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A Critical Structured Review of Economic Evaluations of Interventions for the Prevention and Treatment of Osteoporosis

Mark Sculpher
David Torgerson
Ron Goeree
Bernie O'Brien

DISCUSSION PAPER 169

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Mark Sculpher[*]

David Torgerson[*]

Ron Goeree[†]

Bernie O'Brien[†]

[*] **Centre for Health Economics, University of York, UK**

[†] **Centre for Evaluation of Medicines, Dept of Clinical Epidemiology and Biostatistics , McMaster University, Canada**

ABSTRACT

Osteoporosis is a major cause of morbidity, mortality and resource cost amongst the elderly population. Hip fracture is the most serious of the osteoporotic fractures, with approximately 10-20% of patients dying within six months of sustaining a fracture. Furthermore, hip fractures are the most expensive manifestation of osteoporosis, incurring about 87% of the total costs of osteoporotic fractures. This public health and economic burden is likely to increase in developed nations due, in part, to ageing populations. In addition, there is strong evidence that the age-specific incidence of fracture is rising. There are a number of treatments which can be used to prevent fracture including hormone replacement therapy (HRT), bisphosphonates, vitamin D and calcium. These interventions have been used for primary prevention, secondary prevention and the treatment of established osteoporosis.

This Discussion Paper details the results of a structured review, the purpose of which was to identify and critically appraise economic evaluations relating to interventions for osteoporosis. The focus of the work is a critical assessment of the methodology of those studies. A total of 16 economic evaluations was identified on the basis of a computerised search of three bibliographic databases. All studies were based on decision analytical models and all took the form of cost-effectiveness analysis. Seven studies were from the US and four from the UK. The majority of studies focused on either primary prevention alone (seven) or both primary and secondary prevention where high-risk women were identified on the basis of bone mineral density screening (seven). Most studies considered the cost-effectiveness of HRT.

Most of the published studies conclude that treatment using HRT is relatively cost-effective among symptomatic women or women who have had a prior hysterectomy. In contrast, for asymptomatic women, the results are more equivocal. The most recent cost-effectiveness analysis was undertaken by the National Osteoporosis Foundation (NOF) which makes the explicit assumption that HRT is the treatment of choice. For women unwilling or unable to take HRT, the next recommended treatment was alendronate; should alendronate not be tolerated, calcitonin was recommended.

Many of the models included in the review exhibit methodological weaknesses which suggest their results should be treated with some caution. One of these concerns the dearth of formally elicited health state preference data from patients or members of the public: only two studies in the review derive preferences empirically rather than use the authors' judgement. A second limitation of many studies is the inappropriate application of cost-effectiveness decision rules with the frequent use of average cost-effectiveness ratios. Areas of methodological controversy, such as whether or not to include costs unrelated to osteoporosis in life-years added as a result of treatment, increase uncertainty regarding how to interpret the results of the studies.

1. INTRODUCTION

1.1 Background

Osteoporosis is a major cause of morbidity, mortality and cost amongst the elderly population [20]. The main population group affected by osteoporotic fractures is elderly, caucasian women. The estimated remaining lifetime risk of fracture of 50 year old caucasian women has been estimated (from North American data) to be 17.5%, 15.6% and 16% for the hip, spine and forearm respectively [60]. Hip fracture is the most serious of the osteoporotic fractures, with approximately 10-20% of patients dying within six months of sustaining a fracture. Furthermore, hip fractures are the most expensive manifestation of osteoporosis, incurring about 87% of the total costs of osteoporotic fractures [60].

The financial cost to society of osteoporotic-related fractures is particularly large. In the United Kingdom, it has been estimated that the cost of fractures occurring in women over the age of 50 is in excess of £700 million per annum [26]. In EU nations, the annual cost of osteoporosis has recently been estimated to exceed 9 billion ECUs [31], whilst in the USA the burden of fractures has been estimated at $13.8 billion [34]. These estimates may understate the problem as one of the most common fractures - vertebral - is rarely diagnosed. Despite this, such fractures will incur some costs to society through repeated physician consultations due to back pain, the use of pain relieving medications and increased use of the physical therapies and care services.

This public health and economic burden is likely to increase in developed nations due, in part, to ageing populations. In addition, there is strong evidence that the age-specific incidence of fracture is rising [44]. Furthermore, the public health impact of osteoporosis is probably greater than originally assumed as recent evidence suggests that, with the possible exception of skull fractures, most fractures occurring in elderly caucasian women are associated with low bone mass [45,58,71].

1.2. Types of osteoporosis

The World Health Organisation (WHO) [91] defines osteoporosis as:

"a progressive systemic skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"

The WHO has based its definition of osteoporosis, and hence diagnosis, around the use of bone mineral density (BMD). Bone mineral density is a normally distributed clinical variable and there is no obvious diagnostic risk threshold whereby fractures are more likely to occur. Despite this, the WHO has defined the following types of osteoporosis based on individuals' BMD compared with that of the young normal mean. Hence, low bone mass - or osteopenia - is said to be present if an individual's BMD lies between -1 to -2.49 standard deviations

below the young normal mean (i.e. T-score of -1 to -2.49[1]). Osteoporosis, meanwhile, is diagnosed if BMD falls below a T-score of 2.5, whilst established osteoporosis is when an individual has a T-score of less than 2.5 *and* at least one documented fragility fracture, usually of the hip, spine or wrist.

Whilst the above clinical definition has been accepted, it should be emphasised that, for the patient, low bone mass is asymptomatic, which, by itself, incurs no health-related quality of life (HRQL) penalty. The act of measuring bone mass may, theoretically, detract from a person's HRQL, by causing anxiety, if they are found to have low BMD. However, the only empirical study which has attempted to measure this aspect of patient management detected no difference in anxiety levels between women with high and low bone mass [79].

The most important aspect of osteoporosis is its clinical expression in terms of fractures, which are likely adversely to impact on patients' HRQL. Having low bone mass merely increases a patient's relative risk of sustaining a fracture. However, a patient with multiple fracture risk factors (e.g. low body weight, smoker, family history and prior fracture) may actually have a higher absolute risk of fracture compared with an individual whose only risk of fracture is low BMD. From an economic perspective, this issue is important because it may be more cost-effective to treat an individual with multiple fracture risk factors compared with a patient with only one risk factor or low BMD.

1.3 Preventing osteoporosis

There are a number of treatments which can be used to prevent fracture. These interventions have been used for one or more of the following roles[2]:

- Primary prevention: in asymptomatic women with no apparent osteoporosis or elevated risk of the condition, to reduce their risk of its onset in later life.
- Secondary prevention: in asymptomatic women who have been shown to have BMD sufficiently low to place them at elevated risk of fracture, to slow down the decline (or restore) BMD and hence reduce the risk of fracture.
- Treatment: in women known to have osteoporosis and who have already experienced one or more fracture(s), to reduce the risk of further fractures.

Table 1 summarises the effectiveness and UK costs of the most common anti-fracture treatments available. Despite the clinically proven effectiveness of these treatments, they are probably underused. For example, a recent study set within the UK showed that, even when women have had a clinically diagnosed vertebral crush fracture, less than 50% are offered a pharmaceutical therapy and, one year after fracture, 60% are not using any drug which

[1] T-scores represent a number of standard deviations relative to a young adult normal mean. The widely used alternative - the Z score - compares a person's BMD with an age-adjusted mean. Hence, the proportion of women defined as having low BMD by Z-score is constant, whilst with T-scores it increases with age.

[2] This approach to classifying prevention and treatment is widely used in the clinical literature. In principle, the key distinction is between primary and secondary prevention, where the latter can be sub-divided on the basis of a continuum of risk factors.

beneficially affects bone metabolism [76]. In principle, preventive treatments can be used in this patient group: trial data for one of the bisphosphonates (alendronate) used on patients with established osteoporosis (i.e. 1 or more vertebral fractures plus low BMD), who were, therefore, at high risk of subsequent fracture, showed it to be statistically significantly more effective than placebo in reducing subsequent hip fracture [4]. Therefore, for alendronate at least, current evidence would suggest that it is a more effective treatment for patients with established disease. Whilst HRT has been shown to be effective in a small trial among postmenopausal women with prior vertebral fractures [57], the most recent study of HRT failed to show any anti-fracture efficacy [47].

Table 1: Summary of treatments for fracture prevention (in comparison with no treatment)

Treatment	Vertebral fracture effect	Appendicular fracture effect	Annual treatment cost	Side effects
HRT [57]	60% ↓ RCT	30-50% ↓ Hip, Colles CC	£23 → £168	↑Breast cancer, breast pain, unwanted menstruation, ↓ IHD ?
Bisphosphonates				
Etidronate [74]	50% ↓ RCT	34% ↓ Hip, 19% ↓ Colles CC.	£160	?
Alendronate [4]	50% ↓ RCT	51% ↓ Hip, 48% ↓ Colles RCT	£335	Gastrointestinal problems
Calcium + vitamin D [16,18]	31% ↓ RCT	30% ↓ Hip, 60%↓ all non vert RCT	£120	-
Calcitriol [75]	46% → 70% ↓ RCT	50% ↓ Wrist RCT	£160	Hypercalcaemia
Calcitonin [66]	75% ↓ RCT	24% ↓ Hip CC	Nasal*	↓ acute pain
Hip protectors [54]	N/A	50-70% ↓ Hip, RCT	£70	Uncomfortable in hot weather

* Not available in the UK

RCT = randomised controlled trial CC = case control

From an economic perspective, the choice of treatments for patients at risk is partly dependent on their cost. Patients with established disease have a much higher absolute risk of fracture compared with patients who have osteoporosis or osteopenia. Therefore, all things being equal, the cost per averted fracture will be lower among higher risk patients compared with those with a lower absolute fracture risk. Hence, it makes sense from the perspective of costs, to target the most expensive treatments at those patients at highest risk. Furthermore, even if a treatment is relatively inexpensive, it may be best to reserve its use for

the highest risk patients if it has any undesirable side-effects. For example, HRT increases breast cancer risk and alendronate is associated with gastrointestinal complaints. If a patient's absolute fracture risk is low, then giving these agents to such patients could be inefficient in the sense that they may reduce HRQL more from the side-effects than they increase it through fracture avoidance.

1.4 Aims of the review

Given the burden of osteoporosis, and the potentially widespread use of these interventions - many of which have high acquisition costs - for long periods of time, there has been a number of attempts over the last two decades or so to assess their cost-effectiveness relative to other uses of health care resources. The increasing need for economic data, in some countries, to support applications for public reimbursement of pharmaceutical products is a further factor that has stimulated economic evaluation in this area [12,19].

Economic studies in osteoporosis have been constrained by the availability of adequate clinical data, and they have typically taken the form of decision analytical models. Models offer a valuable framework for synthesising clinical, resource use and valuation data from a range of sources, together with plausible assumptions, and for assessing the sensitivity of results to particular key parameters [2,6,30,42,72]. For interventions where clinical effectiveness has been measured over a relatively short period, but cost-effectiveness ultimately rests on long-term costs and benefits, models offer a means of extrapolating clinical measurements over time [11,70]. In addition, where measurement of effectiveness is in terms of intermediate clinical end-points (which predominate in regulatory drug trials), models can provide a way of making a link to the ultimate measures of benefit that are necessary for cost-effectiveness analysis, such as life expectancy or quality-adjusted life expectancy [11,70].

