NCCHTA

09 July 2008

HTA Reference No. 06/31

TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

REVISED 11 November 2006

1. Title of the project:

A study to establish the feasibility of a trial that would investigate the clinical and cost-effectiveness of stopping bisphosphonate treatment after 5 years in post-menopausal women with osteoporosis who have already had a fracture.

2. Name of TAR team and 'lead'

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3. Plain English Summary

Osteoporosis is condition commonly found in older people. It can cause fractures which adversely affect the patient's quality of life and are also costly to treat. Under existing guidelines, treatment is recommended for patients who have already sustained an osteoporotic fracture provided that they also meet specific criteria in terms of their age, their bone mineral density, and other clinical risk factors. Bisphosphonates are recommended as the first line of therapy. These guidelines are currently being updated and are likely to recommend that treatment is also offered to some individuals who have not previously sustained a fracture; the lead of the proposed team undertook the cost-effectiveness analyses underlying this decision.

The object of the proposed project is to assess the feasibility and cost-effectiveness of a trial to estimate the long-term efficacy of bisphosphonate treatment in preventing osteoporotic fracture. Such a trial is needed because the long-term effects of bisphosphonates are unknown: most randomised controlled trials were of less than 5 years' duration. Recent cost-effectiveness analyses undertaken for NICE [1] assumed a 5-year treatment period with some residual benefit after treatment has been discontinued. However, as current guidance does not impose a limit on the duration of bisphosphonate treatment, clinicians may view this therapy as life-long. This approach has two disadvantages: it foregoes any possible residual benefit which would essentially be received without further cost and, potentially more importantly, it does not take account of concerns that, because of their mechanism of action, lengthy treatment with bisphosphonates may leave an individual with a weakened bone structure.

The proposed project will calculate the numbers of patients that would need to be recruited to each arm of the trial to detect surmised reductions in fracture rates, at proposed power levels. If the numbers are such that they may feasibly be recruited, the estimated expected value of the information garnered from the trial will be calculated and compared with the estimated costs of running the trial in order to determine whether it would be cost-effective to undertake the trial.

4. Decision problem

The initial question to be answered is whether a trial of the long-term effects of bisphosphonates in reducing fractures is feasible. Should it be deemed feasible, additional work will be undertaken on whether conducting the trial is a cost-effective use of the resources that would be required.

The trial under consideration would recruit postmenopausal women who have sustained a previous fracture and who have been taking bisphosphonates for close to 5 years. Once women have reached the end of the nominal 5-year treatment period, they would be randomised to receive either an additional 5 years treatment with bisphosphonates, or to receive placebo.

[1] http://www.nice.org.uk/page.aspx?o=273846

There are a number of factors that affect the feasibility of a trial that are currently unknown. These include, but are not limited to,

a) The number and profile of women on bisphosphonates, in terms of age, number of clinical risk factors, current duration of treatment with bisphosphonates and history of previous fracture.
b) Whether clinicians would feel it was ethical to place eligible women in the trial. A clinician may feel that bisphosphonates will continue to reduce the risk of fractures and that the patient should continue treatment. In this situation being randomised to a no treatment arm may be unethical. Conversely a different clinician may feel that the potentially weakened bone structure following long term bisphosphonate treatment represented a risk of increased fracture that was unethical to take and would not want the patient randomised to a bisphosphonate arm.
c) Whether eligible patients would wish to enrol in such a trial. For reasons similar to the clinician, a patient may have strong views regarding whether treatment should be continued or stopped.

In cases where a clinician or a patient has strong views regarding the future treatment of a patient, the patient could still be enrolled in an observational arm and the numbers of fractures recorded. However, such an approach is likely to be subject to the bias normally associated with observational studies. The possibility of using the Bradley-Brewin design [2] will be explored. This is a trial design in which the investigators seek each patient's consent for randomisation. Those who consent are then randomly allocated to treatment arms, while those who refuse because they have a preference for one or other treatment receive the treatment of their choice, and are asked only to consent to follow-up of their records. The outcome data are first analysed separately for those patients who were randomised to treatment and those who chose their treatment, and then finally all the results are combined. The advantage of using this design is that all patients can be included in the analysis, avoiding the loss of information or distortion, which might arise from excluding people who did not wish to be randomised to treatment. However, there is a risk of selection bias in the patient preference arms if patients more likely to have good outcomes are more likely to choose one type of treatment above another, or if treatment providers recommend different treatments to different types of patients. Moreover, the results may be difficult to interpret.

