Health economics of osteoporosis

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Rather than reviewing the many studies of cost effectiveness in osteoporosis, this paper reviews the principles of cost-effectiveness analysis and the gaps in our knowledge that are required to improve such analyses in osteoporosis. These include more information on the cost of fractures and their consequences on health states, particularly on an international basis. New developments include the incorporation of adherence into models, the use of the FRAX™ tool to assess cost-effectiveness in individuals with any combination of risk factors for fracture, and the setting of intervention thresholds based on cost-effectiveness.

Key words: osteoporosis; fractures; health economics; cost-effectiveness.

Health Economics is a scientific area that has grown rapidly in the last decade. Its theoretical foundations are based on welfare economics, but it is a hybrid discipline since it is applied to an area of health which incorporates not only different scientific disciplines – such as economics, medicine and statistics – but also has to consider the views of policy-makers in its application. The branch within health economics that has undergone the most rapid development in recent years is economic evaluation, defined as ‘the comparative analysis of alternative courses of actions in terms of both their costs and consequences’.1 One of the most common forms of economic evaluation is cost-effectiveness analysis or cost–utility analysis which gives information on whether one treatment strategy provides any added value relative to other strategies in the same

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patient group, and at what cost. The growth of cost-effectiveness analysis is due largely
to the increased emphasis that decision- and policy-makers place when considering
health-care interventions: for example, in the reimbursement process.

In the context of osteoporosis, the aim of economic evaluation is to estimate the
number of fractures avoided with one intervention compared to others, and to translate
these avoided fracture events into costs and morbidity. Thus, a key variable is the rela-
tive risk reduction of fracture associated with treatment and the absolute risk of
fracture in the targeted population. All consequences related to the intervention should
be considered. Therefore, modelling is often a necessary tool, not only to incorporate
the impact of treatments beyond the time frame of clinical trials, but to incorporate in-
f ormation not usually captured by clinical trials. Modelling is also required to adapt the
analysis for specific country conditions. Thus cost-effectiveness analysis is hungry for
data, requiring information on clinical (effect of treatments), epidemiological (fracture
risk, mortality, and quality of life) and economic (fracture and intervention costs)
factors.

Specific studies of cost-effectiveness of interventions are reviewed elsewhere.\textsuperscript{2,3} In
this article we first provide some background to economic evaluation in general and its
history in the field of osteoporosis. Thereafter, issues are raised that are important to
improve the accuracy of economic evaluation of osteoporosis, such as the choice of
modelling approach and the need for data on costs and quality of life related to frac-
tures. Finally, we discuss the incorporation of adherence into cost-effectiveness, the
use of models that incorporate FRAX\textsuperscript{TM}, the fracture risk assessment tool.

\textbf{SHORT INTRODUCTION TO ECONOMIC EVALUATION}

\textbf{Health economic evaluation}

Health economic evaluation compares two or more treatment alternatives within
a defined patient group. There are four main types of economic evaluation in health
care; all measure costs similarly, but are distinguished by their different approaches to
measuring the consequences.\textsuperscript{1,4} Cost-minimization analysis compares treatments
solely on the basis of costs, and is used when the compared alternatives can be
considered as equivalent. Cost-effectiveness analysis, on the other hand, assesses
both treatment costs and consequences. Effects (treatment outcomes) are measured
in one-dimensional units, such as life years gained or fractures avoided. The main out-
put is the incremental cost-effectiveness ratio (ICER) which is obtained by taking the
ratio of the incremental difference in total cost ($\Delta C$) to the incremental difference in
benefits ($\Delta E$) between the treatment alternatives (A and B)\textsuperscript{1}:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_A - C_B}{E_A - E_B}$$ \hspace{1cm} (1)

The ICER can be interpreted as the incremental cost of producing effects by one treat-
ment alternative compared to the next most effective alternative, and can be
expressed e.g. as the cost per life year gained or cost per fracture avoided. Unidimen-
sional outputs are not without problems. For example, the cost per fracture avoided
has a different significance if the fracture is a forearm fracture rather than a hip frac-
ture with its much higher mortality and morbidity. Moreover, the output cannot be
used to compare different diseases. With the use of cost per life year gained, it is
difficult compare non-fatal diseases with high morbidity, such as osteoporosis, with
other diseases with high mortality but low morbidity. The use of cost–utility analysis overcomes some of these problems.