As for all types of economic evaluation, modelling-based analyses should be carefully assessed for the adequacy and appropriateness of their methods. This is particularly important given the lack of consensus of what constitutes 'good practice' in many aspects of cost-effectiveness research [29]. Furthermore, many economic models are lacking in their clarity and the explicitness of their assumptions, and peer-review of this form of evaluation requires further development [73]. For these reasons, it is important that those seeking to draw policy conclusions from cost-effectiveness models, or to develop their own analyses in a given area, should be aware of the empirical and methodological strengths and weaknesses of published studies.

This document details the results of a structured review, the purpose of which was to identify and critically to appraise economic evaluations relating to interventions for osteoporosis. The focus of the work is a critical assessment of the methodology of those studies. The document is divided into the following sections. Section 2 details the methods used in the review. Section 3 details the results of the review and is split into a brief summary of the studies identified in the review; a consideration of the empirical details of studies, in

particular relating to clinical assumptions and data sources; and the methodological issues raised by the studies. Section 4 offers some conclusions. Given their prominence, Section 3 also contains a summary of, and comment on, the recent US guidelines for osteoporosis published by the National Osteoporosis Foundation.

2. METHODS OF THE STRUCTURED REVIEW

2.1 Inclusion criteria

All economic evaluations relating to osteoporosis were included. The term economic evaluation was taken as including studies which have considered all the important costs and effects of an intervention in comparison with one or more relevant alternative(s), and which have made an attempt to present those data in such a way as to help decision makers establish their relative efficiency. That is, they valued costs and effects in monetary terms to estimate net benefits (cost-benefit analysis), or they identified the clear dominance[3] of an intervention or expressed the differential effects of interventions on a single scale and related this to their differential costs (cost-effectiveness analysis). Therefore, simple cost analyses were not included in the review.

2.2 Search strategy and data extraction

Published economic evaluations were identified from a computer search of three literature databases undertaken in September 1998: Medline from 1975 until the present; the NHS Economic Evaluation Database (Centre for Reviews and Dissemination, University of York); and the Office of Health Economics Health Economic Evaluation Database. For Medline, the Mesh term 'osteoporosis' was used with the sub-term 'economics'. For the two specialist economic evaluation databases, the term 'osteoporosis' was used alone. The titles and (where available) the abstracts of articles were studied by one reviewer (MS) and a decision taken as to whether the study was likely to fulfil the inclusion criteria of the review, in which case a full copy of the paper was ordered. A definite decision was taken regarding inclusion on the basis of the detail provided in the full paper. The reference lists of all included studies was also trawled for further studies.

For included studies, information relevant to the review was extracted onto a *pro forma* by one of the authors (MS). This was subsequently checked by a second author (RG) and differences settled by discussion. This information was then summarised in data tables which provided the basis for the empirical and methodological assessment of the studies.

[3] A dominant intervention is one that is less costly than all its comparators and at least as effective on all dimensions of effect, or no more costly and more effective on some dimensions of effect and no less effective on all others.

3. RESULTS OF THE STRUCTURED REVIEW

3.1 Overview

A total of 16 economic evaluations was identified. Table 2 provides a brief overview of each, and the appendix provides detailed data tables for all studies. All studies were based on decision analytical models and all took the form of cost-effectiveness analysis. Seven studies were from the US (five from the same team), four from the UK (two from the same team), two from Australia and one each from Denmark, Sweden and Italy.

The majority of studies focused on either primary prevention alone (seven) or both primary and secondary prevention where high-risk women were identified on the basis of BMD screening (seven). Two studies looked at the cost-effectiveness of interventions to treat established osteoporosis. The majority of studies considered the cost-effectiveness of HRT (11 studies included oestrogen replacement therapy (ORT), 10 studies considered combined (oestrogen plus progestogen) replacement therapy (CRT)). Two studies included etidronate amongst their comparators (one considered bisphosphonates in general), three included calcitonin, two assessed calcium and one each considered vitamin D, vitamin D plus calcium, calcium plus exercise, fluroide, exercise and calcitonin plus calcium. One study did not include a specific intervention but described a generic cost-effectiveness model for the evaluation of treatments for osteoporosis which was then used on notional interventions [50].

Table 2. Summary of studies in the review

Study	Country	Type of prevention	Interventions	Main stated conclusion
Weinstein [1980] [85]	USA	Primary and secondary	ORT for 10 years, starting at various ages, in women with menopausal symptoms or women with symptoms of osteoporosis or all post-menopausal women	Treatment appears cost-effective in women with symptoms and osteoporosis with a prior hysterectomy.
Weinstein and Schiff [1983] [86]	USA	Primary	Universal ORT or CRT during three alternative age ranges.	Combined therapy seems cost-effective except in women who consider the effects of continued menstruation to be worse than the positive effects on menopausal symptoms
Tosteson et al [1990] [81]	USA	Primary and secondary	No intervention, bone mass measurement and long-term CRT in high-risk women, universal CRT.	Screening asymptomatic, perimenopausal white women to detect low bone mass and to target hormone replacement therapy at women with the greatest risk of fracture is reasonably cost-effective
Weinstein and Tosteson [1990] [89]	USA	Primary	ORT for 5, CRT for 5 or 15 years	The cost-effectiveness of hormone replacement therapy compared favourably with other uses of health care resources but is very sensitive to quality of life effects.

Table 2 cont'd

Tosteson and Weinstein [1991][82]	USA	Primary	ORT vs no intervention (in women without uterus) and CRT vs no intervention (in women with uterus)	ORT in hysterectomised women was considered cost-effective. CRT in non-hysterectomised women would probably only be cost-effective if it is used in women at high risk of hip fracture
Daly et al [1992] [24]	UK	Primary	ORT vs no intervention (in women without a uterus) and ORT vs CRT vs no intervention (in women with a uterus)	Long-term prophylactic treatment of hysterectomised women and treatment of symptomatic women with a uterus is probably cost-effective
Cheung and Wren [1992] [17]	Australia	Primary	ORT, CRT during three alternative age groups and no intervention.	Hormone replacement therapy for symptomatic women is cost-effective when factors that enhance its efficiency are considered
Geelhoed et al [1994] [39]	Australia	Primary	ORT for various durations, dietary calcium supplements plus exercise, no intervention	There is evidence to justify the introduction of treatment at later age
Torgerson and Kanis [1995] [77]	UK	Primary and secondary	Vitamin D, oral vitamin D and calcium in general population or those at high risk	
Office of Technology Assessment [1995][83]	USA	Primary and secondary	HRT in high-risk, HRT universally, no intervention	Life-long therapy and treatment if high-risk women is more cost-effective.
Francis et al [1995] [35]	UK	Treatment	CRT vs etidronate vs salmon calcitonin plus calcium	HRT is the treatment of choice for post-menopausal women with osteoporosis.
Jonsson et al [1996] [50]	Sweden	Treatment	Treatment for 5 years for 62 year-old woman with low BMD vs no treatment	Similar cost-effectiveness ratios to the management of mild hypertension were shown
Ankjaer-Jansen and Johnell [1996] [1]	Denmark	Primary and secondary	Calcium, etidronate, calcitonin, HRT	Prevention of osteoporosis through screening for low BMD should not be recommended at the moment.
Daly ey al [1996] [25]	UK	Primary	ORT vs no intervention (in women without uterus) and CRT vs no intervention (in women with uterus)	Assuming that ORT offers cardiovascular benefits, long-term prophylactic treatment of hysterectomised women would be very cost-effective; lack of data on the effects of CRT on cardiovascular disease make a conclusion about HRT on non-hysterectomised women more difficult.
Visentin et al [1997] [84]	Italy	Primary and secondary	Calcitonin for 1year vs no treatment	HRT appears to be the best option at present for hip fracture prevention.
National Osteoporosis Foundation [1998] [64]	USA	Secondary	HRT, calcium, Vitamin D, Calcitonin, bisphosphonates, fluoride, exercise	BMD testing should be undertaken on the basis of other risk factors. HRT is the most cost-effective intervention, but its optimum use depends on risk factors.

ORT = Oestrogen replacement therapy CRT = Combined (oestrogen plus progestogen) replacement therapy

HRT = Hormone replacement therapy BMD = bone mineral density

3.2 Empirical results

Table 2 details the main conclusions of each of the studies in the review.

3.2.1 Evaluations of hormone replacement therapy

Background. Hormone replacement therapy (HRT) is the oldest and most widely evaluated (in economic terms) of the osteoporosis treatments. Indeed, before 1990 no other intervention for osteoporosis had been subject to cost-effectiveness analysis [78]. However, more recently, other treatments have been licensed in this area and scrutinised with respect to their cost-effectiveness.

Evaluating the cost-effectiveness of HRT is difficult for three reasons. Firstly, its effects are multi-systemic with a putative range of health benefits and disbenefits. Secondly, there is a paucity of randomised trials which have been adequately powered to detect clinically relevant endpoints (e.g. fracture reduction). Although synthesis of observational studies suggests HRT offers a survival benefit [43], this has yet to be demonstrated in trials. Large trials are underway to evaluate HRT in the USA and UK [92]. Thirdly, no RCT has included a contemporaneous economic evaluation. Furthermore, some of the assumptions underlying most of the economic models of HRT have been questioned.

The traditional clinical model for using HRT to prevent osteoporotic fractures is that women would be offered HRT at the menopause (at about 50 years), with a recommendation that they take the hormone for 5 to 10 years. The idea behind this approach was that the median age of hip fracture was about 80 years and, if 5 to 10 years of HRT could delay the time to hip fracture by a corresponding amount, then most women would have reached the end of their natural life span before enduring a hip fracture. Even if this model were correct from a clinical perspective, it has some important implications economically due to the effect of discounting future costs and benefits [15]. In particular, most of the costs of prevention would be incurred 20 to 30 years before the benefit in terms of fracture prevention. Furthermore, some of the unwanted side-effects of treatment (e.g. increased risk of breast cancer) would occur long before the benefits of treatment, thus the relative importance of these side-effects would be accentuated through discounting.

Within the last 10 years some of the key assumptions underlying the clinical model of HRT have been undermined. Recent observational data strongly suggest that the effects of HRT do not persist in the long-term - that is, the beneficial effects on bone are lost shortly after cessation of treatment [14,62]. Thus, for treatment to be effective at preventing fractures, continuous and life-long use is required, which will greatly increase costs and the risk of breast cancer, the latter likely to be detrimental to treatment compliance. Additionally, a large randomised trial of HRT, which was designed to show a benefit to the cardiovascular system, failed to show any effect despite four years of treatment [47]. These most recent data cast doubt upon the cost-effectiveness of long- term use of HRT.

