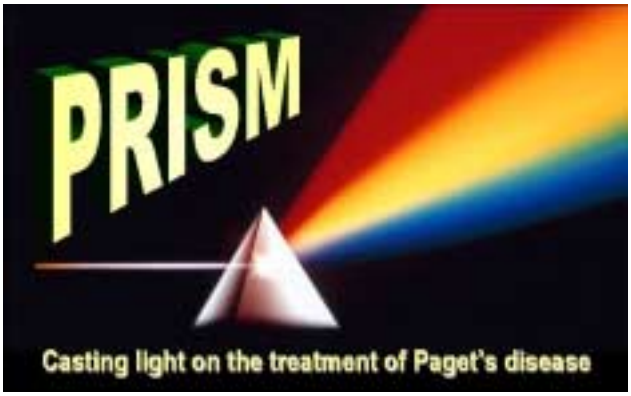


MULTICENTRE RANDOMISED CONTROLLED TRIAL OF SYMPTOMATIC VERSUS INTENSIVE BISPHOSPHONATE THERAPY FOR PAGET'S DISEASE (PRISM)

PROTOCOL

VERSION 2 - September 2001

MULTICENTRE RANDOMISED CONTROLLED TRIAL OF SYMPTOMATIC VERSUS INTENSIVE BISPHOSPHONATE THERAPY FOR PAGET'S DISEASE

This protocol describes a large UK multicentre trial (known as the PRISM trial) to evaluate the clinical and cost-effectiveness of symptomatic versus intensive bisphosphonate therapy for the management of Paget's disease. The trial is designed to be as convenient as possible both for those participating and those involved in the clinical care. Study nurses will provide local co-ordination in clinical centres.

1. THE REASONS FOR THE TRIAL

1.1 The burden of the problem

Paget's Disease is the second most common metabolic bone disease in the UK affecting up to 3% of the population above the age of 55 years [3]. Characterised by focal increases in bone turnover, Paget's disease is a cause of substantial morbidity, causing diverse symptoms such as bone pain, pathological fracture, deafness, bone deformity, and secondary osteoarthritis.

1.2 The rationale for testing intensive versus symptomatic bisphosphonate therapy

Bisphosphonates are regarded as the treatment of choice for Paget's disease; short term studies have shown that they improve bone pain and inhibit biochemical markers of bone turnover in Paget's disease, although the long term effects on disease progression are unknown [1; 4]. Recent studies have shown that new potent bisphosphonates like Alendronate and Risedronate are highly effective in suppressing accelerated bone turnover in Paget's disease and for the first time, it has become possible to suppress biochemical markers of increased bone turnover to normal in a high proportion of cases [6;8]. This has led to the suggestion that intensive therapy with these new potent bisphosphonates may be able to prevent long-term complications of the disease [7]. The long-term effects of bisphosphonate therapy on complications of Paget's disease are unknown however, and there is no evidence that suppression of bone turnover with bisphosphonates improves long-term clinical outcome in Paget's disease. Indeed, virtually all studies of bisphosphonates in Paget's have been short term and have used biochemical markers of bone turnover as the primary endpoint. It is now important to conduct a long-term study to determine if these new potent bisphosphonates

improve clinical outcome when compared with no treatment or symptomatic treatment with older, less effective therapies in Paget's disease.

1.3 The questions which this protocol will address

The trial described in this protocol will, therefore, examine whether intensive therapy with a potent bisphosphonate, sufficient to give long-term suppression of bone turnover, will be superior to symptomatic treatment in improving clinical outcome and preventing complications of Paget's disease.

2. TRIAL RECRUITMENT

Participant progress through the trial is summarised in Figure 1.

2.1 Who will be considered for trial entry?

The trial will involve people aged over 18 with symptomatic or asymptomatic Paget's disease (Paget's disease will be confirmed by standard clinical, radiographic, scintigraphic and biochemical criteria).

Potential participants will be identified by study nurses based in each clinical centre from amongst patients attending hospital bone clinics. The exact recruitment process is likely to be centre specific and may include the organisation of special review clinics for the trial. A log will be kept of patients meeting these criteria, describing the reasons if they are not subsequently recruited to the trial (Appendix I).

Figure 1: Summary of participant progression through the trial

STAGE	Action required by		FORMS
	Consultant	**Study Nurse/Trial Office**	***(to be returned to Trial office)***
Patient deemed potentially eligible	Eligibility determined by consultant and study nurse		Patient Assessment Form
Patient sent postal information		information sent by nurse in advance of clinic appointment	
		informs GP of approach	
Patient approached at clinic	Eligibility confirmed	approaches patient at clinic	
Patient agrees to participate		takes informed consent	Consent Form
		asks patient to complete baseline questionnaire	Questionnaire
	baseline clinical review	completes participant entry form	Participant Entry Form Baseline Clinical Review Form
		checks alkaline phosphatase	
Patient randomised		telephone randomisation	
	letter to GP recommending management	informs consultant, GP, patient	
4 month review	clinical review	completes Clinical Review form	Clinical Review Form
8 month review	clinical review	completes Clinical Review form	Clinical Review Form
12 month review	clinical review	completes Clinical Review form Questionnaire follow-up	Questionnaire Clinical Review Form
16 month review	clinical review	completes Clinical Review form	Clinical Review Form
20 month review	clinical review	completes Clinical Review form	Clinical Review Form
24 month review	clinical review	completes Clinical Review form Questionnaire follow-up	Questionnaire Clinical Review Form
28 month review	clinical review	completes Clinical Review form	Clinical Review Form
32 month review	clinical review	completes Clinical Review form	Clinical Review Form
36 month review	final clinical review	completes Clinical Review form Questionnaire follow-up	Questionnaire 3 year Clinical Review Form