Cost–utility analysis uses a generic outcome measure. The most common measure is quality-adjusted life-years (QALYs), a utility index that combines the consequences of survival and quality of life. QALYs are constructed by multiplying the number of life years gained with a utility value for the level of health status. The utility value ranges between 0 (dead) and 1 (full health). For example, the average utility value for a 70-year-old woman in Sweden is 0.79, and the estimated value for a 70-year-old woman that has just sustained a hip fracture is 0.18.

The fourth type – and perhaps the least used – is the cost–benefit analysis which assesses both costs and outcomes in monetary terms. If the value of the total calculated benefits produced by an intervention exceed the value of its total costs, it is considered to be good value for money.

Modelling

There are two main approaches that can be taken when performing an economic analysis. The within-trial analysis or patient-level analysis is carried out alongside a randomized clinical trial. Resource use and effects are collected simultaneously with the clinical trial. The time frame of a within-trial analysis is the same as the length of the clinical trial. However, the consequences of a treatment often last longer than the intervention period. In health economic evaluation all relevant costs and effects should be considered, regardless of when these occur. This, together with the fact that clinical trial populations rarely fully represent the target treatment population in clinical practice, makes decision-analytic simulation modelling the preferred choice when estimating the cost-effectiveness of a treatment. Simulation modelling integrates epidemiological, clinical and cost data from different sources and over time related to the evaluated treatment strategies.

A model is a simplification of reality with the aim of excluding irrelevant details while incorporating information relevant for the programme under study. The most common modelling techniques are decision tree models, Markov cohort models, and individual-based simulation models (e.g. discrete event modelling).

A Markov model simulates a cohort of patients which is divided into a finite number of states based on, for example, the current health status of the patient. One important assumption of the Markov model is the no-memory assumption or the Markovian property, i.e., future events only depend on the current state of the patient, and not on prior events. Sometimes it might be necessary to model changes in probabilities, costs and effects over time after an event. Because of the no-memory assumption, this cannot be directly included in a health state in a Markov cohort model. This can be solved by adding more health state states; however, this often leads to so many health states that the transparency of the model is heavily undermined. If this is the case, the appropriate modelling technique might be individual-based simulation where patients are moved through the model one by one and not jointly as in the cohort model. This makes it possible to keep track of a patient’s event history. Using individual simulation, a large number of patients must be run through the model, using so-called Monte Carlo simulation, to obtain stable results, and this is usually time-consuming.

As long as all relevant consequences of a treatment strategy are considered, results of economic evaluation should not depend on the choice of model technique. Therefore, the choice of model technique is largely a matter of convenience. An individual simulation model can be replaced by a Markov cohort model with many health states and short cycle lengths which, in turn, can be replaced by a large decision tree.
However, an important factor in choosing the modelling framework is the availability of data. The model technique that best represents available data in the most transparent way is most likely the best choice. Cohort models are often the first choice, since they are generally regarded as a more transparent approach than individual simulation models and, as mentioned, considerably less time-consuming to run.