The association between BMD and breast cancer risk has important implications for the cost-effectiveness of HRT. Evidence from observational studies and the latest trial by Hulley *et al* [47] suggest that HRT is associated with a 30% increased risk of developing breast cancer. On the other hand, two recent observational studies strongly suggest that women at very high risk of osteoporosis (i.e. those with a BMD Z score of about -0.7) have a substantially reduced absolute risk of breast cancer [13,95]. Thus, women with low bone mass are likely to benefit more from HRT use through a greater reduction in the absolute risk of fracture, but with a smaller increase in the absolute risk of breast cancer. For a woman whose BMD is in the lowest quartile, then even if HRT increases the relative risk of cancer by 30%, her absolute cancer risk will still be less than an untreated woman with high BMD, if HRT increases breast cancer risk by the same relative amount regardless of underlying risk. Only if HRT selectively increases breast cancer risk for women at low absolute risk of the disease will the use of BMD measurements not improve cost-effectiveness, in terms of breast cancer risk.

HRT is multi-systemic in its effects. In the following we consider the implications of this for cost-effectiveness models.

Health-related quality of Life (HRQL). Improving HRQL - or, to be precise, individuals' valuation of that improvement in terms of utilities - is, along with extending life, a key objective of any treatment. Given that all the studies in the review were based on models, the term HRQL is used here to refer to the values that have been ascribed to individuals' preferences for health states that are expected to change as a result of the interventions being evaluated. Clearly, there will be a gain in HRQL by avoiding fractures and other clinical events. Conversely, there may be a reduction through side-effects of treatment. This section considers some of the important empirical HRQL issues and whether the published studies have addressed them. Later we consider some methodological issues regarding utility elicitation in this clinical area.

Most treated women will not benefit from HRT for fracture or cardiovascular protection because, without treatment, only a minority would have a preventable fracture or cardiac event. Therefore, it is important that any side-effects of treatment on HRQL are taken into account. All the studies identified in the review included a utility for relief of menopausal symptoms with the exceptions of Geelhoed and Harris [39], the OTA [83] and Tosteson *et al* [81]. Apart from Daly *et al* [25], none of the utilities was derived empirically (that is, they were based on the authors' judgement and were generally taken from Weinstein's original study [85]).

However, the use of utilities for menopausal symptoms when evaluating HRT for use as a preventive treatment for osteoporosis needs to be treated with some care. This is because, for women with menopausal symptoms, the key question is whether the costs of hormonal treatment will be justified by the benefits in terms of alleviation of menopausal symptoms. Two studies - Daly *et al* [22] and Zethraeus [94] - indicate that, for this purpose, HRT is a relatively cost-effective use of resources. Therefore, women with menopausal symptoms,

with no medical contra-indications for treatment, are very unlikely to be denied HRT. In contrast, the decision regarding the use of HRT for osteoporosis prevention is an incremental one of what benefits the patient will receive over and above that of menopausal symptom relief, and at what cost.

The only cost-effectiveness study which has explicitly excluded HRQL gains is by Tosteson *et al* [81]. Indeed, they prudently include HRQL adjustment for the possible detrimental effects of adding progestogen, although trial data, published since they undertook their evaluation, suggest that HRT with progestogens does not adversely effect HRQL [59].

For HRQL effects from fractures, the studies have tended to use Weinstein's original estimates [85]; a small number have used values from Hillner *et al* which were also based on the authors' judgements [46]. More recently, the National Osteoporosis Foundation (NOF) guidelines have used a panel of experts approach to derive utility values for fractures [64]. However, this approach using panel 'surrogate' estimates for utilities can be criticised in that they may not reflect patients' or the public's valuations. This can be illustrated by a recent empirical study of the effect of Colles fracture on utility which produced a value approximately half of that used by the National Osteoporosis Foundation [27].

Curiously, no study has attempted to reflect HRQL loss due to breast cancer, focusing instead on its mortality effects. This is an important omission given that 70% of breast cancer patients will survive for at least five years after diagnosis. Thus, not including a utility for the non-mortality effects of breast cancer will tend to overestimate the cost-effectiveness of HRT. Similarly, only one study (Cheung and Wren [17]) tried to include the HRQL effects of avoiding cardiovascular disease. In contrast, a number of studies have included utility weights for the relatively rare event of endometrial cancer.

As stated above, Tosteson *et al* [81] examined the effects of reductions in HRQL due to treatments. Jonsson *et al's* model demonstrated the importance of negative side-effects of treatment [50]. If treatment reduces HRQL by 1% or more, then the disbenefits of therapy would dominate. Therefore, it is important to quantify and value the HRQL implications of the side-effects of treatment. As discussed further in the methodological section below, the utility data used in the models is one the major areas of weakness.

Clinical events. Most studies have made the assumption that use of HRT reduces hip fractures in the order of 50%. However, this effect size is purely based on observational data, as only one small RCT of HRT has ever shown a reduction in fractures, and these were vertebral fractures [57]. An important effect to consider in evaluations of fractures is how long the effect of the agent persists after cessation of treatment. There is a view that there is a "catch-up" in bone loss after cessation of treatment which has been suggested by one study [55]. Thus, after cessation of treatment, bone loss is increased over and above that which would be expected if treatment had not taken place so that, 2 to 3 years after treatment, a patient is in the same position as an untreated patient. The view of rapid catch-up is disputed,

but it seems likely that bone loss is somewhat accelerated, such that little benefit is seen 10 to 15 years after treatment [33].

Ideally models should take into account the fact that non-fracture mortality risk is increased among women with low BMD [10]. This will reduce the long-term effectiveness of treatment, as a higher proportion of treated women will die from other causes and will not live to enjoy the benefits of avoiding fractures. None of the evaluative studies in the review has reflected this mortality characteristic.

Most of the published studies conclude that treatment using HRT is relatively cost-effective among symptomatic women or women who have had a prior hysterectomy. A recent review, which standardised the incremental cost per QALY ratios of published studies to $US and a common price year, showed that the cost per QALY gained ranged from $12,000 to $23 000 [78]. The exception to this was the study by Daly *et al* which used assumptions of larger QALY gain from relief of menopausal symptoms and produced a cost of $3,000 per QALY gained [25]. In contrast, for asymptomatic women, the results are more equivocal. The cost per QALY ranges from $26 000 to $52 000, with Weinstein [85] concluding that the disbenefits outweighed the benefits (i.e. dominance).

3.2.2 Non-HRT treatments for fracture prevention

Fewer evaluations have been published on non-HRT treatments. This is partly because it is only relatively recently that evidence has emerged that there are non-HRT alternatives for fracture prevention. Non-HRT treatments have a number of advantages over HRT, not least that most can be used to treat men. From a modelling perspective, treatments such as the bisphosphonates, calcium and calcitonin require fewer assumptions with respect to extra-skeletal treatment effects. The dominant clinical effects of these treatments lie in their ability to prevent fractures, although some treatments such as alendronate may require models to include some HRQL weights to take into account unwanted gastrointestinal effects. In addition, other compounds, such as calcium and vitamin D, have relatively robust trial evidence to support their effectiveness assumptions - unlike HRT.

The simplest models of therapies include Francis *et al* [35] and Torgerson and Kanis [77]. Francis *et al* reviewed the evidence with respect to the effectiveness of a number of treatments for preventing vertebral fractures. They then simply divided the annual purchase cost of the compound by the estimated absolute reduction in vertebral fractures. Whilst this study has the merit of being simple there are a number of criticisms. One of the main problems is using the cost per averted vertebral fracture, which makes the results difficult to compare with other evaluations outside the area of osteoporosis prevention. Furthermore, the study used changes in all vertebral fracture rates, not simply reductions in clinically apparent vertebral fracture. A major problem with this approach is that the majority of vertebral fractures are asymptomatic and, as such, do not cause the patient much in the way of HRQL loss. It would have been better to estimate a cost per averted *clinical* fracture as these have clear implications for women, in terms of HRQL, and for health care resource use.

The study by Torgerson and Kanis did include some estimate of averted fracture cost [77]; however, a similar criticism can be applied to it as to the Francis *et al* study in that the denominator in the cost-effectiveness equation was fractures averted (in this instance hip) rather than a more useful measure of quality-adjusted life-years (QALYs). Furthermore, the conclusions of the study that vitamin D alone is highly cost-effective has not been borne out by the latest clinical trial of vitamin D [56]. However, the study does make the valuable point that, for pharmaceutical preparations of calcium and vitamin D to achieve a reasonable cost-effectiveness ratio, targeting patients at high risk of fracture is desirable.

Geelhoed and Harris [39] is one of the few studies to consider non-HRT treatments - in this instance life-long use of calcium and exercise - for all postmenopausal women. In their model, calcium and exercise did not appear particularly cost-effective. However, a better comparator would have been for calcium supplementation to begin in later life, as they modelled HRT. This would have improved significantly its cost-effectiveness ratio. However, the conclusions of studies by Geelhoed and Harris, and the OTA [83], that it is more cost-effective to commence treatment later in life with a bone sparing compound, is likely to be correct.

3.2.3 The National Osteoporosis Foundation Guidelines

The most recently published economic evaluation is contained within the NOF's clinical guidelines for the USA [64]. This represents a comprehensive set of guidelines for the diagnosis and treatment of osteoporosis and, given their high profile in the "bone community", we have chosen to explore their model in more depth.

The NOF guidelines make the explicit assumption that HRT is the treatment of choice. For women unwilling or unable to take HRT, then the next recommended treatment is alendronate; should alendronate not be tolerated, calcitonin is recommended. By using this approach, the NOF makes the assumption that the comparator treatment in all instances is 'do nothing'. Furthermore, it is assumed that all patients are given calcium supplementation. Other treatments, such as fluoride, are not evaluated on the grounds that there is insufficient evidence as to their effectiveness.

A key parameter affecting the NOF's cost-effectiveness model is the use of the Study of Osteoporotic Fracture (SOF) dataset for risk factors for fracture [21]. The risk factors used to target diagnosis and therapy were low body weight, prior fracture, family history and smoking status. The guidelines suggest targeting diagnostic and treatment resources at patients with one or more of the preceding risk factors. Whether these risk factors can be applied to a European population is unknown. Furthermore, the SOF population were all aged 65 and over, so it is doubtful if all these risk factors are relevant for younger postmenopausal women.

With respect to evaluating HRT, the NOF guidelines only consider HRT's effects on fractures: there is no inclusion of cardiovascular or breast cancer effects. Whilst it might be

justifiable not to include cardiovascular endpoints, particularly given the results of the most recent randomised trial [47], it is of some concern that breast cancer effects are not included. Not including breast cancer effects will improve the cost-effectiveness ratios compared with other interventions. In addition, as mentioned previously, their assumptions about the utility loss associated with various types of fracture were derived from a consensus panel rather than empirically from patients or the public.

A problem with applying the NOF guidelines to the UK or Europe is the use of US cost data, which certainly differs from the UK. For example, the price of calcium supplementation used by the NOF was $50 annually; however, in the UK pharmaceutical preparations of calcium are about £100. In contrast, the NOF price HRT treatment in excess of $400 annually, whilst the cheapest UK HRT regime is less than £25. Thus, the NOF analysis makes calcium supplementation for the entire population appear relatively cost-effective whilst HRT is reserved for highest risk women. Furthermore, their costs of bone density scans are relatively high compared with the UK costs and their costs of fractures are greater.