2.2 Informing potential participants about the trial

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

2.3 Ruling out common reasons for exclusion

Amongst those who appear eligible for the trial, the following exclusions will apply:

- Patients with Paget's disease who are judged by the attending clinician to be unsuitable for inclusion in the study
- Patients who are unable or unwilling to give informed consent
- Patients who in the opinion of the attending physician are thought to have limited life expectancy (<1 year) due to malignancy or other serious illnesses.
- Patients who are currently or have within the last 3 months, been involved with another research project.

(NOTE: Current or previous treatment with Risedronate or other bisphosphonates is not an exclusion criterion.)

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 III). (If not, she will arrange to make contact again a few days 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. 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. A supplementary information leaflet containing contact details will be given to the participant upon consent and participants will be issued with a card confirming their participation in the trial, which can be carried with them at all times if they wish.

2.5 Information collected at trial entry

Once a participant has agreed to join the trial, the research nurse will record on standard forms:

Identifying and contact information (Appendix IV)

- Full name, address, telephone number
- Date of birth, gender
- NHS, hospital number and CHI number (if available)
- Marital status, woman's maiden name
- General Practitioner's contact details
- Consultant managing bone disease

Descriptive information (Appendix VI)

- Biochemistry (serum calcium, albumin, liver function (AST, ALT, γGT), bilrubin, serum creatinine, total serum alkaline phosphatase, biochemical markers of bone formation)
- Bones involved (including skull involvement) as determined by isotope bone scan
- Presence and site(s) of any bone deformity
- Presence / absence of bone pain
- Use of hearing aid
- Extent of deafness as assessed by audiometry (for patients with skull involvement only)
- Previous anti-Pagetic treatment including bisphosphonate, analgesics, anti-inflammatory and others
- Other previous bisphosphonate treatment
- Previous fracture history detailing fracture site(s) and whether related to Paget's disease
- Presence of osteosarcoma
- Family history of Paget's disease
- Age at diagnosis

(NOTE: The Laboratory normal range for biochemistry results will be obtained for each participating centre.)

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, including frequency and timing of follow-up contacts (both at clinic and postal contacts). The hospital case notes will be labelled at this time to indicate that the patient has been recruited to the trial.

TRIAL INTERVENTIONS

3.1 Symptomatic therapy (Figure 2)

Participants who are asymptomatic will be given no active treatment. Participants who have bone pain will be prescribed analgesics or anti-inflammatory drugs in the first instance and if these control symptoms adequately then no further treatment will be given. Analgesics and NSAID's will be prescribed at the discretion of the attending physician according to standard dose regimens. In participants whose bone pain persists despite analgesics / NSAID's, intermittent therapy with the bisphosphonates Tiludronate or Etidronate will be given in a dose of 400mg daily for 3 months. Participants unable to take oral medication may be given Calcitonin in standard doses for 4-6 weeks. Participants, whose bone pain persists despite these measures, may be given a course of Risedronate (30mg for 2 months) or a single infusion of intravenous Pamidronate (60mg). Whatever treatment is chosen, no attempt will be made to restore alkaline phosphatase values to normal and retreatment will only be given in the event of symptomatic deterioration, which is judged clinically to be due to Paget's disease.

3.2 Intensive therapy (Figure 3)

The aim of the intensive therapy arm of the trial will be to maintain serum alkaline phosphatase values within the normal range, irrespective of whether symptoms are present or not. This will be achieved with the potent, fourth generation bisphosphonate Risedronate given orally initially in a dose of 30mg daily for 2 months. Subsequent courses of therapy will be adjusted on an individual basis to maintain serum alkaline phosphatase values within the normal range. In participants who are intolerant of Risedronate, intravenous Pamidronate (repeated doses of 60mg up to a total of 360mg) will be given intermittently, to maintain serum alkaline phosphatase values within the normal range.