**HISTORY OF ECONOMIC EVALUATION WITHIN OSTEOPOROSIS**

The history of the economic evaluation of osteoporotic therapies can be divided into two phases. In the first phase, starting in the 1980s, the fracture risk was usually modelled from the relationship between bone mineral density (BMD) and fracture risk. This modelling approach arose because of the dearth of clinical trials that used fracture events as an endpoint. However, the fact that other risk factors are also important for the risk of fracture (height, smoking status, previous fracture, etc), makes BMD alone an incomplete measure of fracture risk. In addition, there are uncertainties concerning the relationship between changes in BMD and changes in fracture risk. The second phase of economic evaluation began in the early 1990s with the introduction of models that incorporated age-specific absolute fracture risks, based on epidemiological data. Also, until the mid-1990s, most cost-effectiveness studies aimed at evaluating the costs and benefits of HRT, and used models including a number of ‘extra-skeletal effects’ such as coronary heart disease (CHD) and breast cancer. In these earlier models only the effects on the risk of hip fracture were included. With the introduction of bisphosphonates, other fracture types (vertebral and wrist fracture) were added to the models whereas the extra-skeletal events were removed. This ‘bone-specific’ model structure, as shown in Figure 1, is still the basis for most models used and developed in recent years. As a guidance and help for researchers working with developing economic models for osteoporosis, a reference model has been made available (at http://www.iofbonehealth.org/health-professionals/health-economics/cost-effectiveness-model.html). The purpose of the reference model is to improve the quality and comparability of cost-effectiveness analysis in the field of osteoporosis and to serve as a tool for validation of present and future cost-effectiveness models.

**FINDING THE RELEVANT COMPARATOR**

Ideally, the cost-effectiveness of a treatment strategy should be compared to current standard care or the best alternative treatment strategy in the targeted patient group.

\[\text{Figure 1. Osteoporosis model structure.}\]
In the published literature of economic evaluations of osteoporotic pharmaceuticals, no treatment (or calcium and vitamin D supplements) has been the most widely used comparator. It could be argued that the current standard of care is actually no treatment, since the majority of patients with osteoporosis do not receive treatment. However, interventions are available for the treatment of osteoporosis which could be considered as standard care or the best alternative treatments. The main problem of comparing different treatment alternatives in cost-effectiveness analysis is that the clinical evidence comes from clinical trials that compare the drugs with placebo, and not with each other. Differences, for example, in study design, patient characteristics and statistical analysis make it difficult to assess the relative efficacy between treatments. The choice of treatment effect assumed is crucial for the results in a cost-effectiveness analysis when a comparison with other treatments is addressed; unfortunately, this choice is very difficult and subject to bias. For example, there are studies that have estimated the cost-effectiveness between osteoporotic interventions and have shown completely opposite results for which treatment is the more cost-effective.\(^{14,15}\) In short, estimating the cost-effectiveness between two treatments is not technically difficult, but it is the interpretability of the results that is problematic. There is, unfortunately, no simple solution. A head-to-head trial comparing two osteoporotic treatments is not very likely to be conducted, because of the large number of patients needed to have sufficient power to detect a significant difference in fracture risk.\(^ {16}\)

When an economic evaluation of a novel treatment is to be assessed, the first step is to base the cost-effectiveness analysis on the best clinical evidence, usually the phase-III study. If the clinical trial compares treatment with placebo, the base-case analysis should also use these comparators. Failure to compare effects with the most relevant comparator limits the usefulness of the economic evaluation, and for this reason decision-makers sometimes demand that the cost-effectiveness between treatments is estimated by making indirect comparisons. When these comparisons are made, the best approach is to derive efficacy estimates from meta-analysis that incorporate studies that are relevant for the target patients in the cost-effectiveness analysis. However, the choice of studies to include for meta-analysis is also subject to opinion and, therefore, it is important that there is an awareness of the inherent uncertainty in such analyses.

**ADHERENCE**

The recent development of new osteoporotic compounds that can be given intermittently (e.g. weekly, 3-monthly or yearly) has the prospect of improved adherence compared to older regimens due to the longer intervals between administration. Studies show that up to 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within 1 year with existing pharmacological agents.\(^ {17,18}\) Treatments that have the potential to improve adherence are likely to reduce the fracture costs and increase the QALYs in the context of an economic evaluation. However, these benefits have to be weighed against a higher treatment cost.

When approaching the concept of adherence, a distinction should be made between adherence, compliance and persistence, since their definitions vary in the literature. One frequently used definition is that adherence is the general term encompassing all aspects of persistence and compliance. Persistence is the duration of therapy, e.g. it can be expressed as the number of days until discontinuation or the proportion of the patients still on medication after a given time. Compliance is the proximity to the recommendations of optimal treatment, which includes how
the drug is taken, and can be simplified as the number of doses taken divided by the number of prescribed doses during a defined period.