Finally, with respect to the use of bone density measurements, the NOF assumes an unrealistic 100% compliance after measurement. Again, this assumption will tend to cast the cost-effectiveness of diagnosis and treatment of osteoporosis in a favourable light.

3.3 Methodological issues

A range of methodological issues relating to modelling-based economic evaluations of osteoporosis interventions has emerged during this review. Most of these issues are discussed across the reviewed studies in general, although illustrations will be made by referring to particular studies.

3.3.1 Types of models

The most frequently used model in the studies that have been reviewed is the state transition model. The advantage of this type of decision model is that it deals explicitly with time, which is important for chronic conditions such as osteoporosis. The state transition model takes the form of a series of states which relate to particular clinical or resource consumption events. Typically, a hypothetical cohort of patients enters the model and, over a series of cycles representing a period of time such as a year, patients make transitions between states and, in the process, accumulate costs. The pattern of transitions, over a number of years, facilitates an estimate of expected costs. One of the states is usually death, and the timing of transitions to that state allows an estimate of life expectancy. Probably the most popular form of state transition model in economic evaluation is the Markov model, where transitions depend only on the current state and are not influenced by earlier states [6,72].

A baseline model reflects the risks of clinical events, such as fracture, that women face in the absence of preventative interventions. The risks take the form of transition probabilities based on the incidence of clinical events in a relevant cohort of women. To estimate the

impact of a particular intervention on costs and outcomes, the model is effectively re-run using a second set of transition probabilities which reflect the relative risk of clinical events under that treatment regimen. In other words, the effectiveness of the intervention manifests itself in the model by modifying some or all of the baseline transition probabilities.

State transition models can be characterised by transition probabilities that are fixed with respect to time. In the case of models for osteoporosis interventions, the key influence of age on clinical risks means that fixed transition probabilities are not a reasonable representation of clinical reality. Therefore, most of the state transition models reviewed here have defined their transition probabilities as a function of age.

Relatively few studies in the review have explicitly described the structure of their models - that is, defining their states and the probabilities of transition between them. One of the clearer expositions of model structure is offered by Tosteson and Weinstein [82]. The structure of Tosteson and Weinstein's model serves as an illustration of how various authors have tackled the problem. The key states in the model were:

- well and living in the community;
- hip fracture;
- nursing home;
- disabled and in nursing home;
- breast cancer ;
- ischaemic heart disease; and
- dead.

With the exception of the disabled and living in a nursing home state (which was arrived at only after a hip fracture) and the dead state (which is a natural absorbing state from which no transitions are possible), transitions between all other states were feasible. All transition probabilities were set up as being age-dependent. Costs were attached to each state and, for states where patients could remain for a number of cycles of the model (most notably the nursing home state), costs were 'run-up' every cycle.

Other state transition models in the review included other states by virtue of including different effects (the effects included in each study are detailed in Column 4 of the Data Tables in Appendix 1). For example, a number of studies included an endometrial cancer state, some modelled several types of fracture separately and some studies evaluating HRT included a state for gallbladder disease.

In general, the baseline transitions between states are a function of estimates of the incidence of clinical events or, in the case of transition to the 'dead' state, of the mortality rates assumed for women in general and for those experiencing particular clinical conditions (Column 5 in the Data Tables in Appendix 1). The effectiveness of interventions (Column 6 in the Data Tables) is used to modify these baseline transition probabilities for the treatment models. Although there are clear methods of how information on rates should be translated

into probabilities [63], none of the papers detail how they have estimated probabilities from data on rates.

State transition models are particularly valuable when the natural history of a condition and the effects of an intervention need to be characterised over a considerable period of time, or when there is a number of possible health events to be modelled. The review shows that this made state transition models particularly popular in evaluations of HRT, where treatments were typically assumed to be long-term and the intervention generated a series of competing risks. In contrast, several studies of non-HRT interventions, such as vitamin D and calcitonin, where extra-skeletal effects are not relevant and where treatment was assumed to be shorter in duration, required much simpler forms of models. These models could be described as simple decision trees, although they were rarely defined in those terms in the papers. This applied in particular to studies using cost per fracture avoided as their representation of cost-effectiveness [35,77].

As a general point relating to the modelling studies in the review, the complexity of the clinical area - particularly in relation to HRT - often precluded full and explicit details of the model. This was particularly the case when the study was published in a clinical journal, as most of them were, with consequent limitations on space. The result of this was that many models took on the appearance of a 'black box', lacking the clarity for the reader that has been urged for model-based economic evaluations [11]. One way around this problem is for authors to make available a technical report giving full details of the model and general methods, but this approach does not seem to have been used by authors of papers in the review.

In recent years, state transition models have more frequently been stochastic in nature; that is, transition probabilities and other parameters have been set up as distributions rather than point values for a given age group [42]. This has the advantage of the estimates of cost and effect (and hence the incremental cost-effectiveness ratios comparing management strategies) including both averages but also a measure of uncertainty - usually in the form of a 95% confidence interval. Only one study in the review included a stochastic analysis [83], which took the form of a first-order Monte Carlo simulation [6]. The approach provides an additional way of expressing uncertainty in cost-effectiveness estimates, but it remains unclear whether this makes the analysis more persuasive to decision makers. There are also limitations to stochastic analysis, such as the need for greater information about the inter-relationships between variables [42]. In general, however, as more information becomes available on the distributions of key clinical parameters, this should be reflected in the structure of decision models.

Some additional aspects of the models can usefully be mentioned. An important issue regarding the effectiveness of preventive therapies for osteoporosis - particularly those that the patient is expected to take for a considerable period - is the extent to which the patient complies with therapy [3]. From the viewpoint of the cost-effectiveness of treatments which are provided without prior screening, however, compliance is not such a key issue as the

absence of compliance is usually assumed to result in no costs (because the medications are not actually prescribed) and no additional benefits. In other words, non-compliant patients take on the characteristics of a patient in the usual care or control arm of a study. In effect, this means that the cost-effectiveness of the interventions in the review are assessed when they are fully complied with by patients, but that reducing compliance rates is unlikely to effect cost-effectiveness ratios markedly. The only situation when this assumption would seem unrealistic is when non-compliance takes the form of medication being prescribed to patients by the patient not actually taking them - they flush the tables down the toilet, for example. In this context, the costs of the drugs are incurred but the benefits that may be derived from their consumption are not realised, and this has the effect of 'watering-down' the benefits experienced by compliant patients. All the models in this review assumed that non-compliance resulted in zero costs and zero additional benefit, which is the same as assuming 100% compliance.

However, as noted above, the assumption of 100% treatment compliance on the part of high-risk patients who are identified using screening may have implications which cast doubt on the validity of the assumption. This is because screening represents a cost for all patients regardless of whether they then comply with treatment. If patients are screened and then do not take treatment when they are identified as high risk, there is no chance of benefits being generated (in the form of improved HRQL and reduced mortality) to justify the cost of the screening. In this context, the cost-effectiveness of screening plus treatment of high-risk patients is likely to be quite sensitive to assumptions regarding treatment compliance. However, studies in the review which evaluated this form of management usually assumed 100% compliance and did not undertake detailed sensitivity analysis of the parameter.

Another important characteristic of the models was the link that was often made between BMD and fracture risk in the context of HRT evaluations. Given the lack of experimental data directly linking HRT use with a reduction in fracture risk, many studies of agents affecting bone metabolism have used changes in BMD to infer changes in fracture risk. However, there have been a number of recent trials which have shown that changes in BMD may not relate to changes in fracture risk. For example, Lips *et al* showed a 20% *increase* in fracture rates (not statistically significant) in a randomised trial of vitamin D supplementation despite a significant increase in BMD in the treated groups [56]. On the other hand, a randomised trial of calcium and vitamin D showed large reductions in hip fracture risk despite only a relatively slight increase in BMD [16]. This unclear relationship between changes in BMD due to treatment and fracture risk has important implications when using BMD in modelling studies, as any inferences between changes and BMD are uncertain. Thus, relying on changes in BMD to inform assumptions with respect to fracture risk may either under estimate or over estimate the effectiveness of any given compound.

3.3.2 Costs

An important characteristic of an economic evaluation is the perspective it takes on costs and benefits [28]. All studies in the review focused on the patient's perspective on the outcomes side, which is typical of economic evaluations in general; that is, the studies focused on changes in mortality and morbidity to the women themselves rather than the effects this might have on other members of the community. On the cost side, most studies adopted the perspective of the health service or payer. At a level of principle, this may be considered a weakness of studies in this area. Undoubtedly, the clinical implications of osteoporosis, and of interventions to prevent and treat it, will have cost implications outside the health service, most notably for patients themselves and their friends and relatives in the form of lost income and out-of-pocket costs. At the level of principle, the societal perspective, which includes all costs no matter on whom they fall, is preferable to that of the health service, as it is less arbitrary, can reflect any costs that are been 'externalised' on others and is more faithful to the tenets of applied welfare economics [48].

However, some have argued that inclusion of non-health care costs in cost-effectiveness analyses is inappropriate as the opportunity cost of those resources includes more than just health outcomes which is the focus of this form of economic evaluation [40]. In addition, there have been recent methodological disagreements in the literature about the appropriate approach to valuing productivity changes - one possible component of non-health service costs [8,9,87]. Recent recommendations for 'good practice' in cost-effectiveness analysis, however, have emphasised the need to include costs across society, at least in a reference case analysis [42]. In the studies reviewed in this document, only one considers costs outside the health service [50]. Given the direction of 'good practice guidelines' in this area, future modelling work in osteoporosis will probably need to take a broader perspective on costs than most studies to date.

On the whole, the estimation of cost parameters in the models in the review was undertaken crudely. As an example, Daly *et al* used average lengths of hospital stay (by age group) for particular conditions, such as hip fracture, and an average cost per in-patient day across specialities as their basis of costing [23,25]. This approach ignores differences in costs per day and non-hospital costs. Whilst this lack of sophistication is not surprising given the large number of cost parameters required for HRT models and the dearth of good-quality cost data in most health care systems, there may be an effect on the acceptability of the studies to decision makers. This may have been accentuated by a focus on average, rather than marginal, costs [78]. In recent years, more detailed cost estimates have become available of clinical events relating to osteoporosis (most notably fractures [34,93]). Hence, future modelling studies in this area should be able to reflect a greater degree of accuracy in their cost parameters.

Another aspect of costing methodology in the papers covered in the review should be mentioned, namely the issue of whether to include the cost of health care, unrelated to osteoporosis or its treatment, in any extra life-years generated by interventions. There has

been a dispute for some years as to whether these costs should be included [69,88]. The recent methods literature has offered a more theoretical insight into the issue [38,61], but no consistent conclusion has been reached regarding inclusion or exclusion. The US Panel reflects this uncertainty and does not take a firm position on this point, although they note that whether or not to include can, in certain situations, have a marked effect on the results of studies [42].

