NIHR Health Technology Assessment programme

NHS National Institute for Health Research

NETSCC, HTA

1 March 2012

The Health Technology Assessment programme is managed by NETSCC, HTA as part of the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton.

Alpha House, University of Southampton Science Park
Southampton SO16 7NS
Suggest a topic for research via our online form at www.hta.ac.uk/suggest

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639
email: hta@hta.ac.uk

www.hta.ac.uk

Technology Assessment Report commissioned by the NIHR HTA – Protocol

1. Title of the project:

Bone turnover markers for monitoring the response to osteoporosis treatment: the secondary prevention of fractures, and primary prevention of fractures in high risk groups.

2. Name of TAR team and 'lead'

Centre for Reviews and Dissemination/Centre for Health Economics Technology Assessment Group, University of York.

Dawn Craig,
Research Fellow,
Centre for Reviews and Dissemination,
University of York, Heslington, York
YO10 5DD
Tel: (01904) 321052
Fax: (01904) 321041
Email: dawn.craig@york.ac.uk

3. Plain English Summary

Bone turnover is the process of bone breakdown and renewal; under normal circumstances, these two parts of the process are balanced to ensure a constant bone density. If this balance is not maintained, bone structure, mass and strength may be altered. Osteoporosis is a disease in which bone mineral density is reduced as a result of increased bone breakdown and/or decreased bone renewal. Osteoporosis is thought to be responsible for 200,000 fractures every year, with broken wrists, hips and spinal bones the most common. The measurement of products in the blood or urine as a result of either bone breakdown or formation can be used to monitor bone turnover. These tests may therefore be useful in monitoring whether a patient has a change in bone turnover in response to osteoporosis treatment. To investigate this, we will undertake a systematic review to determine the clinical effectiveness, accuracy, reliability and reproducibility of these tests; i.e. how well changes in bone turnover markers correlate with changes in bone density and/or the incidence of fractures in people being treated for osteoporosis, how the use of bone turnover markers impact on patient management, and how the test results varies within and between patients. If the tests are shown to be effective in their ability to identify non-responders to treatment and influence patient management decisions and outcomes, the cost-effectiveness of using bone turnover markers in this

situation will be investigated; this investigation will also allow us to estimate the value of conducting further primary research to inform future clinical practice.

4. Background

Osteoporosis

Osteoporosis is a disease of bone in which bone mineral density (BMD) is reduced and bone microarchitecture disrupted. The cause of the disease is still not fully understood, and although younger people can be affected, the prevalence of osteoporosis increases with age.[1] As osteoporosis is associated with low bone density, bone density scanning (using dual energy x-ray absorptiometry (DXA)) has become the most commonly used diagnostic technique to detect osteoporosis prior to, or after, a fracture.[1] A DXA T-score of -2.5 or less (2.5 or more standard deviations below the peak bone mineral density of a young adult) is diagnostic of osteoporosis; osteopenia is diagnosed with a T-score between -1 and -2.5.[2-4]

People at risk of osteoporosis

Risk factors for osteoporosis include: increasing age; female gender; Caucasian; body mass index less than 19 kg/m^2; presence of rheumatoid arthritis; low oestrogen in women; anorexia nervosa or Turners syndrome; low testosterone in men; hyperthyroidism; parathyroid disease; Crohn's and coeliac disease; vitamin D deficiency, and long periods of immobility. Certain drugs can also place a person at risk of osteoporosis, for example: long-term glucocorticoid treatment and some cancer treatments. Smoking and excessive alcohol intake may also increase the risk of osteoporosis.[1, 4]

Risk of fracture

A reduction in bone mineral density result in the thinning of the trabeculae and an increase in the fragility of the bones.[5] Therefore, people diagnosed with osteoporosis have an increased risk of suffering low trauma (fragility) fractures. When bone mineral density is measured by DXA, a reduction of one standard deviation in bone mineral density is reportedly associated with a 50% to 150% increase in the risk of osteoporotic fracture.[6] As osteoporosis causes no symptoms, the first sign of the presence of the disease can be when a bone is broken. One in two women and one in five men over the age of 50 in the UK will fracture a bone, mainly as a result of skeletal fragility.[1] The most common fractures in people with osteoporosis are of the wrists, hips and spinal bones.[5, 7]

An assessment tool for assessing fracture risk, FRAX, has been developed by the World Health Organisation (WHO).[8] The factors taken into account when assessing a person's risk of fracture with this tool are age, gender, weight, height, previous fracture, parental history of

hip fracture, smoking status, the use of oral glucocorticoids, a diagnosis of rheumatoid arthritis, the presence of a disorder strongly associated with osteoporosis (such as type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease), alcohol consumption and bone mineral density as determined using DXA.[8]

Burden of illness

Approximately three million people in the UK have osteoporosis, with about 20% of women aged 60-69 affected.[1] Osteoporosis is thought to be responsible for 200,000 fractures every year, particularly broken wrists, hips and spinal fractures, and reportedly costs the NHS and government £6 million a day.[1, 9] Treatments for osteoporosis include bisphosphonates; strontium ranelate; calcitonin; parathyroid hormone peptides; denosumab; and selective oestrogen receptor modulators. Calcium (with vitamin D) may be used as adjunctive treatment.

Bone turnover

Bone turnover (remodelling) is the process of resorption followed by replacement of bone with little change in shape. Osteoblasts are responsible for bone formation and osteoclasts for bone resorption.

Osteoblasts are mature bone cells responsible for bone formation. They produce the organic portion of the matrix of bone tissue, osteoid, which is composed mainly of Type I collagen, and are responsible for mineralization of the osteoid matrix. Mineralisation fixes circulating calcium in its mineral form, removing it from the bloodstream. Repeated stress, such as weight-bearing exercise, results in the bone thickening at the points of high stress.