Figure 2: Recommended management for participants randomised to the symptomatic treatment arm

SYMPTOMATIC TREATMENT

Philosophy: No deliberate attempt made to restore alkaline phosphatase to within normal range

Recommended management:

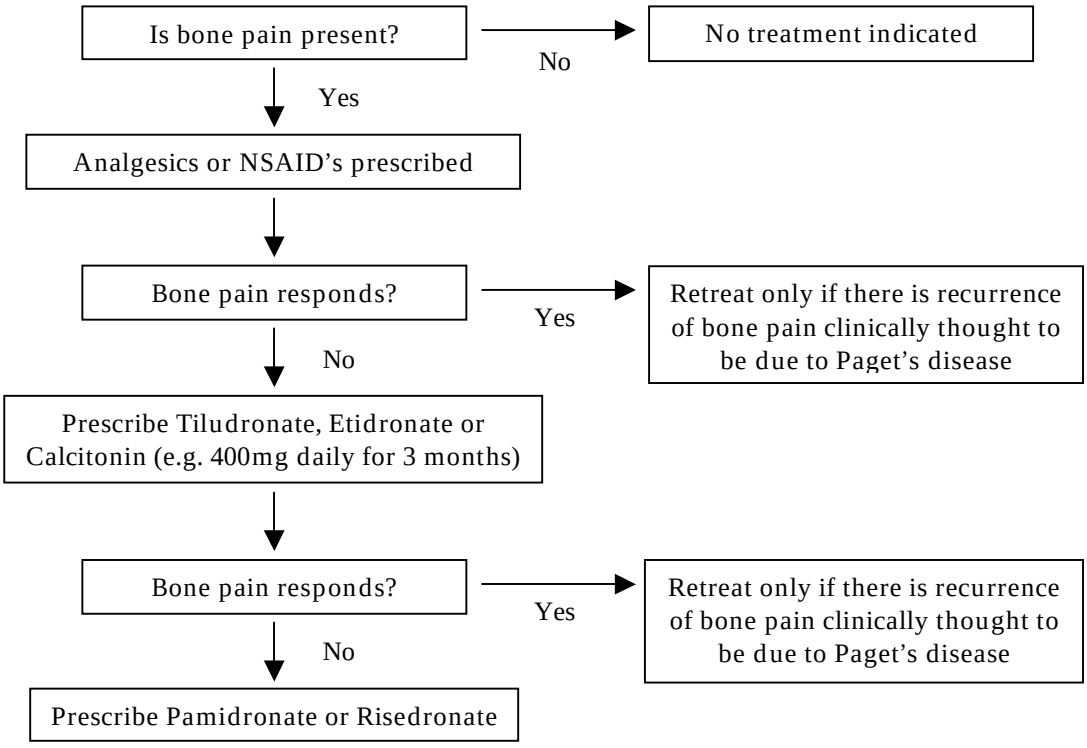
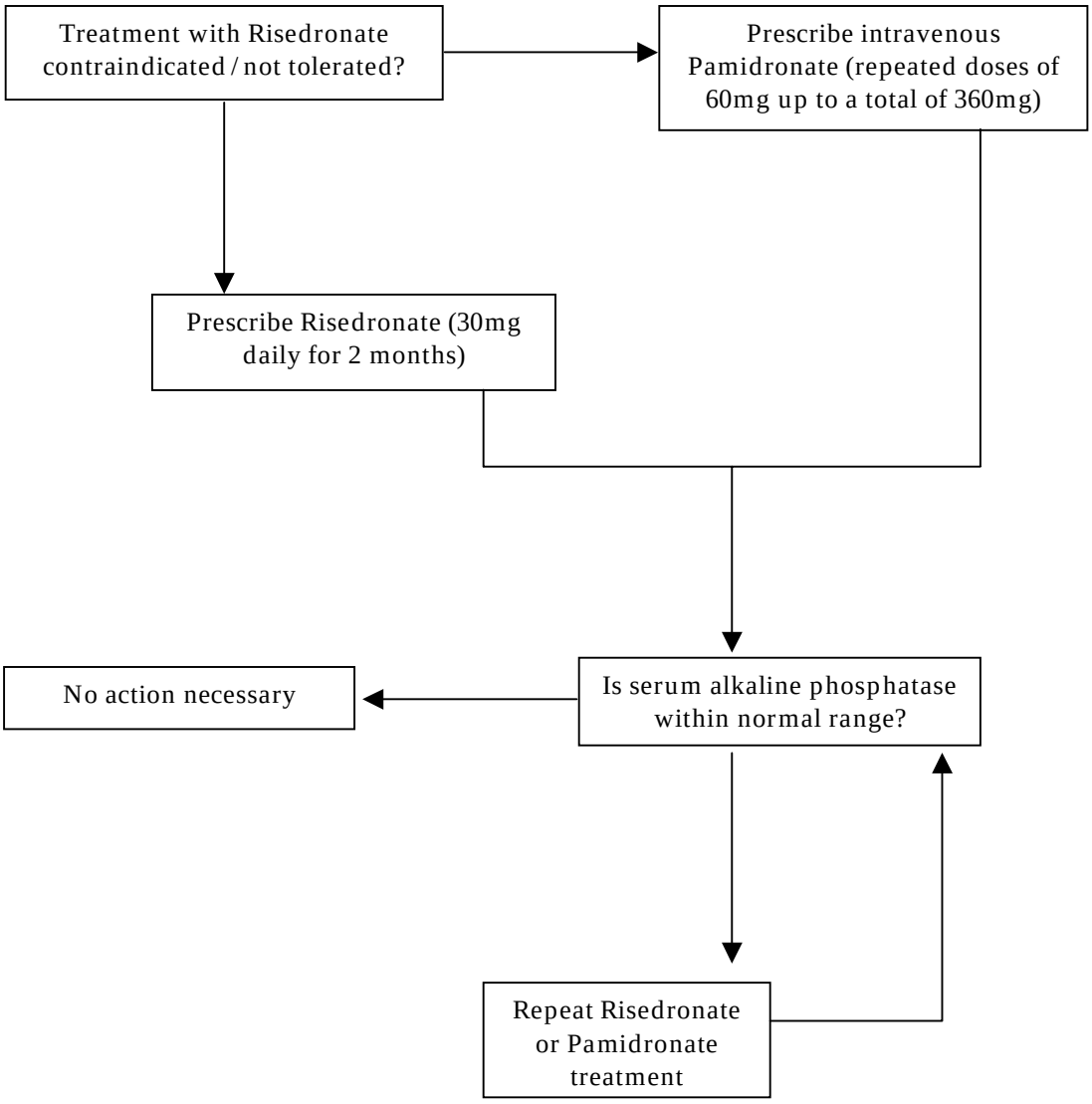