In general, very few economic evaluations include unrelated health care costs incurred through helping people to live longer. However, it is interesting to note that the studies by Daly *et al* do include these costs [23,25], estimating them on the basis of age-adjusted lengths of hospital stay multiplied by an average cost per day in hospital. Whilst the authors are not clear about the sensitivity of their results to the inclusion of these costs, the effect of discounting may minimise their importance in studies with a long time horizon. However, in recent years, it has been felt that preventive treatments for osteoporosis can be given later in life, when fractures are most likely to incur, thus shortening the time horizon of studies. In this context, the inclusion of unrelated costs in added life-years may be more critical. This is an area of methodology that future developers of models in osteoporosis will need to consider carefully.

3.3.3 Decision rules

A crucial stage in a cost-effectiveness analysis is the process by which data on the costs and effectiveness of individual and mutually exclusive interventions are compared and used to identify the most cost-effective option. Although these 'cost-effectiveness decision rules' have been detailed in the health care literature for some time [90], they have frequently been misapplied in studies [49].

The inappropriate use of decision rules is particularly widespread in cost-effectiveness studies in osteoporosis on the basis of this review, as noted in the comments section of the Appendix. Most of the studies in the review compare a number of mutually exclusive management options which differ according to factors such as the actual intervention (e.g. type of drug) and the duration of the treatment. In this multiple option context, the appropriate approach to identifying preferred options in cost-effectiveness analysis can be summarised in the following steps [49,52]:

i. rank all mutually exclusive management options in terms of their cost;
ii. exclude all options that are subject to dominance (more costly and less effective than at least one other option) or extended dominance (have a higher incremental cost-effectiveness ratio than a more effective intervention);
iii. calculate the incremental cost-effectiveness ratios of all remaining options relative to the next least effective;
iv. identify the highest incremental cost-effectiveness ratio that can be funded by considering similar ratios for independent options as calculated in other studies and which may have been funded by the health care system, or by employing a maximum willingness to pay threshold.

A number of studies in the review do not go through this formal process, often calculating average, rather than incremental, cost-effectiveness ratios, which compare the cost and effect of each management option with a notional 'no intervention' and compare these ratios across all options under consideration. This is an area where future studies should attempt to adhere more strongly to established methodology.

3.3.4 Health state preferences

Section 3.2 above discusses some of the empirical issues related to how HRQL has been valued, in terms of health state preferences or utilities, in studies identified in the review. This section considers the methodological issues that are raised. It should be emphasised that, because all the studies in the review were modelling studies, there was no process of HRQL measurement using recognised descriptive instruments, whether generic or disease-specific. Rather the general aim was to ascribe utilities to the various health states that were incorporated into the models. However, this process has generally been undertaken without formal utility elicitation from patients or the general public. Authors of most of the early studies have used the utilities adopted by Weinstein [85], but these were based solely on the judgement of the author himself. Some studies have sought to be rather more rigorous in their choice of utilities by adopting those detailed by Hillner *et al* which 'were determined by a consensus of the persons working on the model and were reviewed by an expert panel' [46] (p.1119).

These approaches to utility estimation do not adhere to what is generally considered good practice [42,67]. Few methodologists working in this area would consider an author's judgement as an adequate source of utility data. Several formal utility elicitation tools are available, such as the standard gamble, time trade-off and rating scale [67,80], with economists often expressing a preference for choice-based elicitation techniques [5,65]. Although utilities are frequently elicited from patients for cost-effectiveness analysis, many economists would argue for the need to use public preferences in studies which are being used to assist allocation decisions for public resources [37]. In part, this is what lays behind the recent development of multi-attribute utility scales, such as the EuroQol (EQ-5D) [53] and Health Utilities Index [32]. These instruments are characterised by a general descriptive system, which generates a number of health states into which patients can be classified at intervals in prospective studies, and a tariff of utilities relating to each health state, based on utility elicitation exercises with members of the public. Incorporation of preference data into studies on the basis of these instruments was an important recommendation in recent guidelines for cost-effectiveness analysis [41].

Some of the later studies in the review have begun to incorporate stronger methods for HRQL valuation. Daly *et al's* second analysis [25] incorporated the results of a utility elicitation exercise with 63 women who were presented with descriptions of mild and moderate menopausal symptoms [22]. A limitation of the study, however, was that HRQL adjustments related only to menopausal symptoms, and not to fractures, hysterectomy, breast cancer, ischaemic heart disease or stroke. In Jonsson *et al's* model assessing the cost-effectiveness

of possible interventions to prevent fracture in established osteoporosis, utility effects of fracture were based on Hillner's judgements [46], but also on the utilities suggested by the Rosser multi-attribute scale [68], based on the original utility tariff and an alternative developed by the authors.

Although some of the later studies in the review looking at the cost-effectiveness of interventions for the prevention and treatment of osteoporosis incorporated utility data based on formal elicitation exercises, it can be argued that, in general, HRQL valuation methods were one of the weakest aspects of the studies in the review. This weakness partly reflects the methods used to ascribe utilities to clinical events, and partly to the fact that the HRQL implications of some events were not estimated at all (in particular, breast cancer - see Section 3.2 above). The utility effects of clinical events should be an important area of focus in future modelling studies in this area.

3.3.5 Handling uncertainty

A very clear characteristic of the studies in the review is the multiple sources of uncertainty that they exhibit in their results. As for all economic evaluations [7], these sources of uncertainty can be placed into four categories:

- uncertainty relating to data inputs - for example, the relative risk of fracture with particular interventions, the utility weight associated with particular clinical events and the cost of events;
- uncertainty relating to analytical methods and assumptions - for example, the discount rate employed;
- uncertainty relating to extrapolation - for example, the assumptions used to predict prognosis with and without HRT outside the period of primary studies from which data were taken, such as those relating to what happens to BMD after HRT therapy is discontinued;
- uncertainty relating to generalisability - for example, the extent to which a study undertaken in the USA has relevance to Europe.

In virtually all studies that tried to assess the importance of uncertainty, sensitivity analysis was the main tool employed. Most studies employed a mixture of simple one-way sensitivity analysis, where one parameter at a time was altered and its effect on the cost-effectiveness results assessed, and scenario analysis where a series of related parameters was altered simultaneously. As mentioned above, only one study employed a stochastic approach to dealing with uncertainty [83], although this is likely to have a more prominent role in future modelling studies.

Whilst one-way sensitivity and scenario analysis are valuable tools in assessing some forms of uncertainty in economic analysis [7], they are not easily employed to evaluate the structural assumptions contained in a model, such as the speed with which BMD declines after treatments are discontinued and the assumption that women with low BMD, who do not experience particular clinical events, have the same age-specific mortality risks as the general

female population. This is because these assumptions may be rooted in the programming for the model and are difficult to alter.

The inevitable requirement in modelling studies to make structural assumptions has led to a recent interest in how decision models used for cost-effectiveness analysis might be validated [36,42]. One of the studies in the review made an attempt to 'validate' its model by comparing some of the intermediate results of the analysis with the results of published studies. Tosteson *et al* undertook several of these comparisons [81]:

- the cumulative incidence of fracture without interventions;
- the average age at first hip fracture for women with no previous hip fracture;
- reduction in hip fracture risk for particular treatment durations.

Developing methods to validate decision models is likely to be an important part of this form of cost-effectiveness in the future, and this should be explicitly considered when planning further research in this area.

4. CONCLUSIONS

This document has reviewed economic evaluation studies relating to interventions to prevent and treat osteoporosis. A total of 16 studies was identified, all cost-effectiveness analyses and all based on decision analytical techniques. The use of interventions for fracture in this area can be divided in those used for primary prevention, in individuals who are at no apparent elevated risk of fracture, and in secondary prevention where individuals have some degree of elevated risk. Often studies use the term 'treatment' to refer to the use of interventions to prevent fracture in individuals at markedly higher risk of fracture (usually characterised by low BMD and a previous fracture). In the review, seven studies looked at primary prevention only, seven looked at both primary and secondary prevention and two looked at treatment of established osteoporosis. In general, interventions were more likely to be considered cost-effective if they focused on individuals at higher risk of fracture. Most studies focus on the evaluation of HRT (11/16).

The development of the models over the 18 years since the publication of the first study [85] illustrates how clinical and epidemiological knowledge in the area has increased. To a lesser extent, the development of the models also reflects changes regarding what is considered good practice in model-based economic evaluation. Many of the studies in the review show important methodological limitations which have been described in this report. These include the use of health state preferences (utilities) which, with a couple of exceptions, are not based on a formal elicitation process with patients or members of the public, and the inappropriate use of cost-effectiveness decision rules. Future analysis in this area will hopefully be strengthened by understanding these weaknesses.

Appendix: Data tables for economic evaluations included in the review (see list of abbreviations at the end of the tables)

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Geelhoed et al [1994] [39] [Primary Prevention] [Australia]	1. ORT for life from 50 years 2. ORT from 50 to 65 years 3. ORT from 65 years 4. Dietary calcium supplements + exercise 5. No intervention [Combined HRT (oestrogen plus progestogen) for non-hysterectomised women in sensitivity analysis	• CEA (life-years and QALYs) • State transition model (variable probabilities) • Cycle length: 1 year • Deterministic • 50 year time horizon • 5% discount rate • Perspective: health service.	• Hip fracture • Stroke • IHD • Breast cancer • Endometrial cancer	*Incidence:* • Hip fracture: mathematical function related to age and BMD (Melton et al); distribution of BMD from Melton et al 'validated' in Australian pop'n. • IHD: provincial data and MONICA study • Endometrial cancer: Australian cancer registry • Hysterectomy: Australian provincial data • Probability of entry into a nursing home after hip fracture (Australian data) • Age-specific probability of entry to nursing home for other reasons (Australian data) *Mortality:* • Case fatality rates from hip fracture (by age: 2%-20%) (Australian pop'n data) • From IHD and breast cancer (Australian admin've data) • From endometrial cancer (Australian cancer registry) • Residual from Australian life tables minus disease-specific rates.	• Effect on BMD: ORT prevents bone loss while on therapy; for ORT for 15 years, protective effect lasts for total of 20 years; for calcium, BMD loss 50% that of no intervention • IHD RR: 0.50; same effect on incidence and mortality • Breast cancer RR: 1.02^x, where x is the duration of exposure to ORT; same effect on incidence and mortality • Endometrial cancer RR: 8.0; effect on incidence only, not mortality • Stroke: no effect in base-case

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Geelhoed et al [1994] [39]	[1991 Australian $] • Hip fracture: 7211/fracture • IHD: 5735/case + 316/year • Breast cancer: 10366/case • Endometrial cancer: 8093 + monitoring • Nursing home: 82 per bed-day • Oestrogen: 108/year including 2 annual GP visits • Calcium: 85/year • Exercise: 4/week	Based on authors' judgement: • Women returning home after fracture (0.9) • Women going to nursing home after fracture: 0.67	• ICER intervention 2 relative to intervention 1: 8725/life-year gained • ICER intervention 3 relative to intervention 1: 32185/life-year gained • Treatment from age 65 most cost-effective because treatment focuses on the years when BMD losses are greatest	Type of analysis: simple one-way. Key variables: • Protective effect of ORT on IHD • Cost-effectiveness of intervention 4 sensitive to cost and effects	• Poor application of cost-effectiveness decision rules