Osteoclasts break down bone, releasing the minerals, resulting in a transfer of calcium from bone fluid to the blood. The osteoclast attaches to the bone and secretes collagenase and other enzymes. Calcium, magnesium, phosphate and products of collagen are released into the extracellular fluid as the osteoclasts tunnel into the mineralized bone.

Implications of high bone turnover

Bone remodelling is thought to impact on bone strength as a result of reductions in bone volume and mineralisation, loss of trabeculae, reduction in trabecular connectivity, and the formation of resorption cavities and trabecular perforations.[10-11] Therefore, an increase in bone turnover is likely to be inversely correlated with bone mineral density, and may alter

bone architecture and porosity, increasing the risk of fracture beyond that due to reduced bone mineral density alone, and therefore be an independent predictor of fracture risk.[10-13]

Osteoporosis therapies

The most common treatments for osteoporosis are bisphosphonate drugs. Bisphosphonates inhibit the activity of mature osteoclasts and reduce the rate of resorption.[11] The most commonly prescribed bisphosphonate is generic alendronate. The recommended dose of alendronate is one 70 mg tablet per week, rather than 10mg daily originally prescribed, to reduce the incidence of gastrointestinal adverse effects and increase adherence. A strict technique must be adhered to when taking bisphosphonates, to ensure satisfactory absorption. They must be taken on an empty stomach first thing in the morning, whilst remaining upright to prevent reflux, at least 30 minutes before the first food, drink or other medication of the day. The tablet should be taken with plain water only; other drinks (including mineral water), food and some medicines are likely to reduce the absorption of bisphosphonates.[14] Intravenously administered bisphosphonates are available; the recommended doses are 3mg three monthly of ibandronate, or 5mg annually of zoledronic acid.[5] Other treatments for osteoporosis include: the selective oestrogen receptor modulator, raloxifene; the monoclonal antibody against RANK ligand, denosumab; the dual acting bone agent, strontium ranelate; and the recombinant form of parathyroid hormone, teriparatide.

Biochemical markers of bone turnover

There are a number of biochemical markers that have the potential to be used as indicators of the rate of bone turnover, which are by-products of either collagen synthesis or breakdown.[15] Some are no longer used, either being superseded by better technology, or due to methodological problems with the assay (urinary calcium; urinary hydroxyproline; tartrate-resistant acid phosphatase; total alkaline phosphatase; urinary pyridinoline (hydroxylysylpyridinoline); urinary hydroxylysine glycosides (galactosyl hydroxylysine); bone sialoprotein).

Biomarkers of bone turnover available in current clinical practice include:

Formation markers

- Procollagen type 1 amino-terminal propeptide (P1NP)
- Bone (Specific) Alkaline Phosphatase (BAP, BSAP or BALP)
- Osteocalcin (OC; bone Gla-protein)
- Procollagen type 1 C-propeptide (P1CP)

Resorption markers

- Urinary and serum C-telopeptide cross-link of type 1 collagen (CTX)
- Urinary and serum type I collagen N-telopeptide (NTX)
- Urinary deoxypyridinoline (DPyr; lysylpyridinoline (LP))

The Supra-Regional Assay Service (SAS) is a UK-based service for the analysis and clinical interpretation of a wide range of specialised diagnostics tests. Designated laboratories include Glasgow, Liverpool, St Mary's, and Sheffield.[16] Liverpool, St Mary's, and Sheffield offer the following bone turnover assays:

- Serum BAP
- Urine NTX
- Serum P1NP
- Serum CTX (Liverpool).
- Serum osteocalcin
- Urine deoxypyridinoline.

CTX, BAP, OC and P1NP are also available on standard biochemical platforms and many hospital labs are considering doing their own assays in house.

Bone turnover markers may have a number of potential uses, including:[13, 17]

1. Predicting bone loss
2. Identifying people at risk of osteoporosis and fracture
3. Predicting treatment response prior to commencement
4. Monitoring the response to osteoporosis treatment
5. Identifying patients not complying with osteoporosis treatment (including patients not taking the medication or not adhering to the instructions for administration)
6. Identifying over-suppression of bone turnover in patient on long-term osteoporosis therapy
7. Monitoring of people who have been on long-term treatment, or shown signs of over-suppression, and are taking a 'treatment holiday'.

The main focus of this systematic review will be: 4. monitoring the response to osteoporosis treatment.

Monitoring the response to osteoporosis treatment

There is currently no standard practice for the monitoring of patients receiving treatment for osteoporosis. The options include the use of repeated DXA, repeated measures of bone

turnover markers, clinical review, or a combination of these. The use of DXA to monitor the response to osteoporosis treatment has limitations. Firstly, detectable changes in bone density due to treatment can take up to two years to become apparent,[18] therefore the identification of non-responders to treatment is delayed. Secondly, there is limited access to the technology, and the test is relatively expensive (approximately £49 per scan). Thirdly there is evidence that there is limited value in regular monitoring of BMD in patients on bisphosphonate therapy.[19-20]

As stated earlier, the relationship between bone turnover and bone density and architecture means the rate of bone turnover may be an independent predictor of fracture risk;[10-13] this can be measured using one or more of the bone biomarkers listed above. However, it is still unclear whether changes in bone turnover detected by bone biomarkers are reliable surrogate measures for improved bone density and architecture, and consequently accurate predictors of future fracture risk. Two studies have suggested that bone markers can have independent predictive value in assessment of fracture risk.[21-22] If biochemical markers of bone turnover are reliable indicators of future fracture risk, their use may prove advantageous compared to serial BMD measurements, as not only are they non-invasive, relatively cheap, and the availability of auto-analysers in clinical chemistry laboratories increasing, but a response to treatment can be detected much earlier than with DXA. Changes in bone turnover rates have been detected in postmenopausal women within as early as two weeks after starting hormone replacement therapy;[23] the peak accuracy of changes in bone turnover markers to predict fracture risk in response to osteoporosis treatment may be later than this, between three and twelve months after initiating treatment, depending on the treatment and biomarker used.[24-27] The ability to identify treatment non-responders early within the treatment can be beneficial for patients by allowing early changes in management strategy if deemed necessary. The definition of treatment success varies depending upon the baseline risk of the patient being treated; in some patients a reduction in bone turnover would be considered a treatment success, but in others success may be a stabilisation of bone turnover. For all patients persistently raised bone turnover rates would be considered a treatment failure. The definitions used throughout this project will reflect clinical practice and be based upon evidence for least clinically significant change.