Figure 3: Recommended management for participants randomised to the intensive treatment arm

INTENSIVE TREATMENT

Philosophy: Aim to keep alkaline phosphatase within normal range

Recommended management:



3.3 Treatment allocation

The trial allocation will be computer-generated in the central Trial Office. After stratification by trial centre, balance in respect of other key prognostic factors (serum alkaline phosphatase values at baseline; previous bisphosphonate treatment (yes/no); presence of the disease in a weight bearing lower limb (yes/no); deformity of bone in weight bearing limb; presence of disease in the skull (yes/no); and presence of bone pain (yes/no)), will be ensured by the process of minimisation.

3.4 Duration of treatment

Treatment will be administered for a period of three years.

4. SUBSEQUENT ARRANGEMENTS

4.1 Informing key people

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

i) the ***general practitioner*** - informing the practice of a patient's participation in the trial and the implications for the practice. This letter (Appendix V) includes a brief description of the trial.

ii) the ***consultant*** – confirming participation in the trial and the allocated treatment

iii) the ***patient*** – confirming treatment allocation

4.2 Baseline clinical measurements (Figure 4)

All participants will undergo clinical evaluation and a radionuclide bone scan at baseline to document which bones are involved. The presence and severity of bone deformity in long bones will be assessed by the attending clinician on a 4-point empirical scale; 0- no deformity; 1 – mild deformity; 2- moderate deformity; 3-severe deformity. All participants will have routine biochemistry including serum total alkaline phosphatase and liver function tests. Disease activity will be defined on the basis of serum total alkaline phosphatase (sAP) values on a 4-point scale: inactive (sAP normal); mild (sAP up to 2x normal); moderate (sAP 2-4 times normal); severe (sAP > 4 times normal). Serum (and urine samples, where possible) will be collected for assessment of specific biochemical markers of bone formation (bone-specific alkaline phosphatase) and bone resorption (collagen N-telepeptides

Fracture history will be determined at baseline. All fractures will be reviewed by a radiologist

in participating centres and classified according to whether they occur in Pagetic or non-Pagetic bone. Radiological "pseudofractures" will not be counted as fractures.

Participants known to have Paget's disease of the skull on X-ray or bone scan will undergo audiometry to document presence and severity of hearing impairment. Weightbearing AP radiographs of the hip joints and knees will also be obtained to document the presence of osteoarthritis.

4.3 Four monthly clinic reviews (Figure 4)

Participants will be followed up in clinic on a 4-monthly basis. At each visit, the participant will be evaluated clinically, adverse effects noted (e.g. side effects of treatment), trial events recorded (eg fractures, the need for orthopaedic surgery, hospitalisations) and blood taken for serum alkaline phosphatase levels. The need for Risedronate treatment and re-treatment will be assessed on the basis of sAP levels taken at these visits. Data will be collected on a Clinical Review Form (Appendix VI). Serum and urine samples will be assessed for more specific biochemical markers of bone formation (bone-specific alkaline phosphatase) and bone resorption (collagen N-telopeptides). These will be assessed centrally if local facilities are not available.