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Weinstein [1980] [85] [Primary and secondary prevention] [USA]	1. ORT in women with menopausal symptoms. 2. ORT in women with symptoms of osteoporosis. 3. ORT in all post-menopausal women. 3 treatment periods: 1. 50-60 years 2. 50-65 years 3. 55-70 years	• CEA (QALYs) • State transition model (variable probabilities). • Deterministic. • lifetime time horizon. • 5% (costs) and 0% benefits discount rates. • Perspective: health service.	• Hip and wrist fracture. • Endometrial cancer • Gallbladder disease. • Uterine bleeding. [Breast cancer in sensitivity analysis.]	*Incidence:* • Hip and wrist fractures: age-specific incidence taken from literature; adjusted upwards to allow for greater risk of fracture in women with osteoporosis (assumed to be 10% by 55 years and 20% by 65 years). • Endometrial cancer: age-specific incidence based on national cancer survey. Adjusted for an estimated 30% hysterectomy prevalence. • Cholecystectomy: age-specific incidence rates from epidemiological surveys. *Mortality:* • Fatality rate from hip fracture: 10%. • Fatality rate from cholecystectomy : 0.28-1.3%. • Fatality rate from endometrial cancer: 10%. • Fatality rate from D&C: 0.1% • Years lost assessed against US life-tables.	• Hip and wrist fracture: RR for women not on ORT of 3.0 during treatment, 2.0 for an equal number of years afterwards, then a return to 1.0. • Endometrial cancer: RR for ORT 8.0 from 5 years after start of ORT until 5 years after. • Cholecystectomy: RR for ORT 2.5 from 5 years after start of ORT until 5 years after. • Uterine bleeding: risk of 0.3% per month for first 2 years of treatment. • Breast cancer: RR of 1.5 in ORT (sensitivity analysis only).

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Weinstein [1980] [85]	[US dollars] • ORT: 65/year including physician visits. • Endometrial biopsy; 100/year. • Endometrial cancer: 3200/case. • Hip fracture: 6000. • Wrist fracture: 250/case. • Cholecystectomy: 3500/case. • D&C (uterine bleeding): 500/case. • Breast cancer: 3500/case (sensitivity analysis only).	Judgement. • Symptoms: 0.99. • Hip fracture: 0.95 for life. • Endometrial cancer: give up 1 year of remaining life to avoid.	• In symptomatic women with uterus: cost/QALY of 7420-18160. • In terms of life-years, ORT reduces life-years (dominated). • In women with osteoporosis: cost/QALY of 5460-15100 • Highly cost-effective in women with uterus or osteoporosis. • In symptomatic women with uterus depends on quality weight for symptoms.	Type of analysis: simple one - way. Key variables: • RR of breast cancer. • RR of fracture.	No consideration of possible protective effects on IHD.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Tosteson et al [1990] [81] [Primary and secondary prevention] [USA]	1. No intervention. 2. Bone mass measurement and long-term CRT in high-risk women (with various screening thresholds). 3. Universal CRT.	• CEA (life-years and QALYs). • State transition model (variable probabilities). • Deterministic • Lifetime time horizon. • 5% discount rate. • Perspective: health service.	• Hip fracture. [Breast cancer and IHD in sensitivity analysis.]	*Incidence:* • Fracture as a function of BMD: distributions of initial BMD from survey; loss of BMD estimated by quadratic function of age; regression model to estimate risk of hip fracture as function of age and BMD based on population survey. • Age-specific rates of entry into nursing home after hip fracture and for other causes. *Mortality:* • Hip fracture: age-specific death rates after fracture from population survey (assuming 50% due to hip fracture). • IHD: death rates based on life-tables (sensitivity analysis only).	• Hip fracture: no bone loss on CRT for duration of therapy, then loss at same rate as 50 year-old when therapy stopped. • IHD: 25-57% reduction in death rate (sensitivity analysis only). • Breast cancer; 25% increase in risk (sensitivity analysis only).

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Tosteson et al [1990] [81]	[1987 US $]: • Hip fracture: 10250-12100/case. • CRT: 200/year. • Nursing home: 25550/year. • Screening: 150.	Use of Hillner et al's [1986] values#: • 0.8 after hip replacement. • 0.4 for long-term nursing home care. • 0.95 for uncomplicated hip replacement .	• Cost per QALY of screening: 4200-37800 depending on screening threshold (<0.9=4200; <1=8,600; <1.1=37,800). • Cost per QALY of universal: 144000.	Type of analysis: simple one-way and scenario analysis. Key variables: • Breast cancer risks; increases ICER of universal. • IHD protection: universal may become dominant depending on cost savings. • Risk of fracture given bone loss. • Relative compliance by strategy.	

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Weinstein and Schiff [1983] [86] [Primary Prevention] [USA]	1. ORT. 2. CRT. Three treatment durations and age ranges: • 5 years (50-55 years) • 10 years (50-60 years) • 15 years (50-65 years)	• CEA (QALYs). • State transition model (variable probabilities). • Deterministic • Lifetime time horizon. • 5% discount rate. • Perspective: health service.	• Hip fracture • Stroke • IHD • Breast cancer • Endometrial cancer	*Incidence:* • Hip and wrist fracture: age-specific incidence from surveys. • Breast cancer: age-specific incidence from surveys adjusted for prevalence of oestrogen use. • Endometrial cancer: age-specific incidence from surveys adjusted for prevalence of hysterectomy and oestrogen use. • Endometrial hyperplasia: 0.75%/year (same as in CRT). • Uterine bleeding: 24% in presence of hyperplasia. *Mortality:* • Endometrial cancer: case fatality rate: 10% in five years with monitoring and 85% without monitoring. • Breast cancer: relative survival rates from National Cancer Institute. • Gallbladder disease (cholecystectomy): case fatality rates 0.28-1.31% depending on age. Hip fracture: case fatality rate of 18%.	• Hip and wrist fracture: RR of 0.4-1.0 depending on ages treated and age at risk. • Endometrial cancer: RR of 1-8 depending on ages treated and age at risk in ORT; RR of 1.0 in CRT. • Endometrial hyperplasia: 9%/year in ORT and 1.5%/year in CRT. First 5 years of treatment only. • Gallbladder disease: RR of 2.5 with ORT. • Uterine bleeding: 24%. • Uterine bleeding: 5% in ORT; 2.5% in CRT or no treatment.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Weinstein and Schiff [1983] [86]	[1982 US $] • ORT: 85/year. • CRT: 145/year. • Monitoring (biopsy); 115 (ORT), 57 (CRT). • Endometrial hyperplasia (D&C): 500/case. • Endometrial bleeding (biopsy): 115/year of bleeding. • Endometrial cancer: 3250. • Breast cancer; 4000. • Hip fracture: 7400. • Wrist fracture: 250. • Cholecystectomy: 3500.	Based on authors' judgement: • Symptoms: 0.99 (women on ORT get 0.01 increase in QALYs for duration of treatment; 50% of that for women on CRT. • Endometrial cancer: 0.8 for 5 years. • Hip fracture: 0.9 for rest of life.	• Costs per QALY: ORT: 130000 (vs. CRT) • Costs per QALY: CRT: 42000 (aged 50-55 years), 29000 (50-60), 24000 (50-65 years) (vs. no treatment). • ORT reduced life expectancy but outweighed by quality of life improvements with symptoms. • CRT increased life expectancy.	Type of analysis: simple one-way Key variables: • ICER of CRT sensitive to the utility loss of continued menstrual bleeding relative to reduction in menstrual symptoms.	• No consideration of protective effect of ORT on IHD.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Cheung and Wren [1992] [17] [Primary Prevention] [Australia]	1. ORT. 2. CRT. 3. No intervention. Three treatment durations and age groups: 1. 5 years (50-55 years). 2. 10 years (50-60 years). 3. 15 years (50-65 years). Other sub-groups: 1. Presence of menopausal symptoms. 2. Presence of progestogen side effects. 3. Hysterectomy status.	• CEA (QALYs). • State transition model (variable probabilities). • Cycle length: 1 year. • Deterministic. • Lifetime time horizon. • 5% discount rate. • Perspective: health service.	• Hip fracture • Wrist fracture. • IHD (AMI). • Endometrial cancer • Uterine bleeding.	*Incidence:* • Hip fracture: annual average (age-specific) incidence from national data sources. • Wrist fracture: annual incidence from Norwegian data source. • Breast and endometrial cancer: age-specific incidence rates from national data sources. • IHD (AMI): incidence in 5-year age groups from published study. • Hysterectomy prevalence of 21% at age 50. *Mortality:* • General: age-specific rates for 5-year periods from life-tables. Breast cancer, hip fracture and endometrial cancer: from published survival rates using DEALE technique.	• IHD: three alternative RRs for deaths from AMI: 1.0, 0.75, 0.5. Assumed to last from 5 years after start of therapy to 5 years after finish. • Fracture: RRs of 0.4-0.8 depending on age. • Endometrial cancer: RRs of 2.0 to 8.0 depending on age for ORT. • Unscheduled bleeding: annual rates of 9% with hyperplasia and 23% without hyperplasia (for ORT) and 2% with hyperplasia and 12% without hyperplasia (for CRT and untreated women)

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Cheung and Wren [1992] [17]	[1988 Australian $] • ORT: 71/year. • CRT: 124/year. • Consultation: 55/year (both). • Endometrial biopsy: 91/year (ORT only). • Hip fracture: 7695/case. • Wrist fracture: 440/case. • D&C (for uterine bleeding): 593/case. • Endometrial cancer: 4370/case. • Breast cancer: 5807/case. • AMI: 5214/case.	• Based on Weinstein and Schiff (judgement). • Symptoms: 0.99 (women on ORT get 0.01 increase in QALYs for duration of treatment; 50% of that for women on CRT. • Endometrial cancer: 0.8 for 5 years. • Hip fracture: 0.9 for rest of life. • In addition to Weinstein and Schiff, AMI given same utility as hip fracture (0.9 for rest of life). • Benefit of ORT on menopausal symptoms assumed to be halved with CRT.	• Costs/QALY: in symptomatic women: 9500-17500 (ORT), 9820-34700 (CRT). • Costs/QALY: in women without symptoms: 45800- dominated (ORT); 26100-1450000 (CRT). • Costs/QALY: in women with hysterectomy: 6510-1020000 (ORT). • Lifetime net increments in costs mainly relate to HRT and consultations. • Net QALY improvements mainly relate to improvements in symptoms - thus lower ICERs in symptomatic women. • In non-hysterectomised women, use of ORT may not be worth increased risk of endometrial cancer unless >50% reduction in risk of AMI.	Type of analysis: scenario analysis. Key variables: • Treatment duration. • Presence of menopausal symptoms. • Presence of side effects from progestogen. • Cardiac benefits.	Poor use of decision rules.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Daly et al [1992] [23] [Primary Prevention] [UK]	In women without uterus: 1. ORT. 2. No treatment. In women with uterus: 1. ORT. 2. CRT. 3. No treatment. [In all cases, 10 years treatment in women aged 50 years.]	• CEA (life-years and QALYs). • State transition model (variable probabilities). • Deterministic. • Lifetime time horizon. • 6% discount rate. • Perspective: health service.	• Fractures (wrist, vertebral and hip). • Stroke. • IHD. • Breast cancer. • Endometrial cancer. • Hysterectomy.	*Incidence:* • Fracture rates based on published surveys. • Breast and endometrial cancer rates and IHD based on UK hospital admissions (age-specific). • Hysterectomy: 18% prevalence in 50-59 year olds. *Mortality:* • For no treatment, cancers and IHD: UK mortality statistics. • Hip fracture: 25% case fatality.	• Fractures: 20% reduction in first 5 years and 60% reduction after that. At end of treatment, effect lasts for as long as the treatment period. • Breast cancer: 0% increase in risk after 5 years, 30% after 10 years, 50% after 15 years. At end of treatment, effect lasts for as long as the treatment period. • Endometrial cancer: 6-fold increase in risk from 5 years after start of ORT treatment until 5 years after finish. No increase in risk for CRT. • IHD: 25% reduction in risk after 5 years, 50% reduction after 10 years (ORT). 50% effect of this effect in CRT. At end of treatment, effect lasts for as long as the treatment period. • Stroke: 25% reduction in risk with ORT, 12% reduction with CRT. • Hysterectomy: 2-fold increase in risk of hysterectomy/D&C in ORT, 25% increase with CRT (for treatment period only).