In most previous economic evaluations, the effect of treatment has been derived from the phase-III clinical trials with fracture as an endpoint. The efficacy, based on intention-to-treat calculations, observed in clinical trials is related to the compliance of the patients in the trial. In the cost-effectiveness studies, patients are usually assumed to have an intervention cost during the whole intervention period which is likely to be an overestimate of the costs, since the persistence is not 100% either in the trial or in clinical practice. The intervention costs could be adjusted to the persistence of therapy – i.e. for the period the patients have the drug prescribed in the clinical trial – which would result in a lower treatment cost. However, then the lower treatment effect for those discontinuing treatment should also be considered. This information is generally not possible to derive on the basis of clinical trial data or register data.

Whereas randomized controlled trials (RCTs) remain the gold standard for comparing alternative treatments, the high internal validity required to demonstrate efficacy comes at the expense of external validity. The results of such trials may therefore generalize poorly to clinical practice. For example, adherence as observed in clinical trials is likely to be higher than in clinical practice, which in the context of the health economic analysis would yield lower benefits of therapy and potentially overestimated cost-effectiveness when using clinical trial data on adherence and efficacy. Poor adherence will not only have an impact on the effect side, but also on costs, because both intervention costs and effects wane when the patients stop taking the medication.

Incorporating adherence in more detail in the economic evaluation requires more sophisticated and complex modelling than previous models. However, this is not the main obstacle for producing cost-effectiveness estimates including adherence. The main hurdle for incorporating compliance in the health economic analysis is the lack of relevant and reliable data. Information about both the actual compliance in clinical practice and the linkage between compliance and treatment effect is needed.

There are some cost-effectiveness studies that have addressed the concept of adherence. The study which incorporates adherence in most detail has recently been published by Ström et al. The model distinguishes between the two components of adherence: persistence and compliance. Persistence is modelled as each patient in every cycle has a defined chance of stopping treatment and thus not getting the same anti-fracture benefit as a persistent patient. In the base case simulations patients were assumed to be at risk of dropping out during the first 3 years, and remaining patients were thereafter assumed to persist. Due to the difficulties in directly linking poor compliance to changes in fracture rates, poor compliance was modelled as a theoretical fraction of benefit (FOB) which ranged from 0 to 100%. The fraction of benefit was related only to treatment effect (i.e. impact on fracture risk) and did not affect intervention cost. FOB is the proportion of the optimal anti-fracture effect that a population receives from treatment. Since this is difficult to accurately represent in a model, due to lack of data, it was only included as a theoretical decrease in anti-fracture effect. An FOB of 80% was used in the base case. That means that a drug that reduces fracture risk by 50% in a fully adherent patient population would reduce the risk by 40% (i.e. 80% of 50%) in a persistent but partially-compliant patient.

The base case results from the analysis in Ström et al. are shown in Table 1. The comparison no treatment versus partial adherence would mirror how a typical anti-fracture drug (e.g. a bisphosphonate) compares to no treatment if adherence is taken into account. The comparison between full adherence and partial adherence can be
interpreted as a potential difference between what is observed in a clinical trial and what is observed in clinical practice.

The drop-out rate and the assumed reduction in FOB markedly reduces the amount of QALYs gained and increases the total drug costs. Since both the outcome and costs are improved, the incremental cost-effectiveness in the two examples is rather similar. Economic evaluation can thus be a method to find out optimal adherence, i.e., whether the extra costs are providing enough benefits to show good value for money. Only if improved adherence can be achieved at no extra cost do we need to look at the incremental cost-effectiveness.

The analysis also showed that improved adherence is most important in high-fracture-risk populations, and that the results were sensitive to assumptions regarding variables such as offset time (the time taken for drug effects to wear off after treatment is stopped) and reductions of drug effect from poor compliance. The main conclusion by Ström et al.\(^\text{23}\) was that high adherence is likely to be associated with added value for the health-care system.