4.4 Additional information sought at yearly intervals (Figure 4)

At yearly intervals, during a clinic visit, the patient will be asked to fill out a questionnaire (with help from the Study Nurse) (Appendix VII) which will collect the following information:

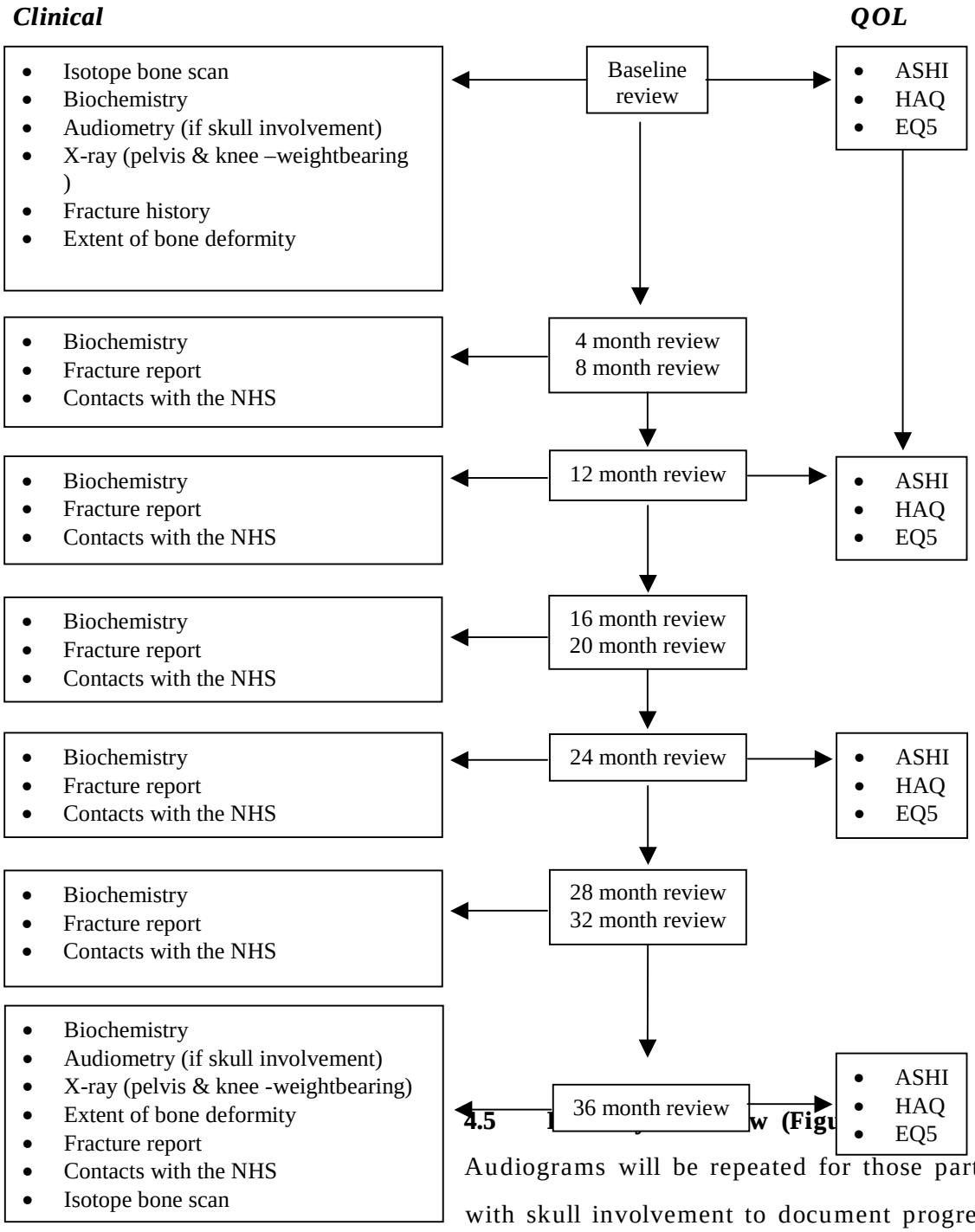
i) Fracture history. Participant - reported fractures will be validated by scrutiny of original hospital records, radiographs and GP records as previously described [10]. Radiological "pseudofractures" will not be counted as fractures.

ii) Disease-specific quality of life as measured by the Arthritis Specific Health Index (ASHI) which is based on the generic SF36 health measurement tool.

iii) Functional status as measured by the Health Assessment Questionnaire (HAQ).

iv) General health status utility as measured by the EuroQol (EQ5D).

Figure 4: Measurements to be taken at each time point



4.5 I w (Figu

Audiograms will be repeated for those participants with skull involvement to document progression of deafness. Isotope bone scans will be repeated, where possible, to document disease progression. Weightbearing AP radiographs of the hip joints and knees will also be repeated to look for evidence of development and/or progression of osteoarthritis. Progression of osteoarthritis will be assessed by measurements of osteophytes and joint space at the knees and hips, using standard techniques [2]. The requirement for joint replacement surgery for

osteoarthritis and orthopaedic surgery for other indications (e.g. osteotomy, spinal surgery) will also be documented.

4.6 Withdrawals

Study medication will be stopped or changed if any of the following events occur:

- The participant is unable, or unwilling to adhere to the randomisation group and treatment protocol.
- Adverse effects develop, considered by the attending physician to be due to the study medication, and to require discontinuation.
- Complications of Paget's disease develop (hypercalcaemia, progressive lytic lesions, and uncontrolled symptoms) in a participant assigned to "symptomatic" therapy, which are considered by the attending physician to require intensive bisphosphonate therapy.