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Daly et al [1992] [23]	[1989-90UK £) • ORT: 12/year. • CRT: 48/year. • GP visits: 14/year. • Endometrial biopsy: 19/year (non-hysterectomised women only). • Unrelated costs in extra life-years: 213/year-1924/year (hospital); 154/year-191/year (GPs), depending on age. • Other costs estimated using age-specific lengths of stay multiplied by cost per day of 135.	Based on authors' judgement: • 0.95 severe menopausal symptoms. • 0.99 mild menopausal symptoms.	• Cost per life-year gained: 2900 in women with no uterus (ORT); 8300 in women with uterus (ORT); 14400 (CRT). • Cost-effective in hysterectomised women and in women with severe symptoms.	Type of analysis: simple one-way and scenario analysis. Key variables: • Increase in quality of life as a result of menopausal symptoms. • IHD protection. • Whether CRT removed IHD protective effect. • Duration of treatment.	Interestingly include cost of health care during life-years saved.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Tosteson and Weinstein [1991] [82] [Primary Prevention] [USA]	1. In women with uterus: ORT vs. no treatment. 2. In women without uterus: CRT vs. no treatment. Two treatment durations: 1. 10 years. 2. 15 years.	Same model as Tosteson et al [1990].	• Hip fracture • IHD • Breast cancer	*Incidence:* • Hip fracture: Estimated relationship between BMD and fracture risk based on population-based survey. BMD levels modelled as function of age. Hip fracture modelled as a function of BMD and age. • Breast cancer: same assumptions as Weinstein and Schiff. *Mortality:* • After hip fracture modelled as a function of age based on population-based survey. • IHD: baseline death rate from US life-tables. • Breast cancer: same assumptions as Weinstein and Schiff. • Death from other causes from US life-tables.	• No bone loss when on HRT; when end therapy bone loss same as at menopause. • Breast cancer: RR of 1.36 from 2 years after start of therapy to 2 years after (ORT only). • IHD: RR of 0.5 for IHD deaths for as long as treatment lasts (ORT only). • Risk of being in a nursing home after hip fracture modelled as a function of age from national survey data. • Risk of being in a nursing home for other reasons from a published study.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Tosteson and Weinstein [1991] [82]	[1990US $] • HRT (including monitoring and physician visits): ORT= 193/year, CRT= 250/year. • Hip fractures: 12810 (50-59 years) to 15125 (80-89). • Breast cancer: 7970/case (assumed non-invasive). • Nursing home: 31940/year. [No allowance for cost savings from IHD.]	Based on Hillner et al [1986]#. • Hip fracture: 0.36 for nursing home care; 0.95 for uncomplicated hip fracture; 0.76 disability due to hip fracture; 0.8 long-term disability; 0.4 long-term nursing home care. • 0.997 for side effects of HRT.	• Gain in life expectancy due to reduction in fractures similar to loss due to breast cancer. • Biggest effect on life expectancy comes from IHD risks. • Side effects are biggest quality of life factor. • If IHD risk reduction excluded and quality of life changes from side effects included, all options have a net loss in QALYs. • ORT (in women without uterus): cost/QALY: 7010-9020; without quality of life effect of side effects; 9930-14940. • CRT: (in women with uterus): cost/QALY: 32660-33780; without quality of life effect of side effects; >150000.	Type of analysis: simple one-way and scenario analysis. Key variables: • IHD risks. • Quality of life effects of side effects.	

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Weinstein and Tosteson [1990] [89]. [Primary Prevention] [USA]	For women aged 50 years: 1. ORT for 5 years. 2. CRT for 5 years. 3. CRT for 15 years.	Same as Weinstein and Schiff [1983].	Same as Weinstein and Schiff [1983].	Same as Weinstein and Schiff [1983]. Except: • Hip fracture: modelled as a function of BMD and age; distribution of BMD at 50 years and annual loss estimated from population-based survey.	Same as Weinstein and Schiff [1983].

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Weinstein and Tosteson [1990] [89].	Same as Weinstein and Schiff [1983].	Same as Weinstein and Schiff [1983].	• ORT for 5 years: cost per QALY of 72100 in asymptomatic women and 12600-33100 in symptomatic women depending on symptom relief. • CRT for 5 years dominates ORT for 5 years assuming quality of life differences are minimal. • CRT for 15 years: cost/QALY of 22650.	Type of analysis: simple sensitivity analysis and scenario analysis. Key variables: • RR of hip fracture. • Quality of life effects of symptoms.	No consideration of protective effect of ORT on IHD.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Daly et al [1996] [25] [Primary Prevention] [UK]	1. In women with uterus: ORT vs. no treatment. 2. In women without uterus: CRT vs. no treatment. Treatment duration: 10 years.	• CEA (life-years and QALYs). • State transition model (variable probabilities). • Deterministic. • Lifetime time horizon • 6% discount rate • perspective: health service.	• Hip, wrist and vertebral fractures. • Stroke. • IHD. • Breast cancer. • Endometrial cancer.	Same assumptions as Daly et al [1992].	Same assumptions as Daly et al [1992] except: • No risk of endometrial cancer in women with uterus because of use of CRT. • Hysterectomy/D&C: 25% risk in women with uterus taking CRT.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Daly et al [1996] [25]	Same assumptions as Daly et al [1992]. [1992-3 UK £] • ORT: 24/year. • CRT: 53/year. • GP visits: 23/year. • Wrist fracture: 170/case. • Vertebral fracture: 170-420/case (depending on age). • Hysterectomy: 1610-3810/case (depending on age). • Breast cancer: 1950-6910/case (depending on age). • IHD: 1540-4750/case (depending on age). • Stroke: 4000-12010 (depending on age). • Hip fracture: 2230-6210 (depending on age). • Health service costs of life-years saved: 361-2363 (depending on age).	Based earlier empirical study by same authors. Assumes: • 90% have relief of symptoms (lasting 5 years). • 5% side effects (only treated for 6 months). • 5% no change on quality of life.	Cost /QALY in mildly symptomatic women: • ORT: 310 (5 year treatment) to 660 (20 years). • CRT: 550 (5 year treatment) to 1250 (20 years).	Type of analysis: scenario analysis. Key variables: • Cardiovascular protection. • Duration of treatment (for asymptomatic women).	

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Ankjaer-Jensen and Johnell [1996] [1] [Primary and secondary prevention] [Denmark]	1. Calcium (5 years). 2. Etidronate (5 years). 3. Calcitonin (5 years). 4. HRT (10 years). Two populations: 1. All women. 2. High risk women on the basis of screening.	• CEA (fractures prevented). • State transition model (variable probabilities). • Deterministic • Lifetime time horizon. • 5% discount rate on costs, 0% on effects. • Perspective: health service.	• Hip fracture • IHD • Breast cancer	*Incidence:* • Fractures (hip, forearm, vertebral): age-specific incidence based on hospitalisation (for hip) and published sources (for others). • Breast cancer: age-specific incidence based on Danish cancer registry. • IHD: age-specific incidence from hospitalisations. *Mortality:* • Underlying age-specific rates based on Danish data.	• Optimistic (O) and pessimistic (P) assumptions for each treatment, and 'realistic' for HRT (R). *Fracture (RRs)* • Calcitonin: O=0.23 for life; P=0.70 from 5 years then linear decrease until year 25. • Etidronate: O=0.5 for life; P=0.50 for 5 years than linear decrease until year 25. • Calcium: O=0.5 for life; P=0.75 for 5 years than linear decrease until year 25. • HRT: O=0.50 (0-30 years); P=0.75 (0-10 years) and 0.85 (10-15 years); R=0.50 (0-10 years); linear decrease (10-35 years). • Breast cancer (HRT only): O=0 (0-10 years); 1.30 (10-20 years); 0 (20 + years). P=linear increase (0-10 years); 1.30 (10-20 years); 0 (20 + years). R=0 (0-10 years); 1.30 (10-20 years); 0 (20 + years). • IHD (HRT only): O=0.50 (0-30 years); P=0.65 (0-10 years), 0.75 (10-15 years); R=0.65 (0-30 years).