Adherence

Adherence with osteoporosis treatment is known to be poor, particularly to oral bisphosphonates which are often associated with gastrointestinal upset and sometimes oesophagitis.[28] According to the summary of product characteristics gastrointestinal upset with alendronate is common (occurring in 1% to 10% of patients), and oesophagitis rare (0.01%

to 0.1% of patients).[14] The incidence of gastrointestinal side effects associated with osteoporosis treatments is thought to be higher than that specified in the summary of product characteristics; NICE guidance states that up to one third of postmenopausal women may experience some type of gastrointestinal upset.[2-3] The occurrence of more severe oesophageal complications reported in post-marketing surveillance has been put down to taking alendronate with little or no water, laying down during or shortly after taking the tablet, continuing to take alendronate after the onset of symptoms, or pre-existing oesophageal disorders.[28] Patients are now given strict instructions on the technique for taking bisphosphonate drugs, as described previously. Adverse events have been reported in nearly 50% of patients, however, a 2006 Cochrane review showed no significant difference in gastrointestinal adverse events between bisphosphonates and placebo.[29] In addition to the potential for adverse events, bisphosphonates are poorly absorbed. Patients have to adhere to strict instructions on how to take oral preparations; if these are not followed, the effectiveness of the drug is likely to be reduced, and gastrointestinal side effects more likely to be experienced.[14, 30]

Bone turnover markers can identify treatment non-responders, therefore they may be a useful method for monitoring non-adherence with treatment, as this is a major reason for non-response.[13] Adherence to treatment can be improved with the introduction of treatment regimens that require less frequent administration of the medication,[31-36] and the availability of intravenously administered bisphosphonates.[30, 36] The move to the use of intravenously administered treatment based on the results of the bone turnover markers could have cost implications, anaphylaxis is a possibility and if experienced, hospitalisation may be required. Monitoring adherence through the use of bone markers is not a main focus of the systematic review, however, where this information is reported it will be extracted and summarised.

Variability in bone turnover markers and their use

Several factors can impact on the bone turnover marker levels, causing variability across samples, which can reduce repeatability and comparability, both within-patient and between patients. These include: specimen collection and storage;[18, 37-38] differences between analytical methods used;[18] temporal variations (diurnal, menstrual, seasonal);[18, 37-38] diet and fasting;[39] patient characteristics (age, gender, ethnicity);[37-38] concomitant medication other than osteoporosis medications (HRT, anabolic agents, glucocorticoids, anticonvulsants, gonadotrophin-releasing hormone (GnRH) antagonists, oral contraception);[37] and co-morbid conditions (renal impairment, liver disease, diabetes, thyroid disease, osteomalacia, systematic inflammatory diseases, degenerative joint disease, conditions causing immobility, eating disorders).[37-38]

The use of bone turnover markers varies greatly across the UK, both in terms of the test used and the frequency of its measurement. Several factors will need to be considered when choosing the bone turnover marker to be used, not least the availability of the assay methods. In addition, intra-patient variability for serum markers is lower than for urinary markers, some tests are more accurate when monitoring the response to specific treatments (e.g. CTX with bisphosphonates), whilst others have the advantage of not requiring the patient to fast prior to sampling (e.g. P1NP), or are less affected by diurnal variations (P1NP and BAP), and lower overall intra-individual variability than other bone markers (BAP).[40] Each of these tests also have disadvantages: CTX has a large circadian rhythm, therefore repeat sampling must be done at the same time of day, fasting is required prior to sampling, and the marker requires freezing soon after sampling as it can be unstable; BAP is affected by cross-reactivity with the liver form of alkaline phosphatase, limiting its use in patients with liver disease; and P1NP has a higher cost compared to other bone turnover markers.[40] Given the advantages that CTX, P1NP and BAP offer, and the availability of NTX, these are the bone turnover markers that will be investigated in the current review.

Summary

Bone turnover markers may be useful for identifying patients with osteoporosis who are not responding to treatment, which in turn will allow changes in management or treatment strategies to be implemented in a timely manner to ensure maximum benefit to the patient. An evidence synthesis using systematic review methodology will be used to investigate potential uses of bone turnover markers, and a decision analytical model developed if sufficient evidence is found to establish clinical effectiveness.

5. Decision problem

The review of the clinical evidence will focus on three key clinical areas:

- Clinical effectiveness: how does bone marker monitoring impact on the decision making process and patient outcomes?
- Test accuracy: how well do the results of the biomarker tests correlate with changes in bone density, architecture and incidence of fracture?
- Test reliability and reproducibility: how much do the results of tests vary within and between patients?

If clinical effectiveness can be established, a decision modelling will be developed and a expected value of perfect information (EVPI) analysis undertaken. Any EVPI analysis is

dependent on the ability to undertake decision modelling. The decision model will focus on the effect of bone marker testing on patient management decisions, and will address the question: 'Which monitoring regimen is the most cost-effective in informing treatment decision.' The treatments being considered are bisphosphonates (oral and intravenous), raloxifene, strontium ranelate, teriparatide, denosumab and no treatment.