Data from these participants will, however, contribute to the final analysis, as data will be analysed on an intention-to-treat basis (see section 6.1 below).

4.7 Roles of study nurses after recruitment

- *If death or severe illness is reported*

  The Trial Office will seek details from the study nurses if any major trial event including hospitalisation 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 participant or GP, such as Paget's 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. In these circumstances the nurse will be supplied with full contact details for the participant 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.

5. DATA COLLECTION AND PROCESSING

This protocol describes follow-up for the duration of the treatment period of 3 years. Further follow-up may be planned depending on initial findings.

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. The data from the various questionnaires will be scanned into a central database, using standardised software, and full verification checks will be undertaken at the time of data capture. 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 the randomised policies ie analysis will be by intention to treat.

6.2 Measures of outcome

The principal clinical outcome measures are:

- All new fractures (principally low trauma fractures)
- Progression of deafness
- Disease relevant health status

Other secondary outcome measures are:

- General health status
- Functional status
- All new orthopaedic surgical procedures
- Development and / or progression of osteoarthritis
- Contacts with the health service after trial entry (reasons, number, length and place)

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

Difference in fracture incidence between the treatment groups will be assessed by 'time to event' techniques. This may include Kaplan-Meier survival analysis or multi-decrement life table analysis. Comparison of treatment groups for continuous variables (eg audiometry and quality of life measures) will be by standard methods such as t-tests or Mann-Whitney U-tests depending on the distribution of the data, with ANCOVA methods to adjust the analysis for stratifying variables if applicable. Comparison of treatment groups for proportions will be by use of Chi-squared tests.

6.3 Timing and frequency of analysis

A single principal analysis is anticipated 3 years after the last person is recruited. The data monitoring and ethics 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) skull involvement (present or absent) (b) disease severity (severe or not severe) (c) bone deformity (present or absent). The Chi-squared test for heterogeneity will be used to explore any apparent differential effects. Stricter levels of statistical significance ($2P<0.01$) will be sought, reflecting the exploratory nature of all these analyses.

6.5 Economic Evaluation

We shall collect details of hospitalisations, requirement for orthopaedic or other surgery, details of concomitant medication use, and details of outpatient attendances and GP consultations for each treatment group. By doing this we shall be able to address issues such as cost-effectiveness of treatment by balancing the costs of giving intensive anti-Pagetic therapy with possible savings that may occur as the result of reduced need for other medications and surgery. This analysis will be conducted in collaboration with David Torgerson at the University of York.

7. SAMPLE SIZE AND FEASIBILITY

7.1 Sample size sought

The aim is to recruit about 1750 people to the trial, based on a wish to identify a halving of fracture rates between treatment groups and the wish to identify a reduction of a third of a standard deviation in the progression of deafness (assuming 25% of the trial population have skull involvement).

A total of 1500 participants would be needed in the analysis to have approximately 80% power ($2P<0.05$) to detect a reduction of 0.3SD in progression of deafness, and a trial of that size would have almost 90% power to detect the desired reduction in fracture rates.

For a trial of 1500 participants, statistical power for the primary comparisons of deafness, fracture and quality of life are presented in Table 1. Power calculations for fractures are based on an annual fracture rate of 2.6% with a 3-year follow-up [5]. As indicated above, progression of deafness assumes that 25% of enrolled participants have skull involvement. A previous study showed that Calcitonin resulted in a 1SD difference in progression of hearing loss when compared with no treatment [9]. Calculations for quality of life (QOL) comparisons are based

on expected changes in the ASHI adaptation of the SF-36. A previous study showed a ~20% difference between Alendronate and Etidronate treatment in a disease-specific QOL measure after 6 months [8]. The table shows that a trial sample size of 1500 participants gives excellent power to detect quite modest beneficial effects of treatment on quality of life and progression of deafness.

Table 1: Statistical power for primary outcome comparisons

Difference to be detected in each outcome	Power
50% difference in fracture rates	89%
0.15 SD difference in QOL	82%
0.3 SD difference in deafness	82%

(Note: 1500 participants and 5% significance level assumed)

The numbers sought have been inflated to 1750 to take account of losses to follow-up. The main reason for 'loss to follow up' in this elderly population will be death due to causes unrelated to Paget's disease. To accommodate for potential losses to follow up, the required sample size has therefore been inflated by 15%.

7.2 Recruitment rates

We anticipate that recruitment will be largely completed within the first 6 months of the study. This is because lead clinicians in the participating centres each have an established cohort of between 50-200 Pagetic patients under regular review, who attend clinics on a 3-6 monthly basis.

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, getting agreement from clinical colleagues, facilitating local research ethics committee approval; identifying and appointing a local study nurse)
  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
  6. Identify control participants for the DNA Repository Sub-study as appropriate.