**Table 1.** Base case analysis including the no-treatment arm (€).\(^\text{23}\)

<table>
<thead>
<tr>
<th></th>
<th>No treatment</th>
<th>Partial adherence</th>
<th>Full adherence</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td>0</td>
<td>1101</td>
<td>3434</td>
<td>1101</td>
</tr>
<tr>
<td>Fracture costs</td>
<td>14,626</td>
<td>14,022</td>
<td>12,401</td>
<td>−604</td>
</tr>
<tr>
<td>Total cost</td>
<td>14,626</td>
<td>15,123</td>
<td>15,835</td>
<td>497</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.400</td>
<td>0.390</td>
<td>0.364</td>
<td>−0.009</td>
</tr>
<tr>
<td>Life-years</td>
<td>15.3985</td>
<td>15.4076</td>
<td>15.4289</td>
<td>0.009</td>
</tr>
<tr>
<td>QALYs</td>
<td>7.7588</td>
<td>7.7739</td>
<td>7.8118</td>
<td>0.0151</td>
</tr>
<tr>
<td>Cost per QALY gained</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life-year.

**COST AND HEALTH-RELATED QUALITY OF LIFE RELATED TO FRACTURES**

Models are very flexible, but their validity and reliability depend largely on the quality of the data used. Intervention costs and cost of patient management can be rather easily calculated, but costs related to different types of fractures need to be collected through registers or observational studies. Registers are the easiest, but limited to the information previously collected. Registries capture hospitalization data very well, but are less effective for ambulatory care and costs in the community. To obtain data on quality of life, informal care and absence from work, there is generally a need for specific studies.

A number of studies has estimated fracture costs that would be appropriate to use in cost-effectiveness studies.\(^\text{26–33}\) A direct comparison of the results between studies is problematic because they are conducted within different health-care systems at different points in time. The studies also differ in costs included and study design. One conclusion that can be drawn is that hip fracture appears to be the most costly fracture type, followed by vertebral fracture and wrist fracture. However, few studies have investigated the costs associated with vertebral, wrist or other fracture types with identical study designs. Also, few studies have investigated fracture-related costs...
in the long term. Fractures, especially at the hip, are likely to be associated with extra costs extending for more than 1 year after the event.

Most of the studies that have estimated the health-related quality of life associated with osteoporotic fracture using a generic instrument – e.g., the EQ-5D or the time-trade off (TTO) instruments – have collected information in such a way that the calculation of QoL loss over a period of time is feasible. Some studies have only examined a certain point in time after fracture or estimated quality of life based on patients who have experienced a fracture in previous years. Also a few studies have followed patients in terms of QoL for longer than 1 year. However, the existing evidence suggests that QoL is reduced for more than 1 year after a hip and a vertebral fracture. Hip fracture is the most thoroughly investigated fracture, whereas investigation of the quality of life related to other fracture sites (e.g., humerus, pelvis, ribs and ankle) is very limited.

When estimating fracture costs for use in health economic studies, it is important that the costs are those that are potentially avoided by avoiding the fracture event. There are different types of study designs that can be considered when setting up a study to estimate the potential cost savings of avoiding a fracture. One study design approach is to use patients as their own controls by relating all costs the year before to all costs the year after fracture. Another method is to use a matched case–control design, i.e., fractured patients are compared with patients as similar in characteristics as possible to the fractured patients except that they have not sustained a fracture. The main disadvantage with the first approach is that it requires large numbers of patients at risk of fracture to be followed over time if this to be performed prospectively. The main difficulty with a matched case–control design is that the matched unfractured patients must reflect the same resource use as would the fractured have they had not fractured. This is important, because patients with osteoporosis have a higher morbidity and mortality than the normal population.

A third study design is to follow patients from the time of fracture and identify the fracture-related resource use. Advantages with this approach are that it is possible to include all relevant cost items, and information prior to the fracture does not have to be collected, thus reducing the time period for the data collection and the sample size because no matched cohort is used. A disadvantage could be that in some cases it might be hard to determine whether a resource is related to the fracture or not. An example of such a study design is a Swedish study estimating the costs and quality of life associated with osteoporosis-related fractures (the KOFOR study). The study followed patients prospectively following a fracture at the hip, spine (clinically defined) and wrist for 18 months after the fracture event. Relevant resource use for the estimation of fracture-related costs was gathered using a societal perspective. Quality of life before the fracture event was determined retrospectively, which could potentially lead to some recall bias.