6. Objectives

The primary aims of the systematic review are to determine the clinical effectiveness, test accuracy, test reliability and test reproducibility, of bone turner markers in people being treated with any bisphosphonate, raloxifene, strontium ranelate, denosumab or teriparatide for osteoporosis. If possible, a decision model will be developed to determine the cost-effectiveness of bone turnover markers for monitoring treatment response and making changes in patient management. If a decision model is produced, EVPI analyses will be used to determine the need for further research, identify the research questions critical to decision making, and help inform the design of future studies and to consider implementation issues.

7. Methods of synthesising evidence of clinical effectiveness

The review will be conducted systematically following the general principles recommended in CRD guidance for undertaking reviews in health care[41] and the PRISMA statement.[42]

Search strategy

The following databases will be searched to identify primary studies, relevant reviews and economic studies:

- CINAHL
- Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Reviews of Abstracts of Effects (DARE), Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED), and the Cochrane Central Register of Controlled Trials)
- EconLit
- EMBASE
- MEDLINE
- Science Citation Index

The following sources will be searched to identify grey literature and ongoing research:

- Clinical Trials.gov
- Conference Proceedings Citation Index - Science
- Controlled Clinical Trials.com

A draft search strategy for use with MEDLINE is provided in Appendix 1. No language or date restrictions will be applied during the search. Additional searches will be conducted as required.

Inclusion and exclusion criteria

Population

Studies eligible for inclusion will be those in adults (>18 years of age) either:

- Receiving any bisphosphonate, raloxifene, strontium ranelate, denosumab or teriparatide for the secondary prevention of osteoporotic fractures, regardless of the baseline pathology, or
- In any high-risk group being treated with any bisphosphonate, raloxifene, strontium ranelate, denosumab or teriparatide for the primary prevention of osteoporotic fractures.

Interventions

P1NP (serum), CTX (urinary and serum), NTX (urinary and serum), and BAP (serum).

Study designs

Effectiveness: RCTs where patients are randomised to a standard monitoring regimen (with or without DXA), or to standard monitoring regimen with additional monitoring with a bone turnover marker. Studies reporting the impact of bone marker test results on the decision making process for management of osteoporosis, that also report the subsequent rate of fracture in the population being assessed, will also be sought ('Decision studies').

Test accuracy: Studies comparing the results of bone marker tests to the results of bone biopsy or a composite reference standard of DXA and subsequent fracture outcome will be included. Given the nature of the review question, we believe it is unlikely that such studies will be available. So in addition we will include prospective studies that measure the association between bone turnover and bone density and/or fracture rates, and that report a correlation coefficient for this association. Prospective studies that evaluate changes in bone biomarkers in patients receiving one of the specified osteoporosis treatments, that provide sufficient data to produce a measure of the risk of fracture, or that report the results of multivariate regression analyses in which a biomarker of interest is an independent variable, will also be eligible for inclusion.

Reliability and reproducibility: Prospective controlled studies of serial bone marker measurements that report a measure of within and/or between patient variability, will be included.

Studies assessing the effectiveness of treatments for osteoporosis using changes in bone turnover biomarkers solely as an outcome will be excluded. Prognostic studies using biomarkers to identify patients at risk of osteoporosis and fracture at baseline, prior to commencing treatment, will also be excluded.

Outcomes

Effectiveness

RCTs and decision studies reporting either change in patient management strategies, the incidence of fracture and/or treatment adherence rates.

Test accuracy

Studies will have to report either:

- Estimates of diagnostic accuracy or sufficient data for these to be calculated
- A correlation coefficient, or sufficient data for this to be calculated, for the association between a bone turnover marker and bone density and/or the incidence of fracture
- The risk/incidence of fracture associated with the bone marker test results
- At least a p-value for a bone marker of interest that is used as an independent variable in a multivariate regression

Reliability and reproducibility

Studies reporting a measure for intra- and/or inter-patient variability in bone marker test results.

Data extraction strategy

Data extraction will be conducted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications of the same study will be extracted and reported as a single study. Where applicable and available, extraction will include data on: study details (e.g. study identifier/EndNote ID, author, year, country, setting, number of participants, and duration of follow up), patient characteristics (e.g. age, gender, ethnicity, duration of osteoporosis, risk group, concomitant renal/liver disease;

baseline P1NP, CTX and/or NTX levels), details of intervention (serum or urine, sample collection details; pre-sampling preparations/restrictions; sample storage details; assay used; adjustments for creatinine excretion; delay between sample collection and assay; single/serial measures; thresholds/cut-offs/reference values), study quality, and reported outcomes as specified above.

Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of included studies will be assessed using standard checklists[41] suitable for the study design, and adapted as necessary to incorporate topic-specific quality issues.

Methods of analysis/synthesis

Key study characteristics, patient outcomes and study quality will be summarised in a narrative and tables. Where appropriate, meta-analysis suitable to the data extracted will be employed to estimate a summary measure of effect based on intention to treat analyses. Potential sources of heterogeneity will explored:

- Subgroups of potential interest will be investigated if sufficient data are available, for example, post-menopausal women (overall and for specific age ranges if data are available), elderly, skeletal site (hip, spine, wrist)), and glucocorticoid-induced osteoporosis
- Sensitivity analyses will be conducted, where appropriate, to investigate potential sources of heterogeneity such as study quality, and differences in sample acquisition, storage and assay methods.

8. Methods of synthesising evidence of cost-effectiveness

• Identifying and systematically reviewing published cost-effectiveness studies

Systematic searches will be undertaken to identify existing published studies reporting the cost-effectiveness of bone-turnover markers for monitoring the response to osteoporosis treatment. The following databases will be searched: MEDLINE, EMBASE, CENTRAL and EconLit. In addition, searches of NHS EED and HEED will be carried out, along with a search of the Economics Working Papers archive (IDEAS).

Only full economic evaluations that compare two or more options, that meet the inclusion criteria for the clinical review and consider both costs and consequences (including cost-

effectiveness, cost-utility and cost-benefit analyses), will be included in the review of economic literature.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond *et al*. (2005)[43] and Philips *et al*. (2002).[44] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence. This information will be tabulated and summarised within the text of the report. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine the full economic evaluations that meet the inclusion criteria in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing economic evaluations.