- 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 and follow-up data, and send these to the Trial Office
  7. 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
  8. seek further clinical details when a major trial event is reported to the Trial Office, even if this occurs in another hospital
  9. provide support for participants in other ways if there are difficulties
  10. represent the centre at trial nurse meetings and collaborators meetings
  11. take and process blood and urine samples

12. arrange transportation of serum and urine samples for biochemical analysis and blood samples for the DNA Repository Sub-study.
13. organise hospital investigations

8.2 Trial co-ordination

- *The Trial Office*

  The Trial Office is based at the Health Services Research Unit, 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.

- *The Project Management Group (Appendix IX)*

  The trial is co-ordinated by its Project Management Group. This consists of grantholders and co-ordinators based in Aberdeen.

- *The Steering Group (Appendix IX)*

  This consists of the project grantholders, a non-professional representative from the National Association for the Relief of Paget's Disease (NARPD) and a representative from the Arthritis Research Campaign (ARC).

8.3 Data and Safety Monitoring

- *Data Monitoring and Ethics Committee*

  A data monitoring and ethics 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 light of these interim analyses, the data monitoring committee will advise the Project Management Group if, in its view, the trial has provided both (a) proof beyond reasonable doubt[1] that for all or some types of participants one intervention is clearly indicated in terms of a net improvement in outcome without any increased risk of

[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 these 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).

complications and (b) evidence that might reasonably be expected to influence materially the care of people with Paget's disease by clinicians who know the results of this and comparable trials, or if (c) evidence that for all or some types of participants no advantage is clearly indicated in terms of outcome and there is little likelihood of subsequently showing such treatment effects. The Project Management Group can then decide whether or not to modify intake to the trial. Unless this happens, however, the Project Management Group, clinical collaborators, and trial office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

- *Other safety concerns*

  Collaborators and participants may write to the chairman of the Project Management Group 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 and Ethics Committee.

9. FINANCE

The trial is supported by a grant from the Arthritis Research Campaign (ARC), with supplementary funding from Aventis Pharma, Proctor & Gamble Pharmaceuticals (makers of Risedronate), and the National Association for Relief of Paget's Disease (NARPD).

10. SUB-STUDIES (Appendix X)

In view of the unique nature of this cohort, we will attempt to obtain blood samples for DNA analysis to assess the role which genetic factors may play in determining natural history of the disease and its response to treatment. In addition to obtaining 30mls blood from each participant who consents, we shall seek to obtain samples from age and sex matched non-Pagetic controls from each centre. DNA from these samples will be archived in Aberdeen and made available to bone-fide investigators who wish to access the samples, subject to the approval of the trial steering committee.

11. INDEMNITY

This study involves standard NHS procedures undertaken within the NHS and is therefore covered by NHS indemnity.

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 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 Project Management Group 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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APPENDICES

APPENDIX I

PATIENT ASSESSMENT FORM

APPENDIX II

PATIENT LETTER OF INVITATION

PATIENT INFORMATION LEAFLET

APPENDIX III

CONSENT FORM

SUPPLEMENTARY PARTICIPANT INFORMATION LEAFLET

PARTICIPATION CARD

APPENDIX IV

PARTICIPANT ENTRY FORM

APPENDIX V

GP INFORMATION

GP LETTER OF APPROACH

GP LETTER OF RECRUITMENT

APPENDIX VI

BASELINE CLINICAL REVIEW FORM

CLINICAL REVIEW FORM

3 YEAR CLINICAL REVIEW FORM

APPENDIX VII

QUESTIONNAIRE

APPENDIX VIII

DUMMY TABLES

APPENDIX IX

PROJECT MANAGEMENT GROUP

STEERING GROUP

PROJECT MANAGEMENT GROUP

Marion Campbell	Aberdeen
Adrian Grant	Aberdeen
Stuart Ralston	Aberdeen
Anne Langston	Aberdeen

STEERING GROUP

Marion Campbell	Aberdeen
William Fraser	Liverpool
Adrian Grant	Aberdeen
Stuart Ralston	Aberdeen
Peter Selby	Manchester

NARPD Non-Professional Representative

ARC Representative

APPENDIX X

THE DNA REPOSITORY SUB-STUDY

X.I Sub-Study Protocol

X.II PRISM Participant Information Leaflet

X.III Control Participant Information Leaflet

X.IV Invitation Letter for Control Participants

X.V PRISM Participant Consent Form

X.VI Control Participant Consent Form

PRISM DNA Repository Sub-Study Protocol.

1. THE REASONS FOR THE SUB-STUDY

1.1 Scientific Background to the Sub-study

Genetic factors play an important role in the pathogenesis of Paget's disease. Familial aggregation has long been recognised to occur in Paget's disease (1) and clinical studies have shown that first degree relatives of Pagetic patients run a 10-15 fold risk of developing the disease themselves compared with population based controls (2,3). Moreover, many families have been described where Paget's disease is inherited in a simple autosomal dominant manner with a high degree of penetrance by the age of 55 (4-7). Recent studies have shown that activating mutations in the RANK gene are responsible for some instances of early onset Paget's disease and the Paget's disease-like condition familial expansile osteolysis (8). However RANK mutations appear to be rare in typical (late onset) Paget's disease (4,9) indicating the involvement of other genes. Despite the importance of genetic factors in Paget's disease, little is known about the molecular genetic-basis of disease susceptibility. Preliminary studies from Belgium have indicated that polymorphism of the osteoprotegerin gene (10) may contribute, but it is generally agreed that many other susceptibility genes remain to be discovered.

