatch to individual participants.

In general, supplies will be posted directly to the participant from the Trial Office. There will, however, be flexibility in the way used to get the initial supply to a participant. At the time of trial entry the study nurse will be able to choose whether the materials are posted or given to a participant directly, and if posted where they should be sent to. Where there are compelling reasons for giving the first supply directly to the participant (for example, because of current in-patient care), the nurse will be sent the materials from the Trial Office and s/he will then pass them on to the participants.

Thereafter, supplies will be posted directly to all participants at four monthly intervals using standardised packaging.

4. SUBSEQUENT ARRANGEMENTS

4.1 Informing key people

Following formal trial entry, the Trial Office will also contact:

i) the ***general practitioner*** - letting the practice know about participation in the trial and the (few) implications for the practice. This letter (Appendix 5) includes a brief description of the trial together with a request that the general practitioner notifies the Trial Office if any prespecified events, such as the patient dying, occur (see section 4.5 below)

ii) the ***'best contact'*** asking for assistance if circumstances change (see below) (Appendix 6)

iii) the ***local study nurse*** to confirm that the participant has been recruited, giving the study number and date of despatch of materials (Appendix 7)

4.2 Checking that all is well

Two weeks after recruitment and thereafter when judged necessary, the enrolling nurse will contact the participant to check the place of residence, and that there have been no problems taking the tablets.

4.3 Four monthly postal contact

Each fresh supply of materials will contain a brief form for completion by the participant (Appendix 8). This has the following purposes:

i) confirmation that the materials arrived safely

ii) collection of information about the preceding four months: any new fracture; any admission to hospital; and any change in residence

iii) details of tablet compliance from the preceding week: whether the tablets have been taken, how often, and reason for stopping if applicable.

As a further measure of compliance, a five percent randomly selected subsample of recruits will be asked to return all unused supplies for a tablet count. A detailed protocol is provided in Appendix 9.

4.4 Additional information sought by post at four, twelve, twenty-four, thirty-six and forty-eight months after entry

Longer forms will be sent at four, twelve, twenty-four, thirty-six and forty-eight months (Appendix 10) which, in addition to the above, will collect the following information:

i) falls in last week

ii) the EQ-5 questionnaire

iii) the SF-12 questionnaire

iv) Diabetic or not, use of oral hypoglycaemics and / or insulin

4.5 Notifications by general practitioners

Stickers and the information sheet will ask the general practitioner to notify the Trial Office by phone if the participant:

(i) sustains a new fracture

(ii) moves to another practice

(iii) has a suspected adverse event related to the trial, specifically developing renal insufficiency (creatinine greater than 250 micromols per l), renal stones, or hypercalcaemia (based on local reference standards)

(iv) develops diabetes mellitus requiring oral hypoglycaemics and / or insulin.

(v) dies (and cause of death)

4.6 Notifications by 'best contact'

The aim of the brief form and freepost envelope sent to 'best contacts' at the time of enrolment is to facilitate notification if the participant:

(i) sustains a new fracture

(ii) changes residence

(iii) is admitted to hospital

(iv) develops a serious illness / dies

(v) has any difficulties with tablet delivery

4.7 Roles of study nurses after recruitment

- ***if a fracture, or death is reported***

  The Trial Office will seek details from the study nurses if any major trial event – new fracture or death – is reported. In most instances, details will be collected from local hospital records, but occasionally this may require contact with other hospital records departments or the general practice.

- ***if the Trial Office is uncertain about other trial outcomes***

  Occasionally the nurse will be contacted by the Trial Office to clarify other outcomes supplied by the patient, best contact or GP, such as, non fracture related admissions.

- ***if the Trial Office fails to make a contact***

  The Trial Office will liaise with the local study nurse if there is ever failure of contact with a participant, such that the materials are not delivered successfully, or a four-monthly form is not returned. In these circumstances the nurse will be supplied with full contact details for the participant, the 'best contact', and the general practitioner, and asked to clarify the situation. Any information being sought from a participant at this time may be most easily collected by telephone, but this will be left to the discretion of the local nurse.

- ***periodically during follow-up***

  The local study nurse will search local information systems for reports of new fractures or deaths amongst local trial recruits.

4.8 Flagging at Office for National Statistics

All participants will be flagged at the Office for National Statistics for notification of:

(i) death

(ii) cancer registration

5. DATA COLLECTION AND PROCESSING

Follow-up will continue for a median period of three years (range two to four years). Although further follow-up is anticipated, this is not part of this protocol.

Data from the various sources outlined above will be sent to the Trial Office in Aberdeen for processing. Staff in Aberdeen will work closely with study nurses to secure as complete and accurate data as possible. A random 10% sample of data will be double-entered to check accuracy. Extensive range and consistency checks will further enhance the quality of the data.