The KOFOR study showed that hip fracture was the most costly fracture, followed by vertebral and wrist fractures, whereas the quality-of-life loss in the year after fracture was the highest for vertebral fracture, followed by hip and forearm fracture (Table 2). The findings for hip fracture regarding cost and quality of life were similar to those of previous studies. Perhaps the most interesting finding in the study was the marked loss in quality of life after a vertebral fracture; however, these results must be interpreted with some caution since the sample size was relatively small (81 patients) and biased towards hospital admissions.

The KOFOR study was based in Sweden, but fracture-related costs will vary between countries due to differences in resource use and price levels. Whether the
fracture-related quality of life differs between countries has not been thoroughly investigated. The International Costs and Utilities Related to Osteoporotic fractures study (ICUROS) is currently in progress and aims to fill the data gap that exists in many countries using a similar study design as in the KOFOR study. By collecting the same type of information in several countries it will be possible to conduct cross-country comparison on fracture costs and quality of life. The ICUROS will also include other fractures than at the hip, vertebral and the wrist. More information about the ICUROS can be found at www.ICUROS.org or www.iofbeonehealth.org/health-professionals/health-economics.html.

COST-EFFECTIVENESS INCORPORATING FRACTURE RISK ASSESSMENT USING FRAX©

Osteoporosis treatments have, in the past, been directed mainly towards women on the basis of a set BMD value. However, since it has been shown that BMD only partly explains the fracture risk, and there are other factors that add to the fracture risk, there is an increasing move to base treatment decisions on fracture probabilities instead of a certain BMD threshold. A new instrument that facilitates individual fracture risk assessment and improves case-finding strategies in clinical practice is the WHO fracture assessment tool (FRAX®) which predicts fracture risk for individuals with different mixes of risk factors. The FRAX® algorithms (http://www.shef.ac.uk/FRAX/) are based on a series of meta-analyses that identified clinical risk factors associated with an increased fracture risk independently of age and BMD at the femoral neck. These included low body mass index (BMI, in part dependent on BMD), a prior fragility fracture, a parental history of hip fracture, long-term use (e.g. for ≥3 months) of glucocorticoids, rheumatoid arthritis, current cigarette smoking and high alcohol consumption (≥3 units/daily). The independent contribution of each of these risk factors to fracture risk has been determined from nine population-based cohorts (190,000 patient years) from Europe, North America, Japan and Australia, and validated in a further 11 independent cohorts (1.2 million person-years).

The FRAX® tool can also be used in health economic modelling to assess cost-effectiveness in patients with different sets of risk factors. This can be especially helpful in the development and support of case-finding strategies to ensure that the criteria for treatment are also cost-effective. In Kanis et al the cost-effectiveness was assessed for postmenopausal women in the UK with one or more clinical risk factors

| Table 2. Costs and quality of life related to fractures estimated in the Swedish KOFOR study. |
|---------------------------------|-----------------|-----------------|
| Fracture-related costs (£ 2005) | Hip fracture    | Vertebral fracture | Wrist fracture |
| 0–12 Months after fracture     | 14,360          | 11,901           | 2316           |
| 13–18 Months after fracture    | 2422            | 3628             | 316            |
| Average quality of life loss (EQ-5D) | 0.16           | 0.26             | 0.059          |
| 0–12 Months after fracture     | 0.16            | 0.26             | 0.059          |
| 13–18 Months after fracture    | 0.05            | 0.11             | 0.01           |

a Assuming the 4-month QoL reached after 1 month.
for fracture using the fracture risk assessment tool. One of the objectives of using clinical scenarios was to test the cost-effectiveness of the guidance for the treatment and prevention of osteoporosis been provided by the Royal College of Physicians (RCP) in the UK. The RCP recommends that BMD testing be undertaken in postmenopausal women with strong risk factors for fracture, and that treatment be considered where the T score for BMD ≤ −2.5 SD. In the base case analysis the generic alendronate (70 mg weekly) was compared to no treatment.