• Development of a new decision-analytic model

If relevant effectiveness evidence can be identified (this may be in the form of an effect measure from an RCT or an appropriate predictive value from a test accuracy study), a decision-analytic model will be developed to determine the cost-effectiveness of bone turnover markers for monitoring treatment response and informing changes in patient management. One possibility is to use an existing peer-reviewed decision model developed by ScHARR (University of Sheffield) to estimate the cost-effectiveness of osteoporosis interventions[45] using the most recent work undertaken.[46] The model developer has agreed to provide access to this model for the purposes of this project (Personal communication: Dr Matt Stevenson). However, potential issues of academic in confidence data will need to be clarified before determining the final version of the model which will be used. If monitoring clinical effectiveness data and adherence data are identified then the Sheffield meta-model could be utilised.[47] The Sheffield meta-model is a simpler summary model of the original individual patient simulation (IPS) model. Cost data in the model will be updated using the most contemporary estimates from national databases (e.g. reference costs), and a literature review will be conducted to identify any relevant utility estimates in addition to those used in the existing model. Discounting will be undertaken at an annual rate of 3.5% on costs and benefits.

If test accuracy data is available and it is possible to utilise these data in the original IPS model then this will also be considered.[4, 19] Additional searching will be undertaken, if required, to identify relevant model structures from published cost-effectiveness analyses. These will be used to help inform this adaption of the IPS model. Further, if the use of the Sheffield model is not an option the published models identified will be utilised in the development of a new decision model.

The presence of any data gaps (e.g. resource use data) that may need to be filled during the development of the model will be identified from the literature identified during the systematic review process and additional searches if required. The primary outcome of the model will be the cost-utility of different monitoring strategies. The number of fractures prevented will also be reported. Cost-effectiveness will be established by estimating incremental cost-effectiveness ratios. The number of fractures prevented will also be reported. The risk-benefit uncertainties such as the clinical effect, adverse event and net-benefit uncertainties, and the model assumptions will be presented clearly.

To consider future research priorities in the NHS, the model will also be used to undertake analyses of the EVPI. Depending on whether a model is built on the fracture risk clinical effectiveness of monitoring strategies or test accuracy, EVPI analyses will be conducted for the relevant data in the model. EVPI represents the expected costs of decision uncertainty since perfect information would eliminate the possibility of making the wrong decision. Hence, EVPI for the overall decision problem represents the value of eliminating all uncertainty and EVPI for key parameters (termed partial EVPI) represents the value of eliminating uncertainties in particular subsets of parameters. Separate analyses will be undertaken to reflect the variability considered in the decision model itself if the model allows. Per patient EVPI estimates will be scaled up to reflect the relevant UK population size and will adopt an appropriate time-horizon. EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI provides an upper bound on the value of additional research. The objective of this analysis (termed partial EVPI) is to identify the model parameters where it would be most worthwhile obtaining more precise estimates. The results from the clinical effectiveness review and the EVPI results will be used to identify future research recommendations.

TAR Centre

The Technology Assessment Review team at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE). This Technology Assessment will be conducted by CRD.

CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). The centre maintains various databases, provides an enquiry service and disseminates results of research to NHS decision makers.

Recent TARs undertaken by CRD/CHE at York relate to the identification of the seizure focus in patients with refractory epilepsy being considered for surgery, aldosterone treatment for post-MI heart failure, treatments for bipolar disorder, sugammadex for the reversal of muscle relaxation in general anaesthesia and photodynamic therapy in the treatment of specified cancer sites.

Expertise in the TAR team and team contributions

Jane Burch, Research Fellow (jane.burch@york.ac.uk). Eight years experience in systematic reviews and systematic review methodology. Has worked on systematic reviews for NICE, the HTA programme and the NHS Cancer Screening Programmes. Will be responsible for all aspects of the clinical effectiveness review and co-ordinating the production of the final report.

Stephen Rice, Research Fellow in Health Economics (stephen.rice@york.ac.uk). Over seven years experience in economic evaluation and evidence synthesis. Will be responsible for the cost-effectiveness review, development of any cost-effectiveness model, and writing the economic sections of the report.

Aileen Neilson, Research Fellow in Health Economics (aileen.neilson@york.ac.uk). Involved with various health outcomes research and economic evaluation studies within the National Health Service setting in the UK, and against a broader European context. Will assist with the cost-effectiveness review, development of any cost-effectiveness model, and writing the report.

Huiqin Yang, Research Fellow (huiqin.yang@york.ac.uk). Six years experience in health services research. Has worked on systematic reviews for NICE and the HTA programme. Will assist with all aspects of the clinical effectiveness review and the writing of the final report.

Professor Roger Francis, Emeritus Professor of Geriatric Medicine, Institute for Ageing and Health, Newcastle University (r.m.francis@newcastle.ac.uk) and formerly Consultant Physician, Bone Clinic at Freeman Hospital, Newcastle upon Tyne. Involved in clinical research related to osteoporosis for 30 years and will provide clinical advice throughout the project commenting on the protocol, results and report.

Dr Peter Selby, Consultant Physician, Manchester Royal Infirmary, Honorary Senior Lecturer, University of Manchester (peter.selby@manchester.ac.uk). Involved in management of patient with osteoporosis and clinical research in bone disease for over 25 years and will provide clinical advice throughout the project, commenting on the protocol, results and report.

Lisa Stirk, Information Officer (lisa.stirk@york.ac.uk). Over twelve year's experience in literature searching for systematic reviews. Has worked on systematic reviews for NICE, the HTA programme and the British Thoracic Society. Will be responsible for devising the search strategy, carrying out the literature searches and maintaining the literature database.