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Ankjaer-Jensen and Johnell [1996] [1]	[DKK] • Calcitonin: 8975/year. • Etidronate: 1919/year. • Calcium: 2369/year. • HRT: 1061-1748/year. • Hip fracture: 146641/case. • Forearm fracture: 6592/case. • Vertebral fracture: 3794/case. • Breast cancer: 96129/case. • Screening: 1000-2000/person screened. • Hospital admission for IHD: 8400/day (day 1); 2000/day (after day 1). Length of stay is a function of age.	None.	• Etidronate has lowest average cost-effectiveness ratio and calcitonin the highest. • Screening approach has lower average cost-effective ratio than population-based approach.	Type of analysis: simple one-way. Key variables: • Treatment efficacy. • Drug acquisition costs. • Compliance.	Inappropriate use of average cost-effectiveness ratios.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Jonsson et al [1995 & 1996] [50,51] [Treatment of established osteoporosis] [Sweden]	1. No treatment. 2. Treatment for 5 years for 62-year old woman with BMD below 1 SD of the mean. [No actual treatments specified.]	• CEA (fractures prevented, life-years and QALYs). • State transition model (fixed probabilities). • Deterministic • Lifetime time horizon. • 5% discount rate. • Perspective: societal.	• Fractures: hip, spine, shoulder, wrist.	*Incidence:* • Risk of fracture is modelled as a function of a range of variables including BMD. • At 1SD below the mean, the RR of hip fracture is 2.16. *Mortality:* • Underlying mortality from general population statistics. • Hip fracture mortality risks in first year after fracture: <65 years of age, 0 excess risk of death; 65-74 10% excess risk; 75-84 20% excess risk; 85+ 50% excess risk. No excess mortality from other fractures.	• Fractures: 50% reduction in risk of fracture. • After a hip fracture, it is assumed that 40% remain in full health, 32% near normal functioning, 8% severely handicapped, 20% die by year 1.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Jonsson et al [1996] [50,51]	[SEK] • Hip fracture: 156000/case in first year. • Spine: 16000/case. • Wrist/shoulder: 4000/case. • Nursing home: 200000/year. • BMD measurement 350/test. • Indirect costs of treatment: 250/year/ • Intervention (drug): 6000/year.	From Hillner et al [1986]: • After hip fracture: 0.95 (uncomplicated); 0.76 (disability); 0.36 (requiring nursing home); 0.8 (long-term disability); 0.4 (long-term nursing home). Average of first year: 0.82 based on probability of outcomes. As alternative set of values: Rosser based on original scaling: • First year average after hip fracture: 0.83. • Following years: 0.99 if return to full function and 0.85 if severely handicapped. As a further alternative, Rosser based on Swedish re-scaling: • First year average after hip fracture: 0.56. • Following years: 0.90 if return to full function and 0.35 if severely handicapped. Base-case uses 0.80 in first year and 0.40 after for hip, and 0.90 or 0.95 in year 1, then return to full function (1.0).	• Costs per hip fracture avoided: 60000-1000000 for 5 year treatment depending on reduction in annual fracture rate, annual risk of fracture and treatment cost. • Cost per life-year gained: 190000-819000 depending on discount rates. • Cost per QALY: 92000-318000 depending on discount rates and quality of life weights.	Type of analysis: multi-way analysis. Key variables: • Discount rates. • Effectiveness of treatment. • Cost of treatment. • Quality of life loss due to side effects of drugs.	

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Visentin et al [1997] [84] [Primary and secondary prevention] [Italy]	1. Calcitonin for 1 year in women over 50 years of age. 2. No treatment. [Population-based and high-risk only based on screening.]	• CEA (hip fractures prevented). No further details.	• Hip fracture	*Incidence:* • Hip fracture: 2.51/1000 (overall); 7.53/1000 in high-risk group (lowest quartile).	• Calcitonin: RR for fracture of 0.69.

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Visentin et al [1997] [84]	[US $, 1995] • Calcitonin: 1907/year • Hip fracture: 82508/case. • Screening: 61/test.	None.	• Cost per hip fracture avoided: 2367987 for population; 838,120 for high-risk women based on screening.	Type of analysis: simple one way. Key variables: • Acquisition price of drugs.	

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Francis et al [1995] [84] [Treatment of established osteoporosis] [UK]	1. CRT. 2. Etidronate. 3. Salmon calcitonin plus calcium. [In established osteporosis.]	• CEA (vertebral fractures avoided). • Decision tree. • Deterministic. • 1 year time horizon. • 6% discount rate. • Perspective: health service drug budget.	• Vertebral fractures.	*Incidence:* Incidence of further vertebral deformation in women with existing vertebral fracture. Taken from control groups of trials of osteoporosis treatments. Assumed 33.7% annual incidence.	• Reduction in fractures 53-60% depending on treatment, Based on trials where a statistically significant effect was detected.

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Francis et al [1995] [84]	[UK £] Annual drug costs ranging from Premarinm at 26.38 to Miacalcic at 2602	None.	Cost per vertebral fracture avoided: • 138-680 HRT • 1880 etidronate • 9075-25,013 salmon calcitonin	Type of analysis: none.	Average cost-effectiveness ratios

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Office of Technology Assessment [1995] [83] [Primary and secondary prevention] [USA]	1. Screening for low BMD and HRT in high-risk. 2. HRT for all women. 3. No intervention. Two age groups: 1. 50 years. 2. 65 years.	• CEA (life-years). • State transition model (variable probabilities). • Stochastic. • Time horizon: until 90 years of age. • 5% discount rate. • Perspective: health service.	• Hip fracture • IHD (AMI) • Breast cancer • Endometrial cancer • Gallstones.	*Incidence:* • Hip fracture: modelled as a function of BMD and age from SOF study. BMD given an initial distribution and annual decline with out treatment. Assumed to be normally distributed. • Limited information on other baseline incidence rates. *Mortality:* • Hip fracture: elevated risk of death (as function of age) in year after fracture, then same as general population. • Breast cancer: age of death from tumour registry (by stage). • Endometrial cancer: when on HRT age of death same as general population. When not on HRT, age of death set by tumour registry. • Gallstones: no excess mortality. • Risk of death from AMI same as in general population.	• Hip fracture: HRT eliminates bone loss while on treatment after which rate of loss same as menopause. • Breast cancer: RR of 1.35 after 10 years treatment and this remains until death. • IHD (AMI): RR for ORT of 0.50 and for CRT of 0.80 for duration of therapy. • Endometrial cancer: RR for ORT of 3.5 for 10 years. 7.0 after 10 years. Returns to 1.0 after treatment. No increased risk for CRT. • Gallstones: RR of 2.5.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Office of Technology Assessment [1995] [83]	[1993 US $] • ORT: 269/year. • CRT: 258/year. • BMD screening: 150/test. • Cost of fatal AMI: 14470/case. • Cost of non-fatal AMI: 74217/case. [Ratio of non-fatal to fatal AMI: 2.6] • Hip fracture: 22912. • Cholecystectomy: 11160. • Breast cancer: 45043-78153 (by stage). • Endometrial cancer (without HRT): 6000. • Endometrial cancer (with HRT): 15702-21552 (by stage).	None.	• Mean costs per life-year gained for screening and ORT:22431-151392 depending on duration of therapy and screening threshold. • Mean costs per life-year gained for population-based approach and ORT: 23334-126876 depending on time on therapy. • Life-long therapy more cost-effective. • CRT has lower ICERs because of lower protective effect regarding IHD. • Non-HRT drugs only have a chance of being cost-effective if used in established osteoporosis.	Type of analysis: simple 1-way and extreme scenario analysis. Key variables: • Duration of therapy (compliance). • Protective effect against IHD (for ORT).	Doubtful use of cost-effectiveness decision rules.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
Torgerson and Kanis [1995] [77] [Primary and secondary prevention] [UK]	1. Vitamin D injection (for four years). 2. Oral vitamin D and calcium (for three years). In 3 populations: 1. Women with low BMD in the community. 2. Women with low BMD in nursing homes, 3. Women in the general population.	• CEA (fractures avoided). • Decision tree. • Deterministic • 3-4 year time horizon. • 6% discount rate (costs and effects). • Perspective: health service.	• Fractures	*Incidence:* • Fracture incidence from survey data in both general population and nursing homes. • General population (cumulative 4 years); 11.25% all fractures and 5.4% hip alone. • Nursing home population (cumulative 4 years); 44% all fractures and 22% hip alone. • 21.6% of all hip fractures in women with BMI <20kg/m^2, (12.2% of the population).	• Vitamin D injection: over four years, 25% reduction in all fractures; 22% in hip fractures. • Vitamin D and calcium: over three years, 21% reduction in all fractures and 28% in hip fractures. • In women with low BMI, Vitamin D for four years reduces the incidence of hip fracture by 55%.

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
Torgerson and Kanis [1995] [77]	• [UK £] • Vitamin D injection: 28.10 over four years. • Oral vitamin D and calcium: 103/year. • Hip fracture: 5000.	None.	• Cost per hip fracture avoided (including cost of hip fractures) for oral vitamin D + calcium: £17379 in community; 1800 in community (low BMI); 4735in nursing homes; cost saving overall in nursing homes (low BMI). • Cost per hip fracture avoided (including cost of hip fractures) for vitamin D injection: all options save costs overall.	None.	Use of average cost-effectiveness ratios.

Appendix: Data tables cont'd

Study	Comparators	Methods of evaluation	Effects considered	Methods relating to baseline estimates	Methods relating to effects of interventions
National Osteoporosis Foundation [1998] [64] [Secondary prevention] [USA]	1. HRT 2. Calcium 3. Vitamin D 4. Calcitonin. 5. Bisphosphonates. 6. Fluoride. 7. Exercise.	• CEA (QALYs) • State transition model (variable probabilities) • Cycle length: 1 year • Deterministic • 50 year time horizon • 0% discount rate as time horizon and sequencing identical for each option.	• Hip fracture • Wrist fracture • Vertebral fracture. • Other fracture.	*Incidence:* • Fractures modelled as a function of age and BMD using SOF data. *Mortality:* • Hip fracture: 0.05. • No elevated risk from other fractures.	Reduction in fracture rate: • Calcium + vitamin D: >=10% hip, >=10% vertebra, >=10% wrist, >=10% other. • Bisphosphonates: 50% hip, 50%vertebra, 50% wrist, 0% other. • Calcitonin: 0% hip, 75% vertebra, 0% wrist, 0% other. • HRT (5 year treatment): 25% hip, 50% vertebra, 25% wrist, 25% other. • HRT (10 year treatment): 75% hip, 75% vertebra, 75% wrist, 75% other.

Appendix: Data tables cont'd

Study	Cost inputs	Utility assumptions	Main base-case results	Sensitivity analysis	Comments
National Osteoporosis Foundation [1998] [64]	[1992 US $] • Calcium+vitamin D: 50/year. • Bisphosphonates: 740/year. • Calcitonin: 740/year. • HRT (5 years): 430/year. • HRT (10 years or more): 430/year. • Hip fractures: expected costs for first year: 28242 (50-64 years), 26227 (>=65) years); some disability in 27% 600/year; moderate disability in 28% 2400/year; nursing home in 7% 27516/year.. • Wrist fractures: 1000 (acute), 2400/year (dependency in 2%). • Vertebral fractures: 1000 (acute); dependency in 5% 2400/year. • Other fractures: 3266 (acute).	Based on authors' judgement and published estimates: • QALYs losses varying posited for a range of possible outcomes from hip, wrist, vertebral and other fractures (e.g. the expected loss in QALYs during the year of a hip fracture were 0.6183, implying a utility value for this year of 0.3817. For cost-effectiveness analysis, a monetary value of $30,000 per QALY employed.	• Number of balance sheets presented detailing fractures rates and treatment and fracture costs with and without interventions. • Also use of nomograms to identify optimal management of individual women with particular characteristics. • As regards the use of testing for BMD, this should not be done on all women, but depend on each individual's risk factors. • HRT is the most cost-effective treatment for osteoporosis. • The sub-groups on whom it should be used depend on BMD and number and type of previous fracture.	Type of analysis: scenario analysis. • Cost of the drugs. • QALY effects of side effects of drugs.	This analysis was undertaken to inform clinicians about the optimal treatment of individual women.

Abbreviations used in data tables

AMI	Acute myocardial infarction
BMD	Bone mineral density
BMI	Bone mineral index
CEA	Cost-effectiveness analysis
CRT	Combined (oestrogen plus progestogen) replacement therapy
D&C	Dilatation and curettage
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
ORT	Oestrogen replacement therapy
RR	Relative risk
SD	Standard deviation

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