The cost-effectiveness of alendronate directed to women at the threshold of osteoporosis is shown in Table 3. In women with osteoporosis (i.e. a femoral neck T score equal to −2.5 SD) the ICER was stable up to the age of 60 years and, thereafter, decreased progressively with increasing age. Treatment was cost-effective at all ages, even assuming a willingness-to-pay of £20,000/QALY. Treatment was also cost-effective at all ages in women who had previously sustained a fragility fracture with a BMD set at the threshold of osteoporosis. Indeed, treatment was cost-saving from the age of 75 years. A prior fragility fracture was a sufficiently strong risk factor that treatment was cost-effective even in women without other risk factors in whom BMD was not known (see Tables 3 and 4).

The effect of different clinical risk factors at different T scores for BMD is shown in Table 4. Prior fractures and a parental history of hip fracture were the strongest risk factors, and treatment was cost-effective across all ages and T scores. The use of glucocorticoids and the presence of rheumatoid arthritis had a lesser impact on cost-effectiveness, but across all ages and T scores the ICER lay above a £20,000 threshold but below a £20,000 threshold of cost-effectiveness. Current smoking and excessive alcohol intake were the weakest of the clinical risk factors, and cost-effectiveness was confined to the lower T scores and higher ages using a £20,000 threshold.

The current RCP guidelines provide for the treatment of patients with a previous fracture without the need for a BMD test. The cost-effectiveness analysis in Kanis et al suggests that this can be justified from a health-economic viewpoint, since the ICERs fell much below a £30,000 threshold or even a £20,000 threshold.

| Table 3. Cost-effectiveness of intervention with alendronate in women at the threshold of osteoporosis with or without a prior fracture and in women with a previous fracture without bone mineral density (BMD) a, b. |
|---|---|---|
| Age (years) | Cost (£000)/QALY gained |  |
| | T score = −2.5 no previous fracture | T score = −2.5 + previous fracture | No BMD + previous fracture |
| 50 | 14.7 | 6.7 | 14.6 |
| 55 | 16.2 | 7.3 | 14.1 |
| 60 | 14.3 | 7.3 | 11.6 |
| 65 | 7.0 | 2.9 | 5.0 |
| 70 | 3.7 | 0.8 | 2.1 |
| 75 | 3.0 | c.s. | c.s. |
| 80 | c.s. | c.s. | c.s. |

BMD, bone mineral density; c.s., cost saving.

a Body mass index (BMI) set to 26 kg/m².
The FRAX™ will considerably improve the assessment of fracture risk. However, this information will be of limited use if there is no information at what levels of fracture risk treatment should be initiated. The criteria for when an intervention becomes acceptable differ between health-care systems. One option to define intervention thresholds (ITs) is to assess at what fracture risk an intervention becomes cost-effective.

In osteoporosis, the IT has been commonly expressed as the 10-year probability of hip fracture at which intervention is cost-effective. However, the clinical manifestation of osteoporosis constitutes several different fracture types with different consequences for health and costs. Only considering hip fracture in the IT assessment will lead to too high probabilities at which intervention is considered to be cost-effective, since the benefit of osteoporosis treatments will be underestimated. Therefore, hip fracture equivalents have been developed in order to account for the consequences of all fracture types by using hip fracture as a common denominator.

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Intervention thresholds have been estimated in detail for Sweden and the UK. However, the IT is likely to vary between countries due to differences in epidemiology, ability to pay, fracture-related costs, and intervention costs. In order to study differences in intervention thresholds between countries, Borgström et al. assessed ITs for women in seven high-income countries representative of different regions around the world: Australia, Germany, Japan, Sweden, Spain, the UK and the USA. The cost-effectiveness analysis was estimated on the basis of a societal perspective with the intention of including morbidity costs, indirect costs, and costs of increased survival where available. The willingness to pay for a QALY gained was assumed to be twice the gross domestic product (GDP).