Dawn Craig, Research Fellow (dawn.craig@york.ac.uk). Over eight years experience in economic evaluation and health technology assessment in a wide variety of areas. Contributed to the drafting of the protocol and will provide input at all stages of the project and comment on draft/final report. Has overall responsibility for the management of both the clinical and economic components of the project.

Advisory group

Dr Paul Holloway (paul.holloway@imperial.ac.uk). Clinical and academic interest in metabolic bone disease since training as senior registrar and clinical lecturer in Oxford in 1980's. Has run a metabolic bone clinic at St Mary's since 2004 and is acting director of the St Mary's SAS for bone markers. Will provide advice and comments on the protocol and report.

Professor John Kanis (w.j.pontefract@sheffield.ac.uk). An expert on metabolic bone diseases and director of the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield. He has a long experience in Health Technology Assessment, guideline development and WHO Scientific Study Group reports. Will provide advice and comments on the report.

Timetable/milestones

Submission of:	
Draft protocol to HTA	15th February 2012
Expected date for HTA to send comments on draft protocol	28th February 2012
Commence project	1st March 2012
Team submit assessment report to HTA	1st September 2012

References

1. Paker N, Bugdayci D, Tekdos D, Dere C, Kaya B. Relationship between bone turnover and bone density at the proximal femur in stroke patients. *J Stroke Cerebrovasc Dis* 2009;18:139-43.

2. Collette J, Bruyere O, Kaufman JM, Lorenc R, Felsenberg D, Spector TD, et al. Vertebral anti-fracture efficacy of strontium ranelate according to pre-treatment bone turnover. *Osteoporos Int* 2009.

3. Shidara K, Inaba M. [Bone metabolic marker for osteoporosis]. *Nippon Rinsho* 2009;67:927-31.

4. Claudon A, Vergnaud P, Valverde C, Mayr A, Klause U, Garnero P. New automated multiplex assay for bone turnover markers in osteoporosis. *Clin Chem* 2008;54:1554-63.

5. Anastasilakis AD, Polyzos SA, Avramidis A, Papatheodorou A, Terpos E. Effect of strontium ranelate on lumbar spine bone mineral density in women with established osteoporosis previously treated with teriparatide. *Horm Metab Res* 2009;41:559-62.

6. Sodi R, Hazell MJ, Durham BH, Rees C, Ranganath LR, Fraser WD. The circulating concentration and ratio of total and high molecular weight adiponectin in post-menopausal women with and without osteoporosis and its association with body mass index and biochemical markers of bone metabolism. *Clin Biochem* 2009.

7. Bonjour JP, Benoit V, Pourchaire O, Ferry M, Rousseau B, Souberbielle JC. Inhibition of markers of bone resorption by consumption of vitamin D and calcium-fortified soft plain cheese by institutionalised elderly women. *Br J Nutr* 2009:1-5.

8. Przedlacki J, Bartoszewicz Z, Ksiezopolska-Orlowska K, Kondracka A, Grodzki A, Bartuszek T, et al. [The role of bone metabolic markers in qualification for treatment of osteoporosis. Results of POMOST study]. *Endokrynol Pol* 2009;60:25-32.

9. Wislowska M, Jakubicz D, Stepien K, Cicha M. Serum concentrations of formation (PINP) and resorption (Ctx) bone turnover markers in rheumatoid arthritis. *Rheumatol Int* 2009.

10. Fassbender WJ, Godde M, Brandenburg VM, Usadel KH, Stumpf UC. Urinary Bone Resorption Markers (Deoxypyridinoline and C-Terminal Telopeptide of Type I Collagen) in Healthy Persons, Postmenopausal Osteoporosis and Patients with Type I Diabetes. *Adv Med Sci* 2009:1-6.

11. Recker RR, Marin F, Ish-Shalom S, Moricke R, Hawkins F, Kapetanos G, et al. Comparative Effects of Teriparatide and Strontium Ranelate on Bone Biopsies and Biochemical Markers of Bone Turnover in Postmenopausal Women with Osteoporosis. *J Bone Miner Res* 2009.

12. Kunchur R, Need A, Hughes T, Goss A. Clinical investigation of C-terminal cross-linking telopeptide test in prevention and management of bisphosphonate-associated osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;67:1167-73.

13. Bitto A, Polito F, Burnett B, Levy R, Di Stefano V, Armbruster MA, et al. Protective effect of genistein aglycone on the development of osteonecrosis of the femoral head and secondary osteoporosis induced by methylprednisolone in rats. *J Endocrinol* 2009;201:321-8.
14. Peris P, Ruiz-Esquide V, Monegal A, Alvarez L, Martinez de Osaba MJ, Martinez-Ferrer A, et al. Idiopathic osteoporosis in premenopausal women. Clinical characteristics and bone remodelling abnormalities. *Clin Exp Rheumatol* 2008;26:986-91.
15. Stoch S, Zajic S, Stone J, Miller D, Van Dyck K, Gutierrez M, et al. Effect of the Cathepsin K Inhibitor Odanacatib on Bone Resorption Biomarkers in Healthy Postmenopausal Women: Two Double-Blind, Randomized, Placebo-Controlled Phase I Studies. *Clin Pharmacol Ther* 2009.
16. Trento LK, Pietropolli A, Ticconi C, Gravotta E, De Martino MU, Fabbri A, et al. Role of type I collagen C telopeptide, bone-specific alkaline phosphatase and osteocalcin in the assessment of bone status in postmenopausal women. *J Obstet Gynaecol Res* 2009;35:152-9.
17. Garnero P. Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring. *Mol Diagn Ther* 2008;12:157-70.
18. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. *Int J Clin Pract* 2009;63:19-26.
19. Anastasilakis AD, Bhansali A, Ahluwalia J, Chanukya GV, Behera A, Dutta P. No difference between strontium ranelate (SR) and calcium/vitamin D on bone turnover markers in women with established osteoporosis previously treated with teriparatide: a randomized controlled trial. *Clin Endocrinol (Oxf)* 2009;70:522-6.
20. Kumm J, Ivaska KK, Rohtla K, Vaananen K, Tamm A. Urinary osteocalcin and other markers of bone metabolism: the effect of risedronate therapy. *Scand J Clin Lab Invest* 2008;68:459-63.
21. Bezza A, Ouzzif Z, Naji H, Achemlal L, Mounach A, Nouijai M, et al. Prevalence and risk factors of osteoporosis in patients with Parkinson's disease. *Rheumatol Int* 2008;28:1205-9.
22. Choi HJ, Im JA, Kim SH. Changes in bone markers after once-weekly low-dose alendronate in postmenopausal women with moderate bone loss. *Maturitas* 2008;60:170-6.
23. Zikan V, Stepan JJ. Marked reduction of bone turnover by alendronate attenuates the acute response of bone resorption marker to endogenous parathyroid hormone. *Bone* 2009;44:634-8.
24. Miyauchi A, Matsumoto T, Shigeta H, Tsujimoto M, Thiebaud D, Nakamura T. Effect of teriparatide on bone mineral density and biochemical markers in Japanese women with