1.2 Outline of the Sub-study design

A case-control design will be used for the genetic part of the study, since the main objective is to determine if allelic variants of specific candidate genes are over-represented in patients with Paget's disease as compared with controls. In each centre, patients with Paget's disease who are enrolled in the PRISM trial will be asked if they are interested in agreeing to take part in the genetic sub-study. Patients who consent to take part will have blood samples (30ml) taken for DNA analysis at the time of routine clinic visits to avoid additional venepuncture. We anticipate that this blood sample will, on most occasions, be taken at the first follow-up visit at 4 months. This will give patients ample opportunity to reflect on genetic aspects of the study after enrolment to the main trial.

1.3 The aim of the sub-study

The PRISM trial provides an ideal opportunity to further investigate this important aspect of disease pathogenesis. Preparation of a DNA repository from PRISM offers the prospect of better defining the molecular-genetic basis of Paget's disease and discovering if allelic variants of candidate genes influence natural history of the disease or its response to treatment.

2. SUB-STUDY RECRUITMENT

2.1 Who will be considered for recruitment to the sub-study?

All patients who consent to participate in the main PRISM trial will be approached about the DNA Repository Sub-study.

PRISM participants enrolled in this sub-study at each centre will be age- and sex-matched with non-Pagetic controls. We anticipate that these controls will be identified by the lead clinician at each centre from routine clinic referrals who are being investigated for medical, rheumatological or orthopaedic conditions other than Paget's disease. The importance of local matching of cases and controls is supported by epidemiological studies that show marked variation in prevalence of Paget's disease within the UK (11). By matching cases with controls locally it is possible to account for geographical variation in susceptibility genes for Paget's disease.

2.2 Informing potential participants about the trial

The study nurse will describe the sub-study to PRISM participants backing oral information with the PRISM Participants Genetics Sub-Study Information Leaflet (Appendix X.II). Those approached may choose to involve an accompanying person.

Controls will be approached by letter (Appendix X.IV) enclosing a Control Participants Genetics Sub-study information leaflet (Appendix X.III) informing them about the study and asking them if they would like to take part. The nurse will then approach the patient at their next routine clinic visit. The nurse will describe the study backing oral information with the information leaflet.

2.3 Consent to participate- PRISM Participants

The study nurse will obtain the separate written consent of the participant for this sub-study. At their 1st follow-up clinic visit the nurse will ask if the potential participant is ready to decide whether or not to join the sub-study. If so, she will give the participant a consent form (Appendix X.V). 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. 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 PRISM Trial Office.

2.4 Consent to participate- Control Participants

At their next clinic visit, after the approach by letter, 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 X.VI). (If not, she will arrange to make contact again a few days 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. One copy will be given to the participant, another will be filed in the hospital case notes, and the third will be posted to the PRISM Trial Office.

3. COLLECTION OF BLOOD SAMPLES

3.1 Allocation of a Repository Number

Prior to the blood sample the study nurse will telephone the Trial Office and provide participant information on:

- Title
- First name(s)
- Surname
- Date of Birth
- Date of sample
- PRISM Study Number (if applicable)

The Trial Office will then issue a repository number. The repository number will be used to label blood samples.

3.2 PRISM Participants

Upon consent the nurse will take a blood sample of 30 mls. The sample will be taken at the time of the PRISM trial blood sample to avoid additional venepuncture. We will ensure that the total volume of blood taken in any single clinic visit (i.e. blood for DNA and routine investigations) does not exceed 50mls.

3.3 Control Participants

Controls who consent will be studied at their next routine clinic visit when a blood sample (30ml) will be taken for DNA analysis. Since the vast majority of controls will be undergoing routine biochemical and haematological screening as part of their usual clinical care, additional venepuncture would not generally be required, thus minimising discomfort to the patient. Since routine biochemical screens almost always include measurement of serum alkaline phosphatase levels, this will enable us to exclude individuals with asymptomatic Paget's disease from the control group (serum alkaline phosphatase is almost invariably elevated in untreated Paget's disease). We will ensure that the total volume of blood taken in any single clinic visit (i.e. blood for DNA and routine investigations) does not exceed 50mls.

4. Sample size and statistical power

The large sample size (n=1750) will give us excellent power to detect modest genetic effects on disease susceptibility. For example, assuming that we enrolled the projected 1750 patients and matched them with 1750 controls, we would have 90% power to detect an allele that increased the relative risk of Paget's disease by 25% (i.e. odds ratio 1.25), assuming an allele frequency of 0.5 in controls.

5. Ethical Issues

We do not feel that the genetic sub-study raises any major ethical issues. Patients and controls will be reassured that participation in the study does not constitute a genetic test as defined by insurance companies (see information sheet). They will also be reassured that they will not be identified by name in any report arising as the result of the studies.

References

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