6. ANALYSIS PLANS

6.1 Ground rules for the statistical analyses

The statistical analyses will be based on all people randomised, irrespective of subsequent compliance with pill taking. The principal comparisons will be:

(i) all those randomised vitamin D versus all those not allocated vitamin D

(ii) all those randomised calcium versus all those not allocated calcium

(iii) all randomised vitamin D and calcium versus all randomised Vitamin D alone versus all randomised calcium alone versus all randomised placebo

Evidence will be sought for an interaction between vitamin D and calcium.

The analyses will be based on two denominators:

(i) all participants with data irrespective of length of follow-up, using 'time to an event' and multidecrement life-table analysis techniques

(ii) all those with follow-up to 24 months

6.2 Measures of outcome

The principal clinical outcome measure is:

- all new low-energy fractures (other than face or skull) or clinical, radiologically-supported, vertebral fractures reported.

Any apparent differences in fracture rates will be explored by subdivision into: proximal femoral, other lower limb / pelvis, distal forearm, other arm, clinical vertebral, and other fractures.

Other secondary outcome measures are:

- New radiologically-confirmed fractures
- Death after trial entry; the possible link between death and fracture will be examined in analyses of deaths occurring within three months of a new fracture
- General health status as measured by SF-12 and EQ-5D
- Hospital admissions after trial entry (number, length, place, and association with fracture)
- Change of residence category
- Falls (within five one-week window periods)
- Possible adverse effects (e.g. renal stones, gastrointestinal symptoms)
- New cancer registrations (Total, colon, breast, other)
- Deaths attributed to cardiovascular or cerebrovascular disease
- New cases of diabetes, taking oral hypoglycaemics and / or insulin

The ways in which these data will be displayed in the final report are illustrated in Appendix 11.

It is anticipated that other variables, such as bone density, genetic polymorphisms, and balance will be measured in explanatory studies and these will be described in separate protocols.

6.3 Timing and frequency of analyses

A single principal analysis is anticipated two years after the last person is recruited. If considered appropriate, follow-up of recruits will be extended at this time. The data and safety monitoring committee (see below) will determine the frequency of confidential interim analyses.

6.4 Secondary sub-group analyses

Sub-group analyses similar to the principal analyses will be performed after stratification by (a) the type of fracture sustained prior to trial entry (proximal femur, distal forearm, clinical vertebral, or other), (b) age at entry (70-74, 75-79, 80-84 and 85 or over), (c) sex, (d) latitude of recruitment centre (northern versus central versus southern), (e) time of enrolling fracture (within 3 months of recruitment or longer), (f) dietary calcium (high or low) and vitamin D exposure (high or low), (g) high or low weight (less than 55kg or not), and (h) level of compliance (completed two years or not). The Chi-squared test for heterogeneity will be used to explore any apparent differential effects. The principal outcome will be subdivided into categories of fracture, again to explore possible differential effects. Stricter levels of statistical significance ($2P<0.01$) will be sought, reflecting the exploratory nature of all these analyses.

6.5 Economic analysis

The type and extent of economic evaluation will crucially depend upon the clinical outcome of the trial:

(i) If vitamin D and calcium are shown to reduce fractures in equal amounts compared with the placebo, vitamin D will be the preferred therapy on cost grounds. Given the lower cost of vitamin D, it is very likely that resource savings will occur. Thus, the economic evaluation will mainly consist of quantifying the cost savings that will accrue in order to encourage implementation of the research findings.

(ii) If vitamin D alone is ineffective but calcium alone or in combination is effective, this may lead to a net cost to society. If this proves to be the case we will estimate the incremental cost per fracture prevented and per quality adjusted life year (QALY) gained.

(iii) If vitamin D is effective alone but is even more effective in combination with calcium then, again, the extra cost per fracture prevented and per QALY will be estimated to aid a decision about whether the additional effectiveness gained from the addition of calcium is worthwhile.

The underlying aim is to keep economic data collection as parsimonious as possible to minimise the burden for this elderly population.

Outcome Data

To generate a cost per QALY, data on utility or health gain are required and these will be gathered primarily using the EQ-5D. However, the EQ-5D is a relatively insensitive measure, particularly for the less severe fracture categories (eg Colles' fracture). The SF12 will therefore also be used to assist in estimating the utility values from the less disabling fractures.

Cost Data

The acquisition costs of calcium and vitamin D can be simply ascertained from published sources (eg MIMS), and different prices from different suppliers will be used in a sensitivity analysis.

To elicit subsequent costs two main methods will be used. Midway through the trial a questionnaire survey of all study participants will be used to describe subsequent costs (Appendix 12). This will provide data on use of NHS-funded resources, such as general practitioners', hospital doctors' and other NHS professionals' time, together with non-NHS resource use, such as contacts with social services, privately funded help and more informal care. Those who have had a further fracture will be divided into those who had fractured recently, those who have fractured in the previous 1 to 6 months, and those who fractured more than 6 months previously. They will be compared with the surveyed participants who have not fractured again, but who were recruited at the same time. Data on these representative (sub-) groups will be used as a basis for modelling such resource use amongst the study groups.

Whilst certain costs will increase should a patient return home after fracture (such as home help) the dominant cost is likely to be that incurred when a patient has to go into long-term care as a result of a fracture. This information on location and duration of care will be collected at each follow-up contact (i.e. every four months).

With respect to price data, published price estimates will be used. Two detailed studies of hospital hip fracture costs have been undertaken in Aberdeen and Cambridge [19,20]. When these studies have been adjusted to a common length of stay they give similar estimates (£4018 and £4808 per hip fracture). Therefore, these costs will be used to price acute hospital episodes of care for hip fracture. For Colles fracture, costs from a recently published costing study of osteoporotic fractures will be used[2]. For vertebral fractures, at some point in the trial, the incidence of clinically significant fractures amongst the whole study population will be calculated. If this incidence is sufficiently high to affect the relative costs of the interventions, a separate costing study of such fractures will be carried out. For other items of resource use, such as general practitioner consultations, social services and long-stay care we will use the price estimates generated by the Personal and Social Services Research Unit[21]. For visits to hospital doctors, we will use published tariffs for the cost of outpatient visits as a basis of estimation.

Finally, modelling will be used to extend the analysis beyond the time course of the trial.

7. SAMPLE SIZE AND FEASIBILITY

7.1 Sample size sought

The aim is to recruit about 6,500 people to the trial. This is based on a wish to identify a reduction of one fewer person per hundred allocated an active treatment sustaining a fracture each year over a median period of three years, if this was the true effect. Based on data from published trials in similar contexts the anticipated all fracture rate in the control groups is 15%. A total of 4000 participants would be needed in the analysis to have 80% power ($2P<0.05$) to detect an overall reduction to 12%. If the true effect is somewhat larger, say a 4% absolute benefit, the power will be over 90%. A trial of this size also has over 80% power to identify a 2% absolute difference in hip fracture rates (from 6% to 4%, or 5% to 3%).

The numbers sought have been inflated to 6,500 to take account of losses to follow-up. The main reason for 'loss to follow up' will be death. In the large Dutch trial[12] the rate was about 20% over three years, but we expect it to be higher overall (about 30%) because some of our participants will have sustained a recent proximal femoral fracture. Losses for other reasons, principally moving to other areas, are estimated from observations in one participating centre to be about 5%. The sample size has therefore been inflated by 35%.

7.2 Recruitment rates

The aim is to recruit an average of 65 participants per week over a two-year period. Recruitment will be primarily from out-patient clinics and inpatient fracture units, although additional patients may also be identified from medical records as having sustained an eligible fracture in the preceding two years. It is expected that 50% of eligible patients will agree to participate and so 6500 will need to be approached per year. In the United Kingdom, a centre serving a population of 500,000 would expect approximately 750 eligible new fracture attendances each year, of whom around a third will have sustained a proximal femoral fracture. Taking into account that some centres will be smaller, the trial will have about 15 centres recruiting at rates between 2 and 5 per week.

8. ORGANISATION

8.1 Local organisation

- Each collaborating centre will identify a ***clinical co-ordinator***. The responsibilities of this person will be to:
    1. establish the trial locally (for example, by getting agreement from clinical colleagues, facilitating local research ethics committee approval; identifying and appointing a local study nurse; and ensuring that all clinical staff involved in the care of people with fractures are informed about the trial)
    2. take responsibility for clinical aspects of the trial locally (for example, if any particular concerns emerge)
    3. notify the Trial Office of any unexpected clinical events which might be related to trial participation
    4. provide support and supervision for the local study nurse
    5. represent the centre at collaborators meetings

- Each clinical centre will appoint a ***study nurse*** to co-ordinate the day to day aspects of the trial. The responsibilities of this person will be to:
  1. keep local staff informed of progress in the trial
  2. keep regular contact with the local clinical co-ordinator, with notification of any problem or unexpected development
  3. to maintain regular contact with the Trial Office
  4. identify potential participants and keep a log of whether or not they are recruited (with reasons for non-participation)
  5. check eligibility, give information about the trial, and seek consent
  6. collect baseline data describing participants, and send these to the Trial Office
  7. supply initial materials to patients, if applicable
  8. telephone each person recruited two weeks after trial entry to check all is well and subsequently when judged necessary
  9. clarify the situation when the Trial Office fails to make a contact with a local participant, getting in touch by phone or a visit, if necessary
  10. seek further clinical details when a major trial event (such as a fracture or death) is reported to the Trial Office, even if this occurs in another hospital
  11. assist in the conduct of explanatory studies, if applicable
  12. provide support for participants in other ways if there are difficulties
  13. represent the centre at trial nurse meetings and collaborators meetings

8.2 Trial co-ordination

- *The Trial Office*

  The Trial Office is in the Health Services Research Unit at Aberdeen and gives day to day support to the clinical centres. It is responsible for collection of data (in collaboration with the local study nurses), data processing and analysis. It is also responsible for randomisation, despatch of trial materials to participants, and unblinding, as clinically necessary.

- *The Project Management Group*

  The trial is co-ordinated by its Project Management Group. This consists of representatives from six of the clinical centres, and representatives from the Trial Office. Observers may be invited to attend at the discretion of the Project Management Group.

- *The Steering Committee*

  The trial is supervised by an MRC Steering Committee. This is made up of three independent members selected by the MRC, together with those originally granted funds to mount the trial. Observers from the MRC and host university (University of Aberdeen) may also attend. Other members of the Project Management Group may attend as observers at the invitation of the Chair of the Steering Committee.

8.3 Data and safety monitoring

- *The Data Monitoring Committee*

  A data monitoring committee will be established. This will be independent of the trial organisers. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the data monitoring committee, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the data monitoring committee will advise the Steering Committee if, in its view, one or more of the randomised comparisons in the trial has provided both (a) proof beyond reasonable doubt[1] that for all or some types of patients one particular type of intervention is clearly indicated in terms of a net reduction in fracture risk without any increased risk of death (or clearly contraindicated because of a net increase in fracture risk or mortality), and (b) evidence that might reasonably be expected to influence materially the care of people who sustain a fracture by clinicians who know the results of this and comparable trials. The Steering Committee can then decide whether or not to modify intake to the trial. Unless this happens, however, the steering committee, project management group, clinical collaborators, and trial office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

Note:

[1] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criteria were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed (Peto R et al *Br J Cancer* 1976; 34: 584-612).

The frequency of interim analyses will depend on the judgement of the chairman of the committee, in consultation with the Steering Committee. Initially, the principal concern will be possible adverse effects. Data on new fractures will accumulate slowly so the committee is unlikely to be able to consider these reliably until some way into the trial.

- *Other safety concerns*

The incidence of adverse effects from the proposed dosage of vitamin D and calcium is anticipated to be very low - in the systematic review renal insufficiency or stones were reported for 4/4025 (0.1%) and gastro-intestinal disturbances for 93/3892 (2.4%).

Collaborators and participants may write to the chairman of the steering committee about any worries they may have about the trial. If concerns arise about particular side-effects or about particular types of participants, these will be relayed to the Chairman of the Data Monitoring Committee.

If clinically indicated, rapid unblinding of trial materials will be available through the trial office.

The Multicentre Research Ethics Committee for Scotland has approved the trial. The trial will be conducted according to the MRC Good Clinical Practice Guidelines (1998)[22].

9. FINANCE

The trial is supported by a grant from the Medical Research Council. Shire Pharmaceuticals Group plc will donate the trial materials, after manufacture by Nycomed Ltd.

10. EXPLANATORY STUDIES

The funds provided by the Medical Research Council are to conduct the main trial as described in this protocol. It is recognised, however, that the value of the study will be enhanced by smaller ancillary studies of specific aspects. Plans for some of these are being submitted to grant funding bodies. Further suggestions would be welcomed and should be discussed in advance with the Project Management Group, and agreed with the MRC Steering Committee.

11. INDEMNITY

The following is a statement from the UK Medical Research Council outlining their position on indemnity:

'The MRC as a sponsor of a trial or work involving human subjects accepts responsibility attached to its sponsorship of the work, and as such would give sympathetic consideration to claims for any non-negligent harm suffered by a person as a result of participating in a trial or other work. This would not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. The Council acts as its own insurer and does not provide advance indemnity cover for participants in MRC-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not that patient is participating in an MRC-supported study. The MRC does not accept liability for any breach in the hospital's duty of care, or for any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS trust or not.'

The calcichew, calcichew-D_3 forte, vitamin D, and matching placebos, carry a product indemnity provided by Shire Pharmaceuticals Group plc.

12. PUBLICATION

The success of the trial depends entirely on the wholehearted collaboration of a large number of nurses and doctors. For this reason, chief credit for the trial will be given, not to the committees or central organisers, but to all those who have wholeheartedly collaborated in the trial. The trial's publication policy is described in detail in Appendix 13. The results of the trial will be reported first to trial collaborators. The main report will be drafted by the Project Management Group, and circulated to all clinical co-ordinators for comment. The final version will be agreed by the Steering Committee before submission for publication, on behalf of the Collaboration.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies would not be submitted for publication without prior discussion with the Project Management Group.

Once the main report has been published, a lay summary will be sent to participants who have indicated they would like to receive one.

13. REFERENCES

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