postmenopausal osteoporosis: a 6-month dose-response study. *J Bone Miner Metab* 2008;26:624-34.
25. Binkley N, Silverman SL, Simonelli C, Santiago N, Kohles JD, Dasic G, et al. Monthly ibandronate suppresses serum CTX-I within 3 days and maintains a monthly fluctuating pattern of suppression. *Osteoporos Int* 2009.
26. Herrmann M, Wildemann B, Wagner A, Wolny M, Schorr H, Taban-Shomal O, et al. Experimental folate and vitamin B12 deficiency does not alter bone quality in rats. *J Bone Miner Res* 2009;24:589-96.
27. Lukaszkiewicz J, Karczmarewicz E, Pludowski P, Jaworski M, Czerwinski E, Lewinski A, et al. Feasibility of simultaneous measurement of bone formation and bone resorption markers to assess bone turnover rate in postmenopausal women: an EPOLOS study. *Med Sci Monit* 2008;14:PH65-70.
28. Minuk GY, Greenberg R, Uhanova J, Hawkins K, Leslie WD. Bone mineral densities in individuals with Gilbert's syndrome: A cross-sectional, case-control pilot study. *Can J Gastroenterol* 2009;23:431-6.
29. Delmas P, Munoz F, Black D, Cosman F, Boonen S, Watts N, et al. Effects of Yearly Zoledronic Acid 5 mg on Bone Turnover Markers and Relation of PINP with Fracture Reduction in Postmenopausal Women with Osteoporosis. *J Bone Miner Res* 2009.
30. Sugimoto T. [Progress in the treatment of osteoporosis]. *Rinsho Byori* 2008;56:887-93.
31. Karsdal MA, Byrjalsen I, Riis BJ, Christiansen C. Investigation of the diurnal variation in bone resorption for optimal drug delivery and efficacy in osteoporosis with oral calcitonin. *BMC Clin Pharmacol* 2008;8:12.
32. Engvall IL, Svensson B, Tengstrand B, Brismar K, Hafstrom I. Impact of low-dose prednisolone on bone synthesis and resorption in early rheumatoid arthritis: experiences from a two-year randomized study. *Arthritis Res Ther* 2008;10:R128.
33. Souberbielle JC, Cormier C. [Daily clinical practice: Biological testing in osteoporosis]. *J Soc Biol* 2008;202:275-80.
34. Bjarnason NH, Nielsen TF, Jorgensen HL, Christiansen C. The influence of smoking on bone loss and response to nasal estradiol. *Climacteric* 2009;12:59-65.
35. Fernandes CE, Zerbini C, Russo LA, Albernaz MA, Eis SR, Szejnfeld VL, et al. Effects of short-term risedronate on bone resorption and patient satisfaction in postmenopausal osteoporosis patients. *J Clin Densitom* 2009;12:77-83.
36. Jansen NW, Roosendaal G, Lundin B, Heijnen L, Mauser-Bunschoten E, Bijlsma JW, et al. The combination of the biomarkers urinary C-terminal telopeptide of type II collagen, serum cartilage oligomeric matrix protein, and serum chondroitin sulfate 846 reflects cartilage damage in hemophilic arthropathy. *Arthritis Rheum* 2009;60:290-8.

37. Massart F, Marini F, Bianchi G, Minisola S, Luisetto G, Pirazzoli A, et al. Age-specific effects of estrogen receptors' polymorphisms on the bone traits in healthy fertile women: the BONTURNO study. *Reprod Biol Endocrinol* 2009;7:32.
38. Katsarou O, Terpos E, Chatzismalis P, Provelengios S, Adraktas T, Hadjidakis D, et al. Increased bone resorption is implicated in the pathogenesis of bone loss in hemophiliacs: correlations with hemophilic arthropathy and HIV infection. *Ann Hematol* 2009.
39. Bjarnason NH, Henriksen EEG, Alexandersen P, Christgau S, Henriksen DB, Christiansen C. Mechanism of circadian variation in bone resorption. *Bone* 2002;30:307-13.
40. Brown JP, Albert C, Nassar BA, Adachi JD, Cole D. Bone turnover markers in the management of postmenopausal osteoporosis. *Clinical Biochemistry* 2009;42:929-42.
41. Tomimori Y, Mori K, Koide M, Nakamichi Y, Ninomiya T, Udagawa N, et al. Evaluation of pharmaceuticals with a novel 50-hour animal model of bone loss. *J Bone Miner Res* 2009;24:1194-205.
42. Diaz-Curiel M, de la Piedra C, Romero FI, Montero M, Gomez S, Lefort M, et al. Effect of risedronate on bone mass, remodelling and biomechanical strength in orchidectomized rats. *Horm Res* 2008;70:93-9.
43. Maimoun L, Simar D, Caillaud C, Coste O, Barbotte E, Peruchon E, et al. Response of calciotropic hormones and bone turnover to brisk walking according to age and fitness level. *J Sci Med Sport* 2009;12:463-67.
44. Bitto A, Burnett BP, Polito F, Marini H, Levy RM, Armbruster MA, et al. Effects of genistein aglycone in osteoporotic, ovariectomized rats: a comparison with alendronate, raloxifene and oestradiol. *Br J Pharmacol* 2008;155:896-905.
45. Ambroszkiewicz J, Gajewska J, Chelchowska M, Oltarzewski M, Laskowska-Klita T, Nowacka M, et al. [Concentration of osteoprotegerin, bone formation and resorption markers in patients with phenylketonuria]. *Pol Merkur Lekarski* 2008;25:57-60.
46. Navarro Casado L, Blazquez Cabrera JA, Del Pino Montes J, Almar Marques E, Chafer Rudilla M, Mateos Rodriguez F. [Clinical usefulness of biochemical markers of bone turnover in early postmenopausal women: two years longitudinal study]. *Med Clin (Barc)* 2008;131:333-8.
47. Stevenson M, Lloyd-Jones M, Papaioanno D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1-158.