### Table 4. Cost-effectiveness of intervention (cost [£000]/QALY gained) in women with clinical risk factors according to age and T score for femoral neck bone mineral density (BMD).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>T score (SD)</th>
<th>0</th>
<th>−1</th>
<th>−2</th>
<th>−3</th>
<th>0</th>
<th>−1</th>
<th>−2</th>
<th>−3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Prior fracture</td>
<td></td>
<td></td>
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<td>(e) Alcohol &gt;3 units daily</td>
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c.s., Cost-saving. Note: body mass index (BMI) set to 26 kg/m².
The estimated age-differentiated intervention thresholds – i.e. the 10-year risk of hip fracture at which treatment becomes cost-effective – are presented in Figure 2. The intervention threshold rises with an increased starting age of treatment for all countries. Intervention thresholds were found to be lowest for the UK and Japan and highest for Spain. Sensitivity analysis showed that the variables that appeared to have the largest impact on the intervention thresholds were treatment effect, willingness to pay (WTP) per QALY gained, and intervention cost. The major contributors to the difference in estimated thresholds between countries seem to be fracture-related costs, intervention costs and the WTP per QALY gained. When assuming these variables to be the same, the intervention thresholds were more or less equal for all countries. The study shows that it is important, as for fracture-assessment algorithms, to assess intervention thresholds on a per-country basis. Country-specific thresholds have recently based these on fracture probabilities.49–56

SUMMARY

The economic evaluation of osteoporosis treatments have evolved from being based on simulation models linking fracture risk via changes in the BMD to models that are based on fracture risk efficacy estimated in phase-III clinical trials. As an aid for the researcher, an osteoporosis reference model has been suggested. Because most phase-III studies compare the active agent against placebo and not to other treatments, cost-effectiveness analyses that directly compare interventions have to be interpreted with caution. Current challenges for health-economic evaluation of osteoporosis are to incorporate the likely improved adherence with newly developed treatments and to produce better estimates on costs and quality of life related to fractures in an international perspective. The main obstacle for incorporating adherence in the economic evaluation is the lack of data, especially concerning the actual compliance in clinical practice and the linkage between compliance and treatment effect. The ICUROS is a large ongoing study that is collecting information on fracture-related costs and quality of life. Another current development is the incorporation of WHO fracture risk assessment tool (FRAX®) into the cost-effectiveness framework which will facilitate cost-effectiveness analysis to support and develop national case-finding strategies. However, the move to fracture probabilities necessitates the guidance on
the fracture risk at which treatment should be initiated. Such intervention thresholds can be based cost-effectiveness analysis.

**Practice points**

- the results of the economic evaluation should not be dependent on the choice of model technique as long as all relevant consequences of a treatment strategy are considered
- models are very flexible, but their validity and reliability depends largely on the quality of the data used
- cost-effectiveness analyses that compare different treatments without direct comparator trials should be interpreted with caution
- high adherence is likely to be associated with added value for the health-care system
- a new fracture risk assessment tool (FRAX™) will improve cost-effectiveness models to support and develop case-finding strategies
- by moving the treatment decision to be based on fracture probabilities, it will be important to assess at what fracture risk treatment becomes cost-effective (intervention thresholds)

**Research agenda**

- more information about the actual compliance in clinical practice and the linkage between compliance and treatment effect is needed for the health economic analysis
- data concerning the quality of life and costs related to osteoporotic fractures need to be collected on an international basis
- intervention threshold needs to be assessed on a per country basis

**CONFLICT OF INTEREST STATEMENT**

JAK and FB have both undertaken health-economic analyses in the field of osteoporosis for several agencies, including Health Technology Assessment NHS R&D HTA Programme (UK), the National Osteoporosis Society (UK), the Alliance for Better Bone Health (Sanofi and Proctor and Gamble), Amgen, Lilly, Merck, Servier Laboratories, Roche and Wyeth Research.

**REFERENCES**