In the course of a number of NICE assessments of osteoporotic interventions, HTA reviews of osteoporotic interventions, and as a member of the NICE Guidelines Development Group for osteoporosis, the lead team member has built up relationship with a number of nationally recognised clinicians in the field of osteoporosis and patient representatives. It is proposed that these relationships be exploited in order to try and gauge the views of both clinicians and patients to the possibility of enrolment in a trial determining whether bisphosphonate treatment should be continued further than a 5-year time horizon.

The likely fracture rates for women in the trial can be calculated from models previously built by the lead reviewer. [1 3 4 5] Additionally, the mathematical model provides end-points

[2] Brewin CR, Bradley C. Patient preferences and randomised controlled trials. BMJ 1989;289:313-315
[3] Stevenson MD, Lloyd-Jones M, De Negris E, Brewer N, Davis S, Oakley J. *A systematic review and economic evaluation of interventions for the Prevention and Treatment of Postmenopausal Osteoporosis*. Health Technol Assess. 2005 (9) 22 pp 1 -160

of the costs of fracture and the quality of life of patients associated with relative risk of fracture.

The estimated fracture rates will give an indication of the number of patient years that will need to be observed for the trial to be powered to show a significant reduction in fracture incidence. For reference, two large randomised controlled trials of bisphosphonates [6] [7] recruited thousands of patients to statistically show a reduction in hip fracture. The numbers required for the proposed trial are likely to be greater than these, as the patients will be older, and more likely to die from other causes, and also because the residual effect of bisphosphonate treatment will persist throughout the 5 year period in the placebo arm.

The fact that more than one bisphosphonate is licensed for the treatment of postmenopausal osteoporosis will require more assumptions to be made in the analyses of the trial results. At present, NICE guidance allows alendronate, risedronate and etidronate to be prescribed, with the majority of clinicians preferring the former two due to more evidence from randomised controlled trials. The efficacies for each drug have been previously meta-analysed with different midpoint values, although the confidence intervals overlap.[8] For example, the efficacy for hip fracture are 0.62 (0.40 –0.98), 0.50 (0.05 – 5.34) and 0.74 (0.59 – 0.93) for alendronate, etidronate and risedronate respectively, although in previous cost-effectiveness analysis etidronate has been set to no effect due to the wide confidence intervals. More recent work for NICE has focussed solely on the two newer bisphosphonates (alendronate and risedronate) and these are the drugs that will be considered within the trial. It is likely that the trial would assume a class effect for these drugs when undertaking power calculations. However, if the majority of patients continuing on bisphosphonate treatment are taking one particular bisphosphonate (either alendronate or risedronate), the assumption that the results are applicable to all bisphosphonates may not necessarily be correct were there a real differential in efficacy.

If it is considered feasible to conduct a trial to look at the efficacy of bisphosphonate treatment beyond a 5 year treatment period, the mathematical model would be used to look at the likely benefits that can be accrued by conducting the trial. In order to do this, the most likely treatment approach, be it a 5-year treatment period or lifelong treatment, must be determined. We will liaise with clinicians to decide the ratio of patients that are expected to continue bisphosphonate treatment for life in the current climate of uncertainty around long-term effectiveness.

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[4] Stevenson MD, Brazier JE, Calvert NW, Lloyd-Jones M, Oakley J, Kanis JA. *Description of an individual patient methodology for calculating the cost-effectiveness of treatments for osteoporosis in women.* Journal of Operational Research Society. 56 (2005) 214-221.

[5] Kanis JA, Brazier J, Stevenson M, Lloyd-Jones M, Calvert NW,. *Treatment of Established Osteoporosis.* Health Technol Assess 2002 (6) No 29. pp 1 –1 46.

[6] Black, D. M., Cummings, S. R., Karpf, D. B., Cauley, J. A., Thompson, D. E., Nevitt, M. C., Bauer, D. C., Genant, H. K., Haskell, W. L., Marcus, R., Ott, S. M., Torner, J. C., Quandt, S. A., Reiss, T. F., and Ensrud, K. E. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 7-12-1996; 348 1535-1541

[7] McClung, M. R., Geusens, P., Miller, P. D., Zippel, H., Bensen, W. G., Roux, C., Adami, S., Fogelman, I., Diamond, T., Eastell, R., Meunier, P. J., Reginster, J. Y., and Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *New England Journal of Medicine* 1-2-2001; **344** 333-340.

[8] http://www.nice.org.uk/page.aspx?o=273738

In order to determine the long-term value of the trial, the number of times that treatment schedules are changed because of the evidence gained from the trial has to be estimated. For example, were the results using evidence from the trial to confirm that the current policy (assumed, here, to be all patients on lifelong therapy) is optimal, the gains from the trial would be small. Conversely, should the results show that the optimal policy was to stop treatment at 5 years, the benefits would include substantially reduced intervention costs, which could offset the costs of the trial over a long time period depending on the incremental cost-effectiveness of stopping treatment compared with continued treatment.

The optimal policy regarding the length of treatment on bisphosphonates is however firmly dependent on the results of the proposed trial, which are unknown. These would need to be forecasted, and the optimal policy calculated under a number of different estimates of efficacy.

Our proposed method to do this would be to elicit distributions of the likely ratio of fracture reduction after 5 years of treatment compared with the first 5 years of treatment. Elicitation is a developing science and has been used by the lead reviewer in the recent NICE review of the cost-effectiveness of single-use instruments to minimise the spread of iatrogenic vCJD. [9] We would use the relationship developed with clinicians to form an expert panel from which the elicited distributions would be formed. Ideally, elicitation is undertaken simultaneously with a number of clinicians in the same room, so that thoughts and data can be discussed. However, given the prominence of our clinicians, it is likely that elicitation would be undertaken one at a time and individual distributions merged to form a final distribution. The elicitation process would also formally address whether there was sufficient equipoise amongst clinicians to enter patients into the trial. If the generated distribution of assumed fracture prevention in the treatment period beyond 5 years is wide, then there will exist a good deal of uncertainty in the clinicians mind over the long term effects. If the distribution is relatively narrow with a significant effect on fracture reductions, then clinicians may not wish to remove patients from treatment. The final distribution would then be sampled from with the values entered into the mathematical model to determine the optimal policy regarding the duration of bisphosphonates treatment. The model would also provide a measure of the incremental cost-effectiveness between the optimal policy and the sub-optimal policy. In order to minimise the effects of the results being heavily influenced by one GP, the elicitation exercise will be undertaken with a minimum of 4 clinicians.

The sample size required to have sufficient power to test for an observed effect will depend on the assumed longer-term efficacy of bisphosphonates, as well as other epidemiological parameters such as the absolute risks of fracture in the patient group and the natural rate of mortality. Since estimating confidence intervals on the epidemiological data will prove difficult we will calculate the sample size assuming that only the efficacy of bisphosphonates will vary, with the other parameters remaining at their mean values. The predicted sample size required will be reported for a range of efficacy assumptions.

Data on the costs of running and disseminating the results from a randomised controlled trial will be sought from the published literature. Advice will also be taken from colleagues at ScHARR who have experience in running large trials.

[9] http://www.nice.org.uk/page.aspx?o=337325

5. Report methods for synthesis of evidence of clinical effectiveness

The systematic review of evidence of clinical effectiveness of alendronate, etidronate and risedronate which was carried out for NICE in 2003 [8] will be updated.

Relevant electronic databases will be searched to cover the period since the date of the previous searches in October/November 2002. Language restrictions will not be applied and, where possible, searches will not be restricted by publication type. However, due to the large number of potentially relevant references, an RCT filter will be used in the major databases. The Medline search strategy may be found in Appendix 1.

- **Inclusion criteria:**

- ***Participants:*** women with primary osteoporosis who are at least 6 months postmenopausal

- ***Interventions:***
  - bisphosphonates
    - alendronate
    - etidronate
    - risedronate

- ***Comparators:***
  - placebo
  - no treatment.

- ***Outcome measures:*** vertebral or nonvertebral fracture, associated effects, quality of life related to the study intervention, continuance and compliance

- ***Study design:*** randomised controlled trials. Trials will be accepted as RCTs if the allocation of subjects to treatment groups is described by the authors as either randomised or double-blind.

- **Exclusion criteria:**

Studies will be excluded if they include participants with secondary osteoporosis (eg related to therapy with corticosteroids), or draw their participants exclusively from patients with specific diseases known to affect fracture rates (eg Parkinson's disease).

Studies that are considered methodologically unsound will be excluded from the review

- **Data extraction strategy**

Data will be extracted independently by one reviewer using a standardised data extraction form based on that proposed by the NHS Centre for Reviews and Dissemination [1010] (see Appendix 2). Studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion.

[10] NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews.* York: University of York; 2001

- **Quality assessment strategy**

Methodological quality of trials which meet the inclusion criteria will be assessed using the tool developed by Gillespie et al.[1111] This tool is selected because it was designed specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis.

The quality assessment tool included the following items:

1. adequacy of randomisation, and masking of randomisation
2. blinded assessment of outcomes - whether outcome assessors were blind to subjects' treatment allocation
3. withdrawals - whether the outcomes of people who withdrew were described and included in the analysis
4. comparability of groups at baseline
5. confirmation of diagnosis of hip or other appendicular skeleton fracture
6. method of diagnosis of vertebral fracture.

- **Methods of analysis/synthesis**

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using a random effects model, using Review Manager software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

6. Report methods for synthesising evidence of cost-effectiveness

- **identifying and systematically reviewing published cost-effectiveness studies**

The mathematical model used in the currently ongoing NICE assessment to evaluate the cost-effectiveness of interventions for osteoporosis [1] has been constructed by the lead of the project team. This, however, uses a confidential algorithm from a yet to be published WHO report, which relates clinical risk factors to overall fracture risk. It is unclear whether permission would be granted for the use of the algorithm in this project. If it is not granted, the overall risk factor would need to be calculated from age, fracture history and BMD alone as in previous reports. No review of other economic models will be undertaken.

- **evaluation of costs and cost-effectiveness, which may include development of a *de novo* economic model**

The costs and utilities in the current model have been recently updated for work undertaken for the Guideline Development Group. These will be used in the analyses. The model structure will be amended where appropriate to take into consideration factors specific to this

[11] Gillespie, W. J., Avenell, A., Henry, D. A., O'Connell, D. L., and Robertson, J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *The Cochrane Library* 2001; **2** 2ROM.

study. This will include, but is not limited to, extending the time horizon of the model and changing to a discount rate of 3.5% for both benefits and costs.

Methods for estimating qualify of life, costs and cost-effectiveness
The key economic outcomes from this review are cost per QALY gained. Costs and utilities will be taken from ongoing work for the Guidelines Development Group, whilst the efficacy of treatment will be updated from the review previously undertaken to include any new trials of alendronate, risedronate or etidronate that may have been published.

Sensitivity analyses will be undertaken to identify the key parameters that determine the cost-effectiveness of the duration of treatment. Multivariate Monte Carlo methods will be undertaken to generate information on the likelihood that each treatment is optimal and to estimate the incremental net benefit of the optimal treatment. Once the expected value of information of the trial is known, the likelihood of whether conducting the trial is likely to be cost-effective can be estimated.

7. Expertise in this TAR team

- **TAR Centre**

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost effectiveness of health care interventions, in a short timescale, for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence. A list of our publications including all osteoporosis publications can be found at: http://www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports. Much of this work, together with our reviews for the international Cochrane Collaboration, underpins excellence in health care worldwide.

- **Team members' contributions**

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Speciality: Protocol development. Analysing the feasibility of the trial and calculating the number of patients that need to be recruited. Developing the mathematical model to evaluate the cost-effectiveness of longer treatment periods. Calculating whether the proposed trial would be cost-effective. Overseeing the project.

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Speciality: Protocol development. Identification of relevant trials, quality assessment, data extraction, data entry, data analysis and review of background information and data relating to clinical effectiveness.

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Speciality: Retrieval of papers and help in preparing and formatting the report.

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All correspondences should be sent to Dr Matt Stevenson (Project Lead)

8. Competing interests of authors

None

9. Timetable/milestones

Progress report (to NCCHTA)
Assessment Report (simultaneously to NICE and NCCHTA)

Draft protocol	**11th August 2006**
Commissioning decision	**1st November 2006**
Progress report	**31st January 2007**
Draft assessment report	**28th Feb 2007**
Assessment report	**31st May 2007**

Note the relatively long duration between the commissioning decision and the production of a draft assessment report. This is due to the likelihood of delays in contacting the key clinicians, awaiting the results from the updated systematic review and acknowledging that the project lead will be simultaneously completing another NICE review.

10. Appendices

APPENDIX 1: MEDLINE SEARCH STRATEGY

#1	Exp osteoporosis/
#2	Osteoporo$.tw
#3	Bone diseases, metabolic/
#4	or/1-3
#5	(Bone adj6 densit$).tw
#6	Bone density/
#7	(Bone or bones).mp
#8	Exp densitometry/
#9	Tomography, x-ray computed/
#10	Densit$.tw
#11	9 and 10
#12	8 or 11
#13	7 and 12
#14	5 or 6 or 13
#15	Colles' fracture/
#16	Exp hip fractures/
#17	Spinal fractures/
#18	15 or 16 or 17
#19	Fractures/
#20	Colles$.tw
#21	(Hip or hips).tw
#22	(Femur adj6 neck).tw
#23	(Femoral adj6 neck).tw
#24	(Spine or spinal).tw
#25	Vertebra$.tw
#26	Lumbar vertebrae/
#27	Or/20-26
#28	19 and 27
#29	Fractur$.tw
#30	((Fractur$ adj6 colles$) or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$).tw
#31	29 or 30
#32	14 or 18 or 28 or 31
#33	4 and 32
#34	Randomized controlled trial.pt
#35	Controlled clinical trial.pt
#36	Randomized controlled trials/
#37	Random allocation/
#38	Double blind method/
#39	Single blind method/
#40	or/34-39
#41	Clinical trial.pt
#42	Exp clinical trials/
#43	((Clin$) adj25 (trial$)).ti,ab
#44	((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab

#45 Placebos/
#46 Placebos.ti,ab
#47 Random.ti,ab
#48 Research design/
#49 or/41-48
#50 Comparative study/
#51 Exp evaluation studies/
#52 Follow up studies/
#53 (Control$ or prospectiv$ or volunteer$).ti,ab
#54 Prospective studies/
#55 or/50-54
#56 40 or 49 or 55
#57 33 and 56

APPENDIX 2: DATA EXTRACTION FORM

Study & Design	Data Extraction	
Trial	Review Details	
	Author, year	
Study design	Objective	
	Publication type (i.e. full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	Interventions	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group	
	T2: Control group	
	Intervention site (health care setting, country)	
	Duration of intervention	
	Length of follow up	
	Study Characteristics	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	
	Numbers included in the study	
	Numbers randomised	T1: T2:
	Population Characteristics	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	

	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean years)	
	Gender (male/female)	
	Mean BMD	
	Mean no of fractures	
	Other information	
	Were intervention and control group comparable?	
	Outcomes	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	
	Analysis	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Compliance with study treatment	
	Adherence to study treatment	
	Results	
	Overall survival	
	Vertebral fractures	
	Nonvertebral fractures	
	Toxicity/adverse effects	
	Health-related quality of life	
	Cost information	
	Other information	
	Summary	
	Authors' overall conclusions	

	Reviewers comments	

APPENDIX 3: QUALITY ASSESSMENT TOOL

	Score
Was randomisation to the study groups blinded?	
not randomised	0
states random but no description or quasi-randomised *(ie allocation by date of birth, hospital record no, admission dates, alternately etc)*	1
small but real chance of disclosure of assignment *(eg sealed envelopes)*	2
method does not allow disclosure of assignment *(eg assigned by telephone communication, or by indistinguishable drug treatments randomly precoded by centralised pharmacy)*	3
Were assessors of outcome blinded to treatment status?	
not mentioned	1
moderate chance of unblinding of assessors	2
action taken to blind assessors, or outcomes such that bias is unlikely	3
Were the outcomes of patients who withdrew described and included in the analysis?	
not mentioned or states number of withdrawals only	1
states numbers and reasons for withdrawal, but analysis unmodified	2
primary analysis based on all cases as randomised	3
Comparability of treatment and control groups at entry	
large potential for confounding or not discussed	1
confounding small; mentioned but not adjusted for	2
unconfounded; good comparability of groups or confounding adjusted for	3
For hip or other appendicular skeleton fracture	
not applicable	0
no confirmation of diagnosis	1
x-ray confirmation of diagnosis	3
For vertebral fracture	
not applicable	0
inadequately described method	1
radiological method: uses anterior/posterior height ratio	2
radiological method: uses anterior, middle and posterior height in criteria OR reports radiologically confirmed clinical events only	3
Total methodology score (actual score as %age of possible score)	