Appendix 1

Draft search strategy for MEDLINE:

No limits applied to publication date/language of publication
MEDLINE dates: 1948 to August Week 1 2011

1725 records retrieved

1. (P1NP or PINP).ti,ab.
2. (procollagen adj3 propeptide).ti,ab.
3. (procollagen adj3 peptide).ti,ab.
4. (collagen adj3 propeptide).ti,ab.
5. (BSAP or BALP or BAP).ti,ab.
6. bone specific alkaline phosphatase$.ti,ab.
7. bone alkaline phosphatase$.ti,ab.
8. bone source alkaline phosphatase$.ti,ab.
9. (CTX or NTX).ti,ab.
10. crosslaps.ti,ab.
11. (telopeptide$ adj3 collagen).ti,ab.
12. (n-telopeptide$ adj3 collagen).ti,ab.
13. (c-telopeptide$ adj3 collagen).ti,ab.
14. bone turnover marker$.ti,ab.
15. bone metabolic marker$.ti,ab.
16. Biological Markers/ and exp "Bone and Bones"/
17. ((biochemical marker$ or biomarker$) adj2 bone$).ti,ab.
18. bone marker$.ti,ab.
19. or/1-18
20. exp osteoporosis/
21. osteoporo$.ti,ab.
22. 20 or 21
23. diphosphonates/ or alendronate/ or clodronic acid/ or etidronic acid/
24. (bisphosphonate$ or diphosphonate$).ti,ab.
25. (alendronate or alendronic acid or fosamax or actimax or alenato or arendal or berlex or brek or elandur or findeclin or lafedam or lendronal or marvil or maxtral or oseotenk or osteofene or osteonate or phostarac or regenesis or silidral or tilios or bonalen or cleveron or endronax or minusorb or norvic or osdron or ossomax or ostenan or osteofar or osteoform or osteoral or osteotrat or recalfe or terost or aldrox or fosval or holadren or leodrin or oseotal or osteofem or osteosan or alefos or fosalen or ostalert or bifosa or osteofos or fosalan or maxibone or adronat or alendros or dronal or genalen or onclast or drovitan or landrolen or sinfract or aldronac or aliot or denfos or fixopan or genalmen or osteodur or porosal).ti,ab.
26. (clodronate or clodronic acid or bonefos or loron or clodron or lodronat or ascredar or ostac or clastoban or lytos or clasteon or climaclod or clodeosten or clody or difosfonal or dolkin or moticlod or niklod or ossiten or osteonorm or osteostab or mebonat).ti,ab.
27. (etidronate or etidronic acid or EHDP or didronel or difosfen or detidron or osteodidronel or bonemass or osteotop or didronate or diphos or anfozan or biotredine or dralen or etidron or etiplus or feminoflex or maxibral or oflocin or osfo or ostedron or osteodrug or osteoton or ostogene or somaflex or sterodome or sviroxit or tilferan or dronate-os or etidrate or osteum).ti,ab.
28. (ibandronic acid or ibandronate or boniva or bondronat or bonviva or bandrobon or bonat).ti,ab.
29. (pamidronate or pamidronic acid or aredia or ADP sodium or aminomux or pamdosa or pandrat or pamisol or pamitor or osteopam or aredronet or pamidria or pamifos or pamidran or linoten or xinsidona).ti,ab.

30. (risedronate or risedronic acid or actonel or ductonar or ribastamin or ridron or risedon or optinate or risofos or benet or acrel).ti,ab.
31. (zoledronic acid or zoledronate or zometa or zomera or aclasta or reclast or zoldria).ti,ab.
32. (tiludronic acid or tiludronate or skelid).ti,ab.
33. (neridronic acid or neridronate or nerixia).ti,ab.
34. (olpadronic acid or olpadronate).ti,ab.
35. (cimadronic acid or cimadronate).ti,ab.
36. (piridronic acid or piridronate).ti,ab.
37. (icandronic acid or icandronate or bisphonal).ti,ab.
38. (minodronic acid or minodronate).ti,ab.
39. (raloxifene or biofem or ciclotran or evista or ketidin or loxifen or raxeto or optruma or bonmax or estroact or ralista or celvista).ti,ab.
40. Raloxifene/
41. (strontium ranelate or protelos).ti,ab.
42. (denosumab or prolia).ti,ab.
43. Teriparatide/
44. (teriparatide or forteo or forsteo).ti,ab.
45. (treatment or treat or treated or treats).ti,ab.
46. dt.fs.
47. or/23-46
48. 19 and 22 and 47
49. exp animals/ not humans/
50. 48